1011

DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1972

DOCUMENTS
JUL 30 1971
LIBRARY
STATE UNIVERSITY



HEARINGS

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS HOUSE OF REPRESENTATIVES

NINETY-SECOND CONGRESS

FIRST SESSION

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

DANIEL J. FLOOD, Pennsylvania, *Chairman*

WILLIAM H. NATCHER, Kentucky
NEAL SMITH, Iowa
W. R. HULL, Jr., Missouri
BOB CASEY, Texas
EDWARD J. PATTEN, New Jersey

ROBERT H. MICHEL, Illinois
GARNER E. SHRIVER, Kansas
CHARLOTTE T. REID, Illinois
SILVIO O. CONTE, Massachusetts

ROBERT M. MOYER and HENRY A. NEIL, Jr., *Staff Assistants*

PART 3

NATIONAL INSTITUTES OF HEALTH

Printed for the use of the Committee on Appropriations

AUTHENTICATED
U.S. GOVERNMENT
INFORMATION
GPO

DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1972

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS HOUSE OF REPRESENTATIVES

NINETY-SECOND CONGRESS

FIRST SESSION

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

DANIEL J. FLOOD, Pennsylvania, *Chairman*

WILLIAM H. NATCHER, Kentucky
NEAL SMITH, Iowa
W. R. HULL, Jr., Missouri
BOB CASEY, Texas
EDWARD J. PATTEN, New Jersey

ROBERT H. MICHEL, Illinois
GARNER E. SHRIVER, Kansas
CHARLOTTE T. REID, Illinois
SILVIO O. CONTE, Massachusetts

ROBERT M. MOYER and HENRY A. NEIL, Jr., *Staff Assistants*

PART 3

NATIONAL INSTITUTES OF HEALTH

U.S. GOVERNMENT PRINTING OFFICE
62-645 O WASHINGTON : 1971

COMMITTEE ON APPROPRIATIONS

GEORGE H. MAHON, Texas, *Chairman*

JAMIE L. WHITTEN, Mississippi
GEORGE W. ANDREWS, Alabama
JOHN J. ROONEY, New York
ROBERT L. F. SIKES, Florida
OTTO E. PASSMAN, Louisiana
JOE L. EVINS, Tennessee
EDWARD P. BOLAND, Massachusetts
WILLIAM H. NATCHER, Kentucky
DANIEL J. FLOOD, Pennsylvania
TOM STEED, Oklahoma
GEORGE E. SHIPLEY, Illinois
JOHN M. SLACK, West Virginia
JOHN J. FLYNT, Jr., Georgia
NEAL SMITH, Iowa
ROBERT N. GIAIMO, Connecticut
JULIA BUTLER HANSEN, Washington
JOSEPH P. ADDABBO, New York
JOHN J. McFALL, California
W. R. HULL, Jr., Missouri
EDWARD J. PATTEN, New Jersey
CLARENCE D. LONG, Maryland
SIDNEY R. YATES, Illinois
BOB CASEY, Texas
DAVID PRYOR, Arkansas
FRANK E. EVANS, Colorado
DAVID R. OBEY, Wisconsin
EDWARD R. ROYBAL, California
WILLIAM D. HATHAWAY, Maine
NICK GALIFIANAKIS, North Carolina
LOUIS STOKES, Ohio
J. EDWARD ROUSH, Indiana
K. GUNN McKAY, Utah

FRANK T. BOW, Ohio
CHARLES R. JONAS, North Carolina
ELFORD A. CEDERBERG, Michigan
JOHN J. RHODES, Arizona
WILLIAM E. MINSHALL, Ohio
ROBERT H. MICHEL, Illinois
SILVIO O. CONTE, Massachusetts
GLENN R. DAVIS, Wisconsin
HOWARD W. ROBISON, New York
GARNER E. SHRIVER, Kansas
JOSEPH M. McDADE, Pennsylvania
MARK ANDREWS, North Dakota
LOUIS C. WYMAN, New Hampshire
BURT L. TALCOTT, California
CHARLOTTE T. REID, Illinois
DONALD W. RIEGLE, Jr., Michigan
WENDELL WYATT, Oregon
JACK EDWARDS, Alabama
DEL CLAWSON, California
WILLIAM J. SCHERLE, Iowa
ROBERT C. McEWEN, New York
JOHN T. MYERS, Indiana

PAUL M. WILSON, *Clerk and Staff Director*

STAFF ASSISTANTS

WILLIAM GERALD BOLING
SAMUEL W. CROSBY
GEORGE E. EVANS
ROBERT B. FOSTER
JOHN M. GARRITY
HAROLD A. GRIFFIN
AUBREY A. GUNNELS
JAY B. HOWE
THOMAS J. KINGFIELD
KEITH F. MAINLAND
MILTON B. MEREDITH
GARY C. MICHALAK
DEMPSEY B. MIZELLE
ENID MORRISON
ROBERT M. MOYER
PETER J. MURPHY, Jr.
HENRY A. NEIL, Jr.
BYRON S. NIELSON
ROBERT C. NICHOLAS III
JOHN G. PLASHAL
SAMUEL R. PRESTON
DONALD E. RICHBOURG
EARL C. SILSBY
G. HOMER SKARIN
CHARLES W. SNODGRASS
HUNTER L. SPILLAN
GEORGE A. URIAN
EUGENE B. WILHELM
THAYER A. WOOD

ADMINISTRATIVE SUPPORT

GERARD J. CHOUINARD
PAUL V. FARMER
DANIEL V. GUN SHOWS
GEMMA M. HICKEY
LAWRENCE C. MILLER
FRANCIS W. SADY
DALE M. SHULAW
AUSTIN G. SMITH
RANDOLPH THOMAS

DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1972

MONDAY, MAY 3, 1971

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. ROBERT Q. MARSTON, DIRECTOR
DR. JOHN F. SHERMAN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ROBERT W. BERLINER, DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DR. LEONARD D. FENNINGER, ASSOCIATE DIRECTOR FOR HEALTH MANPOWER, NATIONAL INSTITUTES OF HEALTH
DR. KENNETH M. ENDICOTT, DIRECTOR, BUREAU OF HEALTH MANPOWER EDUCATION
DR. MARTIN M. CUMMINGS, DIRECTOR, NATIONAL LIBRARY OF MEDICINE
DR. THOMAS J. KENNEDY, JR., ASSOCIATE DIRECTOR FOR PROGRAM PLANNING AND EVALUATION, NATIONAL INSTITUTES OF HEALTH
RICHARD L. SEGGEL, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

INTRODUCTION OF DR. MARSTON AND ASSOCIATES

Mr. FLOOD. Now we have the National Institutes of Health. The presentation will be made by Dr. Robert Q. Marston, the Director.

Doctor, you are accompanied by several people. We do have a biographical sketch of you. We would like a biographical sketch of any of the supporting witnesses you call on.

(The biographical sketch follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

BIOGRAPHICAL SKETCH

Name: Robert Quarles Marston.
Position: Director, National Institutes of Health.
Birthplace and date: Toano, Va., February 12, 1923.
Education: B.S., Virginia Military Institute, 1943; M.D., Medical College of Virginia, 1947; B. Sc., Oxford University, 1949.

Experience: Director, National Institutes of Health, September 1968–present; Administrator, Health Services and Mental Health Administration, April–September 1968; Associate Director, National Institutes of Health and Director, Division of Regional Medical Programs, 1966–68; vice chancellor, the University of Mississippi, and dean, school of medicine, 1965–66; director of the 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; assistant resident, Medical College of Virginia, 1953–54; assistant resident, Vanderbilt University Hospital, 1950–51; intern, Johns Hopkins University, 1949–50.

Association memberships: Alpha Omega Alpha; Association of American Medical Colleges (executive council, 1964–67); American Federation for Clinical Research; Society for Experimental Biology and Medicine; Tissue Culture Association; American Society for Cell Biology; American Association for the Advancement of Science; Association of American Rhodes Scholars; American Medical Association; American Public Health Association Fellow; Association of American Physicians.

Special awards, citations, or publications: Rhodes scholar, 1947–49; Markle scholar, 1954–59.

Mr. FLOOD. You have some new people.

Dr. MARSTON. We have two Institute directors who are new since last year who will be testifying before the committee and who have come in to hear my initial testimony.

The first is Dr. Dewitt Stetten who is the Director of the National Institute of General Medical Sciences. And the second is Dr. David Rall who is the new Director of the National Institute of Environmental Health Sciences.

You know Dr. Sherman, the Deputy Director of the National Institutes of Health; Dr. Fenninger, the Associate Director for Health Manpower, NIH; Dr. Kenneth Endicott, who is the Director of the Bureau of Health Manpower Education; Dr. Cummings, the Director of the National Library of Medicine; Dr. Kennedy, who is the Associate Director for Program Planning and Evaluation, NIH; Mr. Richard Seggel, who is the Associate Director for Administration, NIH; Mr. Sharkey, the Director of Financial Management, NIH; Mr. Leland May, who is the Assistant Director of Financial Management, Budget, NIH. You know Mr. Miller who is the Deputy Assistant Secretary, Budget.

Mr. FLOOD. You have a prepared statement before us, Doctor. How do you wish to proceed?

Dr. MARSTON. I would like to read it.

Mr. FLOOD. Suppose you do.

AN NIH ORGANIZATIONAL OUTLINE

Dr. MARSTON. Perhaps it would be helpful again this year to make available to the members of the committee an outline of the organization of NIH with the dollars of the appropriations that the individual witnesses will be testifying for so that you can follow through as we proceed with the budget discussion.

Mr. FLOOD. This is an excellent chart and we will put it in the record.

(The chart follows:)

NATIONAL INSTITUTES OF HEALTH

April 20, 1971

Dr. Robert Q. Marston, Director

Total FY 1972 NIH Budget: $1,900.3 million

NATIONAL INSTITUTES

16 BUREAU OF HEALTH MANPOWER EDUCATION
Dr. Kenneth M. Endicott
Health Manpower Appropriation
$541.9 million

2 CANCER
Dr. Carl G. Baker
$234.3 million

14 CANCER CONQUEST PROGRAM
$100.0 million

3 HEART AND LUNG
Dr. Theodore Cooper
$195.5 million

17 NATIONAL LIBRARY OF MEDICINE
Dr. Martin M. Cummings
$22.0 million

4 DENTAL RESEARCH
Dr. Seymour J. Kreshover
$39.8 million

5 ARTHRITIS AND METABOLIC DISEASES
Dr. G. Donald Whedon
$135.4 million

6 NEUROLOGICAL DISEASES AND STROKE
Dr. Edward F. MacNichol, Jr.
$96.5 million

7 ALLERGY AND INFECTIOUS DISEASES
Dr. Dorland J. Davis
$99.3 million

8 GENERAL MEDICAL SCIENCES
Dr. DeWitt Stetten, Jr.
$150.4 million

9 CHILD HEALTH AND HUMAN DEVELOPMENT
Dr. Gerald D. LaVeck
$103.2 million

10 EYE
Dr. Carl Kupfer
$32.6 million

11 ENVIRONMENTAL HEALTH SCIENCES
Dr. David P. Rall
$25.3 million

PHYSICIAN AND HEALTH PROFESSIONS EDUCATION
(Health Manpower Appropriation)
Dr. Harry W. Bruce

ALLIED HEALTH MANPOWER
(Health Manpower Appropriation)
Dr. Thomas D. Hatch

DENTAL HEALTH
(Health Manpower Appropriation)
Dr. John C. Cronin

NURSING
(Health Manpower Appropriation)
Miss Jessie M. Scott

MANPOWER INTELLIGENCE
(Health Manpower Appropriation)
Dr. Wilson A. Lybrand

15 SALES INSUFFICIENCIES
(Dr. Endicott will justify)
$4.0 million

LIBRARY OPERATIONS
Dr. Joseph Leiter

EXTRAMURAL PROGRAMS
Dr. Leroy L. Langley

AUDIOVISUAL CENTER
Dr. Charles F. Bridgman

SPECIALIZED INFORMATION SERVICES
Dr. Henry M. Kissman

LISTER HILL COMMUNICATIONS CENTER
Mr. Dana B. McCann

DIVISIONS

Research	*Service*
1 BIOLOGICS STANDARDS Dr. Roderick Murray $8.5 million	**RESEARCH GRANTS** (Funded from NIH Management Fund) Dr. Stephen P. Hatchett
12 RESEARCH RESOURCES Dr. Thomas G. Bowery $68.1 million	**CLINICAL CENTER** (Funded from NIH Management Fund) Dr. Thomas C. Chalmers
COMPUTER RESEARCH AND TECHNOLOGY (Funded from NIH Management Fund) Dr. Arnold W. Pratt	**RESEARCH SERVICES** (Funded from NIH Management Fund) Dr. William B. DeWitt
13 FOGARTY INTERNATIONAL CENTER Dr. Milo O. Leavitt, Jr. $3.3 million	

DOLLAR FIGURES ARE FY 1972 BUDGET ESTIMATES

BOXES ARE NUMBERED IN ORDER IN WHICH APPROPRIATIONS APPEAR IN THE BILL

18	OFFICE OF THE DIRECTOR: S & E Dr. John F. Sherman	$11.4 million
19	BUILDINGS AND FACILITIES Mr. Richard L. Seggel	$ 3.8 million
20	SCIENTIFIC ACTIVITIES OVERSEAS Dr. Milo O. Leavitt, Jr.	$25.5 million for all HEW health activities
21	GENERAL RESEARCH SUPPORT Dr. Thomas G. Bowery	$49.2 million drawn from Institute appropriations

General Statement

Dr. Marston. Mr. Chairman and members of the committee, I always welcome the opportunity to testify before this committee about the goals, the plans, and the needs of NIH in carrying out its responsibilities for medical research, education in the health professions, and biomedical communication. Today I am particularly pleased to do so because you have before you budget estimates for NIH which I feel I can defend not only with a good conscience but with some enthusiasm. This does not mean, of course, that the budget fulfills all our desires or even that it satisfies every identifiable need. In an activity so broad in scope and so varied in substance as that of NIH, it is inevitable that choices have to be made, that priorities must be weighed, and that some desirable—and readily justifiable—projects must be deferred. But the NIH budget as a whole—looked at as a measure of the Federal commitment to the support of medical research and education, rather than merely as a catalog of program estimates—is an encouraging document.

COMPARISON WITH FISCAL YEAR 1970 AND FISCAL YEAR 1971 BUDGET LEVELS

To put the 1972 budget estimates into proper perspective, we must, I think, compare them with the 1970 level of the NIH programs. As you know, we operated during the first half of the current fiscal year (1971) under a continuing resolution which held the programs to their 1970 levels. The increases over that level only became available for obligation 2 months ago when the 1971 appropriations were apportioned by the Office of Management and Budget.

I must say, in all candor, that the apportionment was more generous than we had expected. All of the congressional increases, totaling nearly $147 million, will be available for obligation. The $15 million increase in funds for health facilities construction grants—which remain available until expended—is being held over until next year, but all the other increases are available now. And, what is equally important, they have become part of the budget base and were taken into account in preparing the 1972 estimates.

For NIH as a whole, the funds now available for 1971 provide an increase of more than $209 million over the operating level that obtained during 1970 and the first 8 months of fiscal 1971. The budget request for fiscal 1972 includes an overall increase of nearly $243 million. If the budget request is approved by the Congress, the total increase in the operating level will thus be a little over $452 million. This is an increase of a little over 31 percent in what is nominally a 2-year period. Actually, however, if this appropriation bill comes into effect before the end of this calendar year, a 31-percent increase in funds available for NIH programs will have come about in a little less than a year. The delayed congressional increases in the 1971 appropriations and the requested increases in the 1972 budget, will thus have a combined and cumulative effect on the NIH programs that marks, I believe, the beginning of a new and more vigorous phase in Federal support for both medical research and education in the health professions.

I am particularly hopeful that it will reestablish lost momentum in the research area. As you well remember, Mr. Chairman, the rapid expansion of biomedical research, for which the Congress was largely responsible, began in 1957 and covered a period of 7 years of great plenty. Unfortunately, beginning in 1964, the fortunes of NIH continued to follow that Biblical pattern and we have now had 7 lean years. During this latter period, especially during the past 4 or 5 years, there has been a slow but steady loss of momentum in existing programs and very little opportunity for the initiation of new ones to take advantage of new leads or to meet new needs. Our main concern has been to hold the line and this became increasingly difficult as the number of projects NIH was able to support continued to shrink due to the combined effects of expenditure restrictions and rising costs—particularly for clinical research involving bed patients. I believe that this downward trend can now be halted and I am enough of an optimist to hope that we may, once again, be at the beginning of the Biblical cycle.

INCREASES FOR RESEARCH

The 1972 budget estimates for the research Institutes and Divisions are based on 1971 appropriations that were $128.9 million higher than the 1970 operating level and they include requested increases that total an additional $125.6 million. This overall increase of $254.5 million for the research programs represents a 24 percent increase over their operating level in 1970 and the first half of 1971.

CANCER CONQUEST PROGRAM

The fact that $153 million—or three-fifths—of the total increase in research funds is for cancer research, including the $100 million requested for the new cancer conquest program, will not detract from its effect on the momentum of biomedical research as a whole though it will, to some extent, change its pattern and directions—as, indeed, is the intent. Nearly doubling the funds available for cancer research reflects a choice of priorities—the recognition of a major national health concern and a determination to take advantage of what are thought to be new opportunities for making progress in the attack on cancer. Dr. Baker, the Director of the National Cancer Institute, will testify in detail about these opportunities.

The fear that so much emphasis on a particular group of diseases will distort or detract from research on other serious health problems, while not without foundation, can be exaggerated. Many factors, besides the availability of financial support, determine the directions of research: the existence or absence of enticing leads for further exploration; the scientific background, professional experience, and personal interests of the investigator; the opportunities for research, in terms of available facilities and, in the case of clinical research, an adequate supply of patients with the disease in question; and, in many cases, the intellectual challenge of a particular problem. I doubt that the interplay of these factors has ever produced a balanced pattern of research—if, indeed, balance could be defined in this context. Nor do I think that balance is important in research. The research programs of each of the Institutes must be judged on their own merits. The size of the Federal investment in various fields of

research must be based on the magnitude of the health hazard with which they are concerned, on the importance that the American public attaches to the mitigation or elimination of these hazards, and on the scientific opportunities that are at hand for fruitful research. The latter is particularly important because it is as foolish to force-feed a field in which there are very few leads as to starve a field in which leads are waiting for exploitation. The balance with which we should be most concerned is that between research opportunities and the availability of resources for their exploitation. The funds provided for the uncertain business of probing the unknown in relation to disease problems should reflect the state-of-the-art in the various biomedical disciplines and clinical research fields rather than well-intentioned but extraneous decisions based on political, economic or social factors.

Moreover, cancer research should not be viewed as an isolated—or isolatable—activity. The most important reason for keeping the cancer conquest program within the family of the National Institutes of Health is that cancer research is inescapably intertwined with various aspects of the research missions of the other Institutes. The complex questions to which biomedical research must address itself and the work that goes into their solution are almost never unique to a particular disease or confined to single scientific disciplines.

MEDICAL SCHOOL SUPPORT OF NIH RETAINING CANCER PROGRAM

Mr. FLOOD. I noticed in the paper this morning where a committee of distinguished members of the medical profession very strongly supported your position with reference to maintaining the research in NIH. Did you see that story?

Dr. MARSTON. Yes, sir. That position was taken, as I understand it, by every chairman of a Department of Medicine who was attending the clinical meeting at Atlantic City which is going on at this time. It is my understanding that, without exception, each person who is the chairman of a department signed the resolution as an individual. That was reported in the paper this morning.

Mr. FLOOD. If it is possible, could you get a copy of that resolution for inclusion in the record as part of your testimony?

Dr. MARSTON. Yes, sir.

(The information follows:)

[Telegram]

ATLANTIC CITY, N.J., *May 2, 1971.*

President RICHARD NIXON.
Secretary ELLIOT RICHARDSON.
Senator EDWARD KENNEDY.

We, the undersign chairmen of departments of medicine of the Nation's medical schools, have responsibility for the care of large numbers of our citizens with cancer and for much of the Nation's cancer research. We strongly endorse current efforts to strengthen the fiscal and organizational structure of the Nation's cancer programs. We believe that progress toward this goal can best be achieved through the framework of the National Institutes of Health, because solutions will surely require a cross-fertilization of many disciplines. While we are convinced that the Cancer Institute should remain within the National Institutes of Health and NIH a part of HEW, we recognize that the expanded cancer research effort may be facilitated by establishing the National Institutes of Health as a separate agency of the Government. A paramount consideration, however, is the preserva-

tion of the integrity of the National Institutes of Health, which has played so critical a role in cancer in particular, and in the entire biomedical area.

Signed,

Dr. Robert Abernathy, University of Arkansas School of Medicine, Little Rock.
Dr. Fred Allison, Louisiana State University School of Medicine, New Orleans.
Dr. Thomas Almy, Dartmouth Medical School, Hanover, New Hampshire.
Dr. Alexander C. Bearn, Cornell University, Medical College, New York, N.Y.
Dr. J. Edward Berk, University of California College of Medicine, Irvine.
Dr. Morton Bogdonoff, University of Illinois College of Medicine, Chicago.
Dr. Alfred J. Bollet, Georgia Medical College, Augusta.
Dr. Philip K. Bondy, Yale University School of Medicine, New Haven, Conn.
Dr. Irving Brick, Georgetown University School of Medicine, Washington, D.C.
Dr. David Bristow, University of Oregon Medical School, Portland.
Dr. Evan Calkins, State University of New York, E. J. Meyer Memorial Hospital, Buffalo.
Dr. George Cartwright, University of Utah College of Medicine, Salt Lake City.
Dr. Francis Chinard, College of Medicine & Dentistry of New Jersey, Newark.
Dr. James A. Clifton, University of Iowa, Iowa City.
Dr. Leighton E. Cluff, University of Florida College of Medicine, Gainesville.
Dr. Walter J. Daly, Indiana University School of Medicine, Indianapolis.
Dr. Charles Davidson, Boston City Hospital, Boston, Massachusetts.
Dr. William Deiss, Jr., University of Texas Medical Center, Galveston.
Dr. David P. Earle, Northwestern University Medical School, Chicago, Ill.
Dr. Richard V. Ebert, University of Minnesota Medical School, Minneapolis.
Dr. Ludwig W. Eichna, Downstate Medical Center, Brooklyn, N.Y.
Dr. William W. Engstrom, Marquette University, School of Medicine, Milwaukee, Wis.
Dr. Saul Farber, New York University, College of Medicine, New York, N.Y.
Dr. Edmund B. Flink, West Virginia University, School of Medicine, Morgantown.
Dr. Thomas F. Frawley, St. Louis University Hospital, St. Louis, Mo.
Dr. Philip Freedman, the Chicago Medical School, Chicago, Ill.
Dr. Mario Garcia-Palmieri, University of Puerto Rico, School of Medicine, San Juan.
Dr. Kenneth Gardner, University of Hawaii, School of Medicine, Honolulu.
Dr. Robert Goldstein, New York Medical College, New York.
Dr. James Hammarsten, University of Oklahoma, School of Medicine, Oklahoma, City.
Dr. A. McGehee Harvey, Johns Hopkins University, School of Medicine, Baltimore, Md.
Dr. Harper Hellems, University of Mississippi, School of Medicine, Jackson.
Dr. Howard H. Hiatt, Harvard Medical School, Beth Israel Hospital, Boston, Mass.
Dr. Halsted R. Holman, Stanford University, School of Medicine, Palo Alto, Calif.
Dr. Edward W. Hook, University of Virginia, School of Medicine, Charlottesville.
Dr. William Hollingsworth, University of Kentucky, Medical Center, Lexington.
Dr. Donald Kaye, the Medical College of Pennsylvania, Philadelphia.
Dr. Alexander Leaf, Harvard Medical School, Massachusetts General Hospital, Boston.
Dr. James Leonard, University of Pittsburgh, School of Medicine, Pittsburgh, Pa.
Dr. George D. Ludwig, Medical College of Ohio at Toledo, Toledo.
Dr. Henry D. McIntosh, Baylor University College of Medicine, Houston, Tex.
Dr. Charles Mengel, University of Missouri Medical Center, Columbia.
Dr. George Meiklejohn, University of Colorado School of Medicine, Denver.
Dr. Carl Moore, Washington University School of Medicine, St. Louis, Mo.
Dr. John Moyer, Hahnemann Medical College, Philadelphia, Pa.
Dr. Robert G. Petersdorf, University of Washington School of Medicine, Seattle.
Dr. Charles Ragan, Columbia University College of Physicians and Surgeons, New York, N.Y.
Dr. Arnold Relman, University of Pennsylvania School of Medicine, Philadelphia.
Dr. Joseph C. Ross, South Carolina Medical University, Charleston.
Dr. John Sandson, Albert Einstein College of Medicine, New York, N.Y.
Dr. William B. Schwartz, Tufts University School of Medicine, Boston, Mass.
Dr. Theodore B. Schwartz, Rush Medical College, Chicago, Ill.
Dr. Donald Seldin, University of Texas Southwestern Medical School, Dallas.
Dr. Sol Sherry, Temple University School of Medicine, Philadelphia, Pa.

Dr. Lloyd H. Smith, Jr., University of California School of Medicine, San Francisco, Calif.
Dr. Gene H. Stollerman, School of Medicine, University of Tennessee, Memphis.
Dr. James F. Sullivan, Creighton University School of Medicine, Omaha, Nebraska.
Dr. Scott N. Swisher, Jr., Michigan State University College of Human Medicine, East Lansing.
Dr. Alvin R. Tarlov, University of Chicago, Chicago.
Dr. George W. Thorn, Harvard Medical School, Peter Bent Brigham Hospital, Boston, Mass.
Dr. Oscar A. Thorup, Jr., Arizona University School of Medicine, Tucson.
Dr. William S. Tisdale, University of Vermont College of Medicine, Burlington.
Dr. John Tobin, Jr., Stritch School of Medicine, Loyola University, Hines, Illinois.
Dr. Richard W. Vilter, University of Cincinnati College of Medicine, Cincinnati, Ohio.
Dr. James Warren, Ohio State University College of Medicine, Columbus.
Dr. Louis G. Welt, University of North Carolina School of Medicine, Chapel Hill.
Dr. Arnold Weissler, Wayne State University College of Medicine, Detroit, Michigan.
Dr. Ralph H. Williams, University of New Mexico School of Medicine, Albuquerque.
Dr. William Williams, State University of New York, Syracuse, N.Y.
Dr. Robert Wise, Jefferson Medical College, Philadelphia.
Dr. Lawrence E. Young, University of Rochester, Rochester, New York.
Dr. Stuart Bondurant, Albany Medical College, Albany, N.Y.
Dr. Solomon A. Berson, Mt. Sinai School of Medicine, New York, N.Y.
Dr. Eugene Braunwald, University of California, LaJolla.
Dr. Joseph Shipp, University of Nebraska College of Medicine, Omaha.
Dr. William N. Valentine, University of California at Los Angeles, Medical Center, Los Angeles.

RESEARCH LEADS INTO VIRAL CARCINOGENESIS

Dr. MARSTON. The present excitement about the role of viruses in causing cancer—which is one of the reasons for feeling that the time is ripe for a cancer conquest program—illustrates the way in which progress in one field of research depends on work being done in another. Virologists, who for years have been mainly concerned with unravelling the mysteries of infectious diseases, such as the common cold, for which viruses are thought to be responsible, have provided the leads and are now doing much of the work in viral carcinogenesis. Further refinement of this work is now leading deep into the basic sciences of molecular biology and genetics. For example, a very important development of the past year is the discovery that the cell chemical known as DNA is not the sole and unique determinant of genetic patterns it was heretofore thought to be. It has now been shown that RNA, the chemical messenger that carries instructions inherent in DNA's "code," can, in some cases, dictate how DNA is formed and thus itself control the cell. A series of rapid developments led to the discovery that an enzyme that uses RNA as a blueprint to make DNA is present in more than 30 different viruses that can cause various forms of cancer in birds, mice, cats, and monkeys. Last November one of our own scientists reported that he had found this enzyme in the white blood cells of patients with acute leukemia and it has since been found in patients with breast cancer. It is also known that certain classes of drugs inhibit the activity of this enzyme, at least in the laboratory. However, the next link in this very promising chain of events was the disappointing discovery that the enzyme can also be found in normal cells—which poured cold water on what had been a very hot lead in the search for the mechanism by which a virus can cause some forms of cancer. But further research now

seems to show that there is a significant difference between the enzyme found in normal cells and that found in malignant cells—and the trail is once more warm.

COMPLEX NATURE OP MEDICAL RESEARCH

In so complex a field as medicine in which so much basic information is still lacking, progress frequently involves a few steps forward and a few steps back. For this reason, the aspect of the cancer conquest program that concerns me most is the danger of overpromise—a concern, Mr. Chairman, which I know you share. The progress that has been made in cancer research in recent years is impressive and highly encouraging. It has, as the President said in his health message, opened "many new lines of inquiry and many new opportunities for breakthrough." But he wisely pointed out that the technological challenge of the space program holds no parallel for the more basic scientific challenge of biomedical research and he added that "scientific breakthrough * * * often cannot be forced—no matter how much money and energy is expended." That is a point of which the public should be constantly reminded.

In previous appearances before this committee I have emphasized the indispensability of research in the basic biomedical sciences to future progress in applied clinical research on human disease problems. As Sir Francis Bacon said more than 350 years ago, "Knowledge and human power are synonymous, since the ignorance of the cause frustrates the effect." In the field of medicine, the painstaking and often frustrating burden of assembling the necessary knowledge still rests largely with those engaged in so-called basic research. As the public and national purpose of the research institutes of NIH is to promote the health of the American people through research, they must maintain a judicious balance between empirical, frontal attacks on disease problems—which do sometimes yield practical, though often imperfect, results—and the more analytical and circuitous search for an understanding of the nature of disease. Clearly, the NIH programs must be responsive to national aspirations but the response must not be allowed to deflect them from the dogged pursuit of the scientific knowledge which alone can lead to real solutions of disease problems. As Prof. Joel H. Hildebrand, the eminent chemist at the University of California, has said: "Science is not a sacred cow that sometimes works miracles, but a workhorse that carries loads."

IMPORTANCE OF GENETICS RESEARCH

Among the basic science activities of special importance at this stage in the evolution of medical knowledge is genetics research for which this committee provided an additional $10 million to launch a special program of project grants. In accordance with the committee's wishes, I appointed an Inter-Institute Coordinating Committee on Genetics chaired by Dr. Berliner, Deputy Director for Science, and consisting of the Directors of the National Institute of General Medical Sciences, the National Institute of Child Health and Human Development, the National Institute of Allergy and Infectious Diseases and the National Institute of Arthritis and Metabolic Diseases, and Dr. Lamont-Havers, Associate Director for Extramural Re-

search and Training. This committee has recommended that awards be made for 162 applications that have been approved and given high priority by the advisory councils of seven of the Institutes. These awards will total $7,750,000 bringing the amount invested in the genetics program this year to about $60 million. The increase provided by this committee has made it possible to fund all high-priority applications in genetics of which we previously had a considerable backlog. Dr. Stetten, who rejoined NIH last fall as the new Director of the National Institute of General Medical Sciences which has the major responsibility for the genetics program, will be glad to answer any questions you may have about the future course of these activities.

SICKLE-CELL ANEMIA

In addition to the basic biomedical sciences, there are many areas in more immediately disease-related research in which a number of the Institutes share a common interest. One such area is sickle-cell anemia, an hereditary blood disease that is one of the most common long-term illnesses among black children and young adults. No permanently effective treatment has yet been discovered and most of the victims of sickle-cell anemia die before their 30th year. One of the scientists on the intramural research staff of the Arthritis Institute has done pioneer work on the molecular nature of this disease and four Institutes are at present supporting research on sickle-cell anemia through their grant programs:

the Arthritis Institute which supports work focused on the metabolic nature of the disease;

the Heart and Lung Institute which is concerned with blood abnormalities;

The National Institute of General Medical Sciences which supports research on the basic biochemistry involved; and

the Child Health Institute which is concerned with the diagnosis and treatment of childhood diseases.

Their total investment this year is about $1.5 million. Because of the importance of this disease to the black community and because there has recently been a promising advance in the management of acute crises of sickle-cell anemia, the budget request for the Heart Institute includes an additional $5 million to expand work in this area by all of the interested Institutes. I appointed a small task force, representing the three Institutes most directly concerned, which drew up plans for the expanded sickle-cell anemia program that the President announced in his health message.

Dr. Cooper, Director of the Heart and Lung Institute will be glad to describe this program in more detail.

ADVANCES IN COMBATING VIRAL HEPATITIS

Another area that spreads well beyond the interests of a single Institute is in research on the type of hepatitis that sometimes results from blood transfusions or the use of blood products. Here, I am happy to say, we seem to be on the verge of major advances. You may have seen recent newspaper stories about preliminary reports from Dr. Saul Krugman of New York University which indicate that it may—and here I emphasize the word "may"—now be possible to

develop a vaccine for this type of viral hepatitis which causes about 50,000 illnesses a year.

There have also been some promising developments in devising tests to determine whether blood is free of this hazard. Six components of NIH are involved in research on hepatitis:

The Division of Biologics Standards is responsible for establishing and maintaining standards of quality and safety for all biologic products which, of course, includes human blood for transfusion, products prepared from blood, and the test materials and methods used to assure that they meet the required standards.

The national blood resource program of the National Heart and Lung Institute is responsible for improving blood resources and their usage, including the development of new technology to insure the safety of these uses.

The National Institute of Allergy and Infectious Diseases is responsible for research on the causative agents of viral hepatitis, for development of new methods for detecting hepatitis virus, for vaccine development and for the production and distribution of reference reagents.

The National Institute of Arthritis and Metabolic Diseases has a general responsibility for research in liver diseases including clinical diagnosis, medical management and the fundamental processes underlying these diseases.

The Clinical Center, which is a major user of blood and blood products, is an intrinsic part of our research effort on hepatitis.

BLOOD PRODUCTS

Mr. FLOOD. What is a blood product as distinguished from blood?

Dr. MARSTON. There are a number of blood products. Particles in the blood, such as platelets, are sometimes used in transfusions, particularly in patients with leukemia where the platelet count may have gone down either because of the disease or the treatment.

Mr. FLOOD. Are they solid?

Dr. MARSTON. Yes, sir; they are solid small particles that prevent bleeding when you have a cut. These are particles that come out of the blood.

Mr. FLOOD. Are they taken orally?

Dr. MARSTON. No, sir; these have to be given intravenously. There are other types. None of them are taken orally. Sometimes patients need albumen, sometimes they need a product such as gamma globulin which is now about the only thing one can do to help protect against contacts with another form of hepatitis, infectious hepatitis. Many people going to parts of the world having an even higher incidence than here will have a shot of gamma globulin which is a useful protection.

Mr. FLOOD. Is it a prophylactic or cure?

Dr. MARSTON. In the case of gamma globulin it is almost always a prophylactic although it is used in some children and also in some adults who have a deficiency in their inmmue mechanism and have repeated infections. They may actually be treated with repeated injections of gamma globulin to supply some of the protective antibodies from other people because they are unable to make them themselves.

The Division of Biologies Standards is responsible for certifying that preparations and the use of these various products, including blood, meet needed national standards.

Finally, the broad virologic and immunologic capabilities of the National Cancer Institute are being called on to help solve some of the basic problems involved as well as to assure that new vaccines are free of tumor-inducing viruses.

In addition to the scientific problems, the elimination of the hepatitis risk in blood transfusions will involve complex logistical and legal problems. I have, therefore, appointed a Task Force on Hepatitis to coordinate the activities within NIH and to mesh these with the responsibilities of other agencies, both Federal and non-Federal.

OTHER FISCAL YEAR 1972 BUDGET CHANGES

I shall leave to the Directors of the Institutes the task of setting forth the purposes of the increases in the estimates for the various NIH research programs. It may, however, be useful to summarize for you major changes in NIH research activities as a whole. In addition to the program increases I have already mentioned, a net increase of $9.6 million is requested for the National Institute of Child Health and Human Development for family planning and population research. An increase of $5.3 million is requested for the general expansion of the activities of the still relatively new National Institute of Environmental Health Sciences of which Dr. David Rall is the new Director, succeeding Dr. Paul Kotin who has left us to become vice president for health sciences of Temple University.

For our regular research-grant program, there is a net increase of $18.4 million in the budget. However, as an additional $23 million will be required to honor our moral commitments to ongoing projects, there will be a decrease of $4.6 million for new grants or the renewal of grants beyond their present commitment. There is also a $5 million reduction in the funds requested for the general research support grants of which $2 million reflects the discontinuation of the health sciences advancement awards which were part of this program.

FELLOWSHIPS AND TRAINING GRANTS

A decrease of $7 million for fellowships in part reflects the planned phaseout of predoctoral fellowships. In general, the policy is to hold the postdoctoral and special fellowships to slightly below their 1970 level. Due to the congressional increase in fellowship funds for 1971, the actual number of these fellowships awarded with 1971 funds will be a little higher than in 1970—1,499 instead of 1,385. The budget estimate for 1972 allows for only 1,020 of these fellowships so that the average for the 2 years will be only slightly below the 1970 level. In other words, Mr. Chairman, the number of people holding postdoctoral and special fellowships will be roughly the same in 1970, 1971, and 1972.

I realize that this may be somewhat confusing. Actually some of these fellowships were awarded for a period of 2 years. There will be more in 1971 than in 1970 or 1972, but since some of the ones awarded in 1971 will be for 2 years, the number holding a fellowship at any one time will be approximately the same by our best estimates at present.

In accordance with the agreement of the Office of Management and Budget to defer any modifications of the training grant programs until the training study now underway has been completed, there is no change in the amount requested for training grants. An apparent reduction of $23 million for the training programs, in some budget tables, is due to the transfer of that amount—which represents the faculty salary component of the training grants—from the Institute appropriations to the health manpower appropriation. The amounts for faculty salaries in all research training grants awarded to an institution will be paid by the Bureau of Health Manpower Education, in a lump sum, to the dean so that he will have some flexibility in the use of these funds.

HEALTH MANPOWER PROGRAMS

Since last year's hearings, much thought has been devoted to the development of national policies for health manpower. The administration's study of health options for the Nation came to the conclusion that more health manpower, more evenly distributed geographically, is an essential prerequisite if we are to have a national policy of providing equal access to high-quality health care for all Americans. The Carnegie Commission's report "Higher Education and the Nation's Health—Policies for Medical and Dental Education" has made a number of thoughtful recommendations and has provoked much discussion of the effect of health personnel shortages on our health-care problems. Partly as a result of these two studies, the administration has proposed legislation to stimulate the production and better distribution of more health professionals.

The health manpower programs of NIH are based on four pieces of authorizing legislation. Two of these—the Allied Health Professions Training Act and the provisions in the Public Health Service Act relating to public health training—were renewed last year for a further 3 years. The other two—the Nurse Training Act and the Health Professions Educational Assistance Act—expire on June 30 and their revision and renewal is, as you know, now under consideration by the Subcommittee on Public Health and Welfare of the House Committee on Interstate and Foreign Commerce and there were hearings in the Senate today.

The administration's proposals for the revision of these two pieces of legislation involve a number of important changes in policy and in approach—notably in regard to institutional support and student assistance—which Secretary Richardson has already discussed with you. The budget estimates for the health manpower appropriation reflect these proposed changes. However, a number of alternative bills have also been introduced and I understand, Mr. Chairman, that you have decided to defer consideration of the budget estimates for health manpower until the nature of the authorizing legislation is clear. I shall therefore not comment further on the health manpower programs at this time. However, both Dr. Endicott, the Director of the reorganized Bureau of Health Manpower Education, and I shall be happy to answer any questions you may have about the existing manpower programs or the proposals for their continuation and revision.

NATIONAL LIBRARY OF MEDICINE

There are only modest increases in the budget request for the National Library of Medicine: $471,000 over the 1971 budget authority and $2.2 million over 1970 operating level. Of the increase provided in the 1971 appropriation, $500,000 was earmarked for the development of plans for the Lister Hill National Center for Biomedical Communication which the Congress authorized 2 years ago in honor of Senator Lister Hill who, during his long service in the Senate, did so much to promote Federal health activities, and, particularly, medical research. The National Library of Medicine, whose role is very much broader than that usually brought to mind by the word "library," is an essential adjunct to the research activities of NIH. It plays a major part in the very important—and very difficult—task of making research results readily available to health practitioners and to other researchers. In carrying out this task, the National Library of Medicine—under the dynamic leadership of its Director, Dr. Cummings—has gone far beyond the traditional archival functions of a library to become, in fact, a national communications center for biomedical information.

As I said at the beginning of this statement, the budget estimates for the fiscal year 1972 do not answer all our prayers and they will not meet every need that someone in the biomedical community—or, indeed, on the administrative staff at NIH—regards as urgent and important. But this is inevitable and, in some degree, always has been and always will be true. I am satisfied, Mr. Chairman, that this is not only a good budget but that it provides for a real resumption of initiative in the research area and that the amounts requested—and the purposes for which they are requested—will greatly stimulate progress both in health research and in the provision of adequate health manpower. If the increases in the NIH budget since I appeared before this committee last year are, indeed, the harbingers of future support, we can look forward to another rewarding period of growth in the advancement of the health of the American people.

Mr. FLOOD. Doctor, as in the past years we will save most of our questions regarding the individual categories of diseases until we get to the various categorical institutes.

We do, of course, have some general overall questions and we think you are the best qualified to answer those.

BUDGET FOR FELLOWSHIPS AND TRAINING GRANTS

One thing that stands out when one reads these justifications is that every institute has a reduction in the number of fellowships and training programs to be supported in 1972.

Why the cut back in 1972? Do you have a long-range plan? Is it part of that plan?

Dr. MARSTON. Mr. Chairman, this is a very crucial question and one that stimulated a lot of interest in the biomedical community. It revolves around the $23 million item that I mentioned in my opening statement.

I would like to spend a few minutes in explaining that in somewhat greater detail.

The purpose of the transfer of the $23 million is not to decrease the number of trainees supported in these areas. Indeed, we have said repeatedly that we expect that the same number of research trainees will be maintained.

The second point is that the distribution of those dollars will be determined by the same mechanism that we have used in the past—that is, the various Institutes and their training grant review committees will evaluate, with the fairness they have in the past, the justification for the request for training funds. This will determine the amount of money that will be allocated to a given institution in the country.

Mr. FLOOD. Why 1972? Did this happen overnight? We didn't hear about this last year?

Dr. MARSTON. No, sir. This is completely new in 1972 and is a departure from anything we have done in the past. The purpose is to make in one block award to an institution those components of the training grants that represent the salary components of the training grants, so that the dean of the institution, or the administrative officer, can have somewhat more flexibility in the use of those funds.

I think there is one other clarifying point I should make. In order to do this, an institution must be eligible for support under the manpower legislation. Those institutions, such as postgraduate schools and teaching hospitals, that are not eligible will not be involved in this proposal at all.

DISTRIBUTIONS OF THE TRANSFERS BY INSTITUTE

Mr. FLOOD. There is a pretty wide range between the institute that is cut the most with regard to these fellowships and training programs and the one that is cut the least.

What considerations went into determining this variation between institutes?

Dr. MARSTON. This is purely a mechanical estimate of what proportion of a given institute's funds in training grants will be used for the salary component for the institutions.

I would make the point that the decisions on allocation of training grant funds to a particular medical school will be arrived at in the same fashion as heretofore. Then it is purely a mechanical process to add up the salary components and to transfer them to the Bureau of Health Manpower Education for payments.

PHASING OUT OF PREDOCTORAL FELLOWSHIP PROGRAM

Mr. FLOOD. Are we talking about fellowships and the training program?

Dr. MARSTON. We are talking about the training grants.

Mr. FLOOD. What about the fellowships?

Dr. MARSTON. There is one program that is being phased out, that is the predoctoral fellowship program which has been decreasing over the years. We decided that we could handle the training of predoctoral students in a better fashion than by a national competition when the number of applications became so much higher than the number we could support. This was holding out false hope to individuals and institutions.

We made a program decision to decrease funds for the predoctoral fellowship program from about $5 million in 1970 to $3.5 million in 1971 and to request only $2.5 million for 1972. Other than that, the general intent of the budget is to hold fellowships and training grants at essentially the same dollar level as in previous years.

Dr. SHERMAN. All of the predoctoral fellowships are concentrated in the National Institute of General Medical Sciences.

ANALYSIS OF OVERALL NIH RESEARCH GRANT BUDGET

Mr. FLOOD. Leaving out the special cancer program, the budget for research grants is an increase of less than 5 percent. So the program is dropping back, and with a few exceptions, that same formula seems to be applied pretty much across the board as far as the individual institute is concerned.

Is this an accurate assessment?

Dr. MARSTON. The figures are accurate. I think there are three points one should make.

First, the increase in cancer dollars is a real increase and represents an increase in the support of biomedical research.

The second point is that the budget reflects a series of increases and decreases outside of the cancer area. The third point is that the increases in the last part of fiscal year 1971 in a sense overtook the 1972 budget process. In the research area an increase of $97 million passed by the Congress became available to us in the last 5 months of 1971 with the result that the increase in program level between 1971 and 1972 is smaller than it would have been had we not had such an increase in 1971.

Mr. FLOOD. It is less than 5 percent?

Dr. MARSTON. Yes, sir.

Mr. FLOOD. That is a slight drop back in program level.

Dr. MARSTON. Yes, sir, if one looks at differences between 1971 and 1972.

BREAKTHROUGH POSSIBILITIES IN OTHER INSTITUTES

Mr. FLOOD. Are there any good prospects for breakthroughs in other institutes that would warrant special funding such as you are asking for cancer? Aren't you about to break through any place else that warrants some attention?

Dr. MARSTON. Yes, sir, and we will want to bring to the committee's attention the excitement and progress across the whole range of biomedical research.

There is not an Institute at NIH that doesn't have exciting and promising progress to report to you this year.

So the answer to your question is very definitely yes, there are many areas in biomedical research that are promising and that we are quite enthused about.

BUDGET DECREASE FOR DIRECT OPERATIONS

Mr. FLOOD. For direct operations of the research institutes you are budgeting a decrease from $342,322,000 to 330,843,000. When you also take into consideration, and you have to do this, the increasing cost of doing business, that is a pretty significant reduction isn't it? What prompts this? These are from the schedules in the President's budget.

Dr. MARSTON. Not including manpower and the library and the $100 million for cancer?

Mr. FLOOD. That is correct.

Dr. MARSTON. I think the point is that as far as the Institutes are concerned, if you do in fact eliminate the $100 million which we testified on in the supplemental appropriation, the total increase between 1971 and 1972 is limited to $25,582,000 and out of a total budget for research of almost $1,200 million. That is a small increase.

Mr. FLOOD. Take a look at page 129 of the committee print.

Dr. MARSTON. Right.

Mr. FLOOD. This is where we get these startling figures. You see direct operations—1971 estimated $342,322,000, and 1972 is $330,843,000.

Dr. MARSTON. I think we have two things, Mr. Chairman. One, I do not believe this includes the impact of the $100 million additional funds for cancer.

Mr. FLOOD. It does not.

Dr. MARSTON. And the direct operations figure represents primarily the two items listed. That is, the research that is actually carried on at the Bethesda campus and our contract program.

The contract program is related to work that is done outside of the Federal Government under contract. I believe, Mr. Miller, this does not reflect the impact of the congressional increases.

Mr. MILLER. I think it does.

Mr. FLOOD. This is the kind of a question that is awfully hard for a bureau chief to answer off the top of his head because there are a myriad of facts and figures and details. Also there are some adjustments since the budget was printed. Maybe you would would like to supply a statement on this for the record.

Dr. MARSTON. We would like to supply this for the record. In our preparation of the budget we do anticipate some increase in the financial support for what is called direct operations between 1971 and 1972. We will explain this for the record.

(The information follows:)

RELATIONSHIP BETWEEN 1971 AND 1972 FIGURES FOR DIRECT OPERATIONS

The appropriation figures for direct operations cited in the chairman's testimony are those shown in the printed President's budget. To show a meaningful relationship between the years 1971 and 1972, these figures must be adjusted for comparability, pay raise costs and, most importantly, the final Office of Management and Budget allowance which was received at the time the budget was being printed. For expediency the increase was placed in the grants activity. The justifications reflect the proper distribution of these funds resulting in an increase to the direct operations activities in 1972.

The comparable 1971 figure is $340,207,000 and the 1972 figure, including the redistribution of the OMB allowance is $354,261,000. The increase of $14,054,000 in 1972 over 1971 is made up of $16,414,000 in program increases, $10,906,000 in program decreases, and $8,546,000 in mandatory costs.

NOTE.—The $100 million for the Cancer Research initiatives is not included.

POSSIBILITY OF USING FORT DETRICK FACILITIES

Mr. FLOOD. Since you are not expanding your direct operations, but if anything it seems to us you are going a little bit in the other direction, then why are you even considering expanding your facilities in which to conduct these direct operations by taking over part of Fort Detrick?

Dr. MARSTON. If I could answer the last part of that question first, the decision hasn't been made on the role of NIH in activities at Fort Detrick at present. We have been alert to the conference report which asks us to prepare for this Appropriations Committee information on Fort Detrick and we have had a major study underway in that area.

There are areas of research that could usefully utilize some of the existing resources at Fort Detrick. We have analyzed which of these could be carried out at Fort Detrick and what the advantages and the disadvantages are. We are having discussions with the department concerning this question at present.

Mr. FLOOD. But you are not increasing direct operations?

Dr. MARSTON. We have made the case repeatedly that if we are to expand our activities to take over additional facilities at Fort Detrick, this would require additional resources, both positions and dollars. That is not reflected in this budget.

DISTRIBUTION OF THE NIH MANAGEMENT FUND

Mr. FLOOD. There are several more things we would like for the record.

All the way through your budget there are adjustments "to provide an equitable distribution of the management fund in 1972." Will you have someone prepare a table summarizing the transfers you talk about and a narrative giving some detail on how these transfers were calculated?

Dr. MARSTON. Yes.

(The information follows:)

The amount each appropriation contributes to the management fund is based on a formula designed to provide an assessment in consonance with the services provided. The adjustments necessary in any budget year are accomplished to assure equity in these assessments. The transferring appropriation experiences a reduction in the amount he contributes to the management fund in an amount equal to the transfer with no change in his program operating funds. The receiving appropriation increases his contribution by the amount transferred, likewise, with no programmatic effect.

There were three factors contributing to the seemingly major changes in assessment:

(1) A new appropriation for the Office of Director was added as a contributor which necessitated transferring the management fund portion from other appropriations to permit this new one to participate in the funding.

(2) The contributing appropriations increase and decrease at a different rates dictating changes in the level of their share of central support. Transfers result as a method of assuring assessments are related to the support received.

(3) A recent study of the factors used to determine each contributor's share of the assessment indicated that a change in these factors would provide a more equitable assessment. Application of this new formula required further adjustments among the different appropriations.

The factors used to provide for the assessments are as follows:

Management fund activity (budgeted amounts)	*Factor used to determine contributor's share of the assessment*
Computer services	Budgeted positions in laboratory and clinical research activity.
Engineering services	Total budgeted positions.
Research services	Laboratory and Clinical Research Activity Funds.
Clinical center	Number of bed assignments.
Grant review and approval	Funds in Regular Research Grants and Fellowships.
Administrative services	Total budgeted positions

The specific appropriations selected to receive or give funds to any other specific appropriation was an arbitrary decision to arrive at the end result with the fewest number of transfers. The amounts shown in the justifications as comparative transfers in 1971 to arrive at an equitable 1972 assessment follows:

NIH Management Fund—Comparative Transfers

Division of Biologics Standards:	
Comparative transfers to—	
National Institute of Environmental Health Sciences	$135,000
Research resources	94,000
Health manpower	295,000
Total	524,000
National Cancer Institute:	
Comparative transfers to—	
Fogarty International Center	22,000
Research resources	27,000
Dental health	54,000
Total	103,000
National Heart and Lung Institute:	
Comparative transfers to—	
National Institute of General Medical Sciences	144,000
National Institute of Child Health and Human Development	36,000
Health manpower	281,000
Total	461,000
National Institute of Dental Research: Comparative transfer to National Library of Medicine	112,000
National Institute of Arthritis and Metabolic Diseases:	
Comparative transfers to—	
National Eye Institute	69,000
Office of the Director	744,000
Total	813,000
National Institute of Neurological Diseases and Stroke: Comparative transfer to—National Eye Institute	1,088,000
National Institute of Allergy and Infectious Diseases:	
Comparative transfers to—	
Office of the Director	567,000
Health manpower	103,000
Total	670,000
National Institute of General Medical Sciences: Comparative transfer from; National Heart and Lung Institute	144,000
National Institute of Child Health and Human Development: Comparative transfer from—National Heart and Lung Institute	36,000
National Eye Institute:	
Comparative transfers from—	
National Institute of Arthritis and Metabolic Diseases	69,000
National Institute of Neurological Diseases and Stroke	1,088,000
Total	1,157,000
National Institute of Environmental Health Sciences: Comparative transfer from Division of Biologics Standards	135,000
Fogarty International Center: Comparative transfer from National Cancer Institute	22,000

NIH Management Fund—Comparative Transfers—Continued

Office of the Director:	
Comparative transfer from—	
National Institute of Arthritis and Metabolic Diseases	$744,000
National Institute of Allergy and Infectious Diseases	567,000
Total	1,311,000
Research Resources: Comparative transfers from—	
Division of Biologics Standards	94,000
National Cancer Institute	27,000
Total	121,000
Health Manpower:	
Comparative transfers from—	
Division of Biologics Standards	295,000
National Heart and Lung Institute	281,000
National Institute of Allergy and Infectious Diseases	103,000
Total	679,000
Dental Health: Comparative transfer from National Cancer Institute	54,000
National Library of Medicine: Comparative transfer from National Institute of Dental Research	112,000

TRANSFER OF RESEARCH CONTRACTING FUNCTIONS

Mr. Flood. We would like the same kind of table regarding the transfer of research contracting functions from the NIH management fund to the Office of the Director.

In this narrative suppose you tell how these transfers were calculated and why this function should be shifted to your office?

Dr. Marston. We will be pleased to do that.

(The information follows:)

Research Contracting Funds

In March 1968, at the request of the staff of the Intergovernmental Relations Subcommittee on Government Operations, House of Representatives, the GAO issued a report on "Procurement Procedures Employed in Awarding a Contract to the Regents of the University of California." That report led former Secretary Wilbur Cohen, in October 1968 to direct a joint OS–NIH review of contract policies, practices and procedures at NIH.

In June 1970, following the survey on research contracting management at NIH, Dr. Roger O. Egeberg, Assistant Secretary for Health and Scientific Affairs, directed NIH to create a strong central office for this function reporting directly to the Associate Director for Administration, NIH.

The new organization provides for sound administration and management of research contracting operations to meet the needs and special requirements of NIH programs. It overcomes a previously existing "split" in procurement functions and provides a more efficient base for planning, developing and recommending NIH-wide negotiated contracting policies, procedures and practices.

The following list reflects the 1971 amounts for research contracting functions transferred from the NIH Management Fund portion of each appropriation to the Office of the Director for the new Office of Contracts and Grants. The individual amounts were arrived at by the application of the management fund formula normal for administrative services.

Division of Biologics Standards	$28,000
National Cancer Institute	151,000
National Heart and Lung Institute	71,000
National Institute of Dental Research	31,000
National Institute of Arthritis and Metabolic Diseases	66,000
National Institute of Neurological Diseases and Stroke	67,000
National Institute of Allergy and Infectious Diseases	76,000
National Institute of General Medical Sciences	21,000

National Institute of Child Health and Human Development	$47,000
National Eye Institute	8,000
National Institute of Environmental Health Sciences	22,000
John E. Fogarty International Center for Advanced Study in the Health Sciences	6,000
Research resources	10,000
Health manpower	36,000
Dental health	15,000
National Library of Medicine	38,000
Total	693,000

SALARY INCREASES ABSORBED BY NIH

Mr. FLOOD. Then give us a table showing by institute and in total the salary increases that are being absorbed in 1971 and in 1972.

Dr. MARSTON. Yes.

(The information follows:)

SALARY INCREASES BEING ABSORBED DURING 1971 AND 1972

[In thousands]

	1971				
	Total pay raise absorbed	Obtained from own reserve	Transferred from reserve of other appropriations within NIH		1972 total pay raise absorbed
			Amount	From	
Division of Biologics Standards	$458		$308	NINDS	$281
			150	NIAMD	
National Cancer Institute	2,777		1,879	NINDS	2,228
			898	NIGMS	
National Heart and Lung Institute	1,446		1,446	NIGMS	915
National Institute of Dental Research	572	$389	183	NIGMS	493
National Institute of Arthritis and Metabolic Diseases	1,500	1,500			908
National Institute of Neurological Diseases and Blindness	1,324	1,324			922
National Institute of Allergy and Infectious Diseases	1,251	1,132	119	NIGMS	836
National Institute of General Medical Sciences	378	378			305
National Institute of Child Health and Human Development	874	550	62	NINDS	860
			262	NIGMS	
National Eye Institute	163	163			268
National Institute of Environmental Health Sciences	269	269			337
Fogarty International Center	84		54	NIAMD	55
			30	NINDS	
Research resources	119		75	NIAMD	138
			44	NIGMS	
Total IRD's	11,215	5,705	5,510		8,546
Bureau of Health Manpower Education	1,179		816	NIGMS	1,956
			363	NIGMS	
National Library of Medicine	671		442	NIEHS	471
			229	NIGMS	
Office of the Director	697		461	NEI	556
			236	NIGMS	
Total NIH	13,762	5,705	8,057		11,529

TRANSFERS OUT OF NIH

Mr. FLOOD. We would like another table showing the amounts proposed to be transferred out of the NIH this year and with a narrative explanation of each one of those.

Dr. MARSTON. Yes, sir.

(The information follows:)

PROPOSED TRANSFERS OUT OF NIH, FISCAL YEAR 1971

[In thousands]

	Departmental management [1]	St. Elizabeths Hospital [2]	Tota
Division of Biologics Standards	$19		$19
National Cancer Institute	28		28
National Heart and Lung Institute	24		24
National Institute of Dental Research	10		10
National Institute of Arthritis and Metabolic Diseases	30	$74	104
National Institute of Neurological Diseases and Stroke	17	26	43
National Institute of Allergy and Infectious Diseases	31		31
National Institute of General Medical Sciences		1,282	1,282
National Institute of Child Health and Human Development	13		13
National Eye Institute	2	494	496
National Institute of Environmental Health Sciences		27	27
Total research	174	1,903	2,077
Health Manpower	98		98
National Library of Medicine	4		4
Total, NIH	276	1,903	2,179

[1] Proposed transfer to departmental management for new Facilities Engineering and Construction Agency (FECA) pursuant to reorganization order signed by the Secretary, DHEW, effective Apr. 5, 1970. Includes $180,000 from management fund and $96,000 from health manpower.
[2] Proposed transfer to St. Elizabeths Hospital for increased pay costs.

FUNDS HELD IN RESERVE

Mr. FLOOD. If there are any funds that you have in reserve in addition to what will appear in the two tables I just mentioned, would you show that for the record?

Dr. MARSTON. Yes, sir; the major one is really not a reserve. It is the $15 million for health education facilities construction which will be carried over to next year. But we will describe that in detail.

(The information follows:)

In the Appropriations Bill for 1971 (H.R. 18515), $141,100,000 was appropriated for the Construction of Health Educational Research, and Library Facilities. This was an increase of $15,000,000 over the amount requested in the President's Budget and approved by the House. In the Conference Report on this Bill it was stated:

> The conferees are agreed that the $15,000,000 over the amount proposed by the House shall be applied as follows: $13,500,000 for medical and dental schools and $1,500,000 for nursing schools.

Mr. FLOOD. Of course, we will put in the usual historical tables and the special statements you have already submitted to the committee. We will have those placed in the record at the end of your testimony.

Dr. MARSTON. Yes, sir.

Mr. FLOOD. Mr. Michel?

EFFECTS OF BELATED APPORTIONMENT OF 1971 FUNDS

Mr. MICHEL. Dr. Marston, I will have more specific questions for the individual institutes when they come up, but in a general way you touched on this subject of the lateness of the release of the 1971 funds and, of course, you were in the process of making up your budget for 1972 long before you had any indication what was going to be eventually available in 1971; is that right?

Dr. MARSTON. Yes, sir.

Mr. MICHEL. Do you have sufficient flexibility to make the kinds of adjustments you would need to meet that up-and-down situation the chairman was making reference to by his line of questioning?

Dr. MARSTON. As you recall, in the late winter there was much discussion between the Executive and the Congress on this. As far as we were concerned, the congressional appropriation and an apportionment decision came almost simultaneously. So we did have the opportunity to look, although it was in rather a rush, at the impact of the 1971 increases on the 1972 budget, and to make adjustments to avoid, in all of the instances that we could, a sudden upswing in 1971 and a dropping down in 1972.

The fellowship is a particular example of a program for which we have more money in 1971 than in 1972. But will be able to work it so that we maintain a fairly even program level over the 3 years rather than going up in 1971 and down in 1972.

So whereas I would not make a case for lateness of decisions on funding, I would say it did have some advantages purely from an administrative standpoint in that a number of decisions that determined our program levels were made in a fairly short time frame and were made in relation to each other.

Is that answering the question?

Mr. MICHEL. Yes.

Let me put it another way. If you had put your 1972 budget together after you definitely knew what you had in 1971, would it have been any different?

Dr. MARSTON. I think that is a very, very difficult question to answer. The main point in looking at 1972 was that all of a sudden, in the research area, we had almost $100 million in congressional increases—including an additional $25 million in cancer specified by Congress.

Taking into consideration the congressional initiative and the Presidential initiative and the work that had gone into the 1972 budget, such as an agreement to hold the training grants essentially level, I doubt if we could have done much better than we have done with the 1972 budget.

I think we avoided, and had the opportunity to avoid, major errors.

FISCAL YEAR 1972 PERSONNEL INCREASES

Mr. MICHEL. What will be the total increase in personnel requested in 1972 over 1971?

Dr. MARSTON. 273 in full-time equivalent. That is on the basis of 11,613 positions in 1971 and a request for 11,868 in 1972.

NIH GRANTS TO MEDICAL SCHOOLS

Mr. MICHEL. How many medical schools do we now have in the country, Doctor?

Dr. MARSTON. 104 is still the number, I believe.

Mr. MICHEL. How many of them are now receiving grants from NIH this year?

Dr. MARSTON. All of them.

Mr. MICHEL. Would it follow that in 1972 all of them would be the beneficiary of grants?

Dr. MARSTON. All of the medical schools, yes.

Mr. MICHEL. Do we have a compilation of what each would be getting?

Dr. MARSTON. You mean from all sources at NIH?

Mr. MICHEL. Yes.

Dr. MARSTON. We can't give it for 1972. We can give it for 1970 I would think as the most recent year.

Mr. MICHEL. Why don't you do it for 1970?

Dr. Marston. All right. We will later after the grants have been awarded for 1971 be able to do that. That would make it several months off.

I would say there is one particular point that one should be alert to, and that is the impact of construction that involves large, single shot outlays.

(The information follows:)

NIH OBLIGATIONS TO MEDICAL SCHOOLS
(In thousands of dollars)

School of Medicine	1970 Total Obligations
University of Alabama Medical College of Alabama	$5,745
University of Arizona College of Medicine	1,063
University of Arkansas Medical Center	2,210
Loma Linda University School of Medicine	1,679
Stanford University School of Medicine	13,002
University of California, Davis, School of Medicine	1,691
University of Calfornia, Irvine, College of Medicine	898
University of California, Los Angeles, School of Medicine	13,128
University of California, San Diego, School of Medicine	4,885
University of California, San Francisco, Medical Center	16,029
University of Southern California School of Medicine	4,257
University of Colorado, Denver, Medical Center	8,131
University of Connecticut School of Medicine	970
Yale University School of Medicine	10,215
George Washington University School of Medicine	16,855
Georgetown University School of Medicine	4,227
Howard University College of Medicine	1,390
University of Florida College of Medicine	11,801
University of Miami School of Medicine	10,141
Emory University School of Medicine	6,046
Medical College of Georgia	2,063
University of Hawaii School of Medicine	1,352
Chicago College of Osteopathy	557
Chicago Medical School	1,353
Loyola University Stritch School of Medicine	2,107
Northwestern University Medical School	4,885
University of Chicago School of Medicine	11,218
University of Illinois Medical Center	4,931
Indiana University School of Medicine	6,344

School of Medicine	1970 Total Obligations
Iowa College of Osteopathic Medicine and Surgery	$761
University of Iowa College of Medicine	7,024
University of Kansas School of Medicine	3,454
University of Kentucky College of Medicine	2,164
University of Louisville School of Medicine	1,963
Louisiana State University Medical Center, Shreveport	86
Louisiana State University Medical Center, New Orleans	2,341
Tulane University School of Medicine	4,315
Johns Hopkins University School of Medicine	12,167
University of Maryland School of Medicine	4,713
Boston University School of Medicine	4,791
Harvard University Medical School	14,792
Tufts University School of Medicine	3,914
University of Massachusetts School of Medicine	82
Michigan College of Osteopathic Medicine	162
Michigan State University College of Human Medicine	1,337
University of Michigan Medical School	9,096
Wayne State University School of Medicine	3,167
University of Minnesota Medical School	11,047
University of Mississippi Medical Center	2,996
Kansas City College of Osteopathy and Surgery	727
Kirksville College of Osteopathy and Surgery	1,465
St. Louis University School of Medicine	3,554
University of Missouri School of Medicine	2,422
Washington University School of Medicine	12,419
Creighton University School of Medicine	1,336
University of Nebraska College of Medicine	2,716
University of Nevada School of Medicine	8
Dartmouth College Medical School	2,755
New Jersey College of Medicine and Dentistry, Newark	1,184
New Jersey College of Medicine and Dentistry, Rutgers	1,365
University of New Mexico School of Medicine	1,769

School of Medicine	1970 Total Obligations
Mt. Sinai School of Medicine, City Univ., N.Y.	$7,703
Columbia University College of Physicians and Surgeons	12,027
Cornell University Medical School	5,686
New York Medical College	4,010
New York University School of Medicine	11,532
State University of New York at Buffalo School of Medicine	4,485
State University of New York Downstate Medical Center	3,510
State University of New York Upstate Medical Center	2,795
Union College, University of Albany Medical Center	3,162
University of Rochester School of Medicine and Dentistry	6,609
Yeshiva University, Einstein College of Medicine	12,127
Duke University School of Medicine	12,649
University of North Carolina School of Medicine	14,780
Wake Forest College Bowman Gray School of Medicine	2,777
University of North Dakota School of Medicine	419
Case Western Reserve University School of Medicine	8,263
Medical College of Ohio, Toledo	353
Ohio State University College of Medicine	13,150
University of Cincinnati College of Medicine	39,302
University of Oklahoma School of Medicine	2,814
University of Oregon Medical School	4,163
Hahnemann Medical College and Hospital	2,263
Medical College of Pennsylvania	1,262
Pennsylvania State University, Hershey Medical Center	1,376
Philadelphia College of Osteopathic Medicine	746
Temple University School of Medicine	4,285
Thomas Jefferson University Medical School	4,489
University of Pennsylvania School of Medicine	13,539
University of Pittsburgh School of Medicine	4,742

School of Medicine	1970 Total Obligations
Brown University Program in Medical Science	$1,602
Medical University South Carolina	1,557
University of South Dakota School of Medicine	408
Meharry Medical College	1,868
University of Tennesse College of Medicine	3,484
Vanderbilt University School of Medicine	6,915
Baylor University Medical College	9,826
University of Texas Medical Branch, Galveston	3,444
University of Texas Medical School, San Antonio	1,042
University of Texas Southwestern Medical School	18,492
University of Utah College of Medicine	5,293
University of Vermont College of Medicine	2,575
University of Virginia School of Medicine	4,493
Virginia Commonwealth University, Medical College of Virginia	9,878
University of Washington School of Medicine	17,678
West Virginia University School of Medicine	1,855
Medical College of Wisconsin	2,591
University of Wisconsin Medical School	10,104
University of Puerto Rico School of Medicine	2,228
NIH, TOTAL	601,616

INCREASED COSTS FOR MEDICAL SCHOOLS

Mr. MICHEL. Last year I asked about some of these increased costs for medical schools, and the last figures that you had available were for the year 1967–68. I don't recall the figures. Could we have those updated for this year?

Dr. MARSTON. In terms of what?

Mr. MICHEL. We were talking about the increase in costs of medical schools.

Dr. MARSTON. Yes. The cost of impact of living-in spaces, impact on program.

Mr. MICHEL. Right.

Dr. MARSTON. Do you want that for all of the institutes and all of the programs?

Mr. MICHEL. No, just a general statement.

(The information follows:)

According to information compiled by the Association of American Medical Colleges, 91 medical schools for the academic year 1968–69 reported total expenditures of $1,366 million—an average of $15 million each. For the preceding academic year, 89 medical schools reported a total of $1,175 million—a $13 million average.

These data represent the financial operations of medical schools excluding outlays for construction.

PHYSICIAN-POPULATION RATIO

Mr. MICHEL. Has there been any change in the physician-population ratio for the most current year for which we have statistics?

Dr. MARSTON. The physician-population ratio has been going up a little but slowly. As you know, the real problem has been the distribution of health personnel which is very uneven in this country. We would be glad to indicate the trend which has tended to be upward in recent years.

RESEARCH GRANTS BY NIH SINCE 1967

Mr. MICHEL. I look back in the record here and in 1967 you were supporting 12,000 research grants. Do we have any up-to-date figures now for the succeeding years, 1968 and 1969 and 1970?

Dr. MARSTON. The total number of research grants in what we call our regular program was 10,883 in 1969, dropping to 9,800 in 1970. We expect that there will be 9,423 in 1971 and our estimate for 1972 is 9,249. That is, from 1969 to 1972, there has been a drop from 10,883 to 9,249.

Mr. MICHEL. Would the average size of the grants be increased in 1971 over 1967?

Dr. MARSTON. Yes, sir. We can supply for the record the average size of the grant to give you an idea of this. The 10,883 grants in 1969 were supported by $461 million whereas in 1972 we expect the support for the 9,249 grants to cost us $509 million.

So it will cost us more to support a smaller number of grants both because of the increased costs of doing business and the increased sophistication and complexity of science over this period of time.

Mr. MICHEL. At the time there was this decline in numbers of research grants approved, was there a decreasing number of applications actually received?

Dr. MARSTON. No, sir. In general the applications, and again I can supply the number of applications, stayed up. We have wondered ourselves whether people, particularly youngsters would become discouraged and not submit applications. This did not occur and the number of applications did stay up.

SUPPLY OF MEDICAL RESEARCHERS AND PRACTITIONERS

Mr. MICHEL. You know the discussions we have had in the last several years with respect to the emphasis on research, particularly at medical schools, our problems of trying to get more doctors produced and the questions we raised as to whether or not too many of them were going into the research field as distinguished from ending up being general practitioners or specialists out in delivery of medical service to the people.

Do you think now as we are on the incline again, the availability of money for research will make less problems with the medical schools in making sure there is the proper balance? We all recognize we can't have a real good medical school without conducting some research activities. They kind of fit together hand in glove.

Dr. MARSTON. No, sir; as you know and as I have expressed my views to this committee, this is not an either/or matter. The number of individuals spending full time on biomedical research is very small, compared to the number in practice, and a major part of that group are people with Ph. D's who are not qualified to practice medicine and take care of patients.

The goal of all of the programs at NIH is to improve the health of the American people and on that one cannot have an either/or approach. One has to have the continued application of increased knowledge, to have the type of people who can be recruited as teachers and faculty of the schools of medicine, and to increase the number of people to practice medicine.

I can argue with equal enthusiasm for all of these. I cannot argue for one to the exclusion of the other.

GRANTS FOR RESEARCH IN THE PRIVATE SECTOR

Mr. MICHEL. We confined our questions to the NIH relationship to the medical schools in the field of research. Do you receive applications from the private sector other than medical schools to do medical research?

Dr. MARSTON. Yes. Let me be sure you understand. The figures I gave you on grants were for all the grants. The majority of those numbers were for research but I did include the awards made by the Bureau of Health and Manpower and by the Library of Medicine. We will break this down in a general table for you.

(The information follows:)

RESEARCH GRANTS—REGULAR PROGRAM

	Number of grants funded			
	1969	1970	1971	1972
Institutes/Research Divisions	10,739	9,688	9,322	9,163
National Library of Medicine	46	34	20	17
Bureau of Health Manpower Education	98	78	81	69
Total NIH	10,883	9,800	9,423	9,249

Dr. MARSTON. The only restriction we have on the award of a biomedical research grant is that it must be to a not-for-profit organization. If it is a profit organization—and we do have relationships with many of them—we use the contract mechanism rather than the grant mechanism.

If an institution is a teaching hospital, a research institute, a medical school, a dental school, a school of veterinary medicine, when its application comes in it is reveiwed in competition to buy the best research we can for the Nation without regard to the origin of the application, with the single exception it must be a not-for-profit organization.

As part of the review, of course, we do look at the environment in which the research is to be done and the nature of sponsoring institution.

FISCAL YEAR 1971 RESEARCH CONTRACT FUNDS

Mr. MICHEL. I think it is good to have that distinction made.

What portion of that research money in 1971 went out in the form of contracts?

Dr. MARSTON. We have marked variation between the various institutes. It is dependent upon the nature of their programs.

In the Cancer Institute approximately 40 percent of the total $180 million in 1970 was in direct research of which most was contract research. In other institutes it would be quite low. The overall figure for grants was $592 million and the overall figure for contracts was $96 million.

The Cancer Institute constitutes by far the largest part of the contract program because of its work with industry in supplying drugs, in the chemotherapy program and in the virology program.

Mr. MICHEL. Would you prefer I ask Dr. Baker several questions on this contract business when we get to cancer? I would like to have a little better idea of the nature and form of those contracts.

Dr. MARSTON. I think certainly this would be helpful. The Cancer Institute has had special need to turn to contracts in a number of areas. On the other hand, the question of contract versus grant is a general problem in NIH and if there are any questions about the general criteria we use, I would be pleased to try to answer those.

In fact, Mr. Michel, recently we have sent out—or are sending out within the next week or so—a rather concise description of this very question, of the conditions under which we choose the contract versus the conditions under which we choose the grant.

Mr. MICHEL. I think that would be good to have. We are talking about considerably more money here now, and as you said previously in answer to a question, most of the contract work is in the area of cancer research. I think we ought to have it developed more fully to know exactly what we are talking about here.

Dr. MARSTON. We have tried very hard to choose the method of funding on the basis of the problem. We have avoided having an arbitrary distinction between grants and contracts.

The real criterion is how you get the best results.

GRANTING AND CONTRACTING PROCEDURES

Mr. MICHEL. Is there a different review procedure for grants than for contracts?

Dr. MARSTON. Yes, sir, I think there has to be.

Mr. MICHEL. And different personnel?

Dr. MARSTON. And different personnel, although in both instances we do depend on getting the best advice we can wherever it may be. In the contract area, the Federal Government has determined the need for a special type of research. It may be a cooperative study in leukemia in which you need a number of patients in various parts of the country treated under comparable conditions. In contracts we specify what the Federal interest is and the Federal need is. We may need a pharmaceutical manufacturer to help us in the development of a compound. We go to him and say this is something we need to fill a gap in our supply or, in some instances, as a material to be used by a grantee.

In the grant area, on the other hand, it is the grantee who takes the initiative and asks the Federal Government for support in carrying out his project.

As I said, we have just recently issued a statement to help clarify even further the conditions under which we use one instrument rather than the other one.

RELATION OF BUDGET TO PROPOSED LEGISLATION

Mr. MICHEL. You say in the two acts that are due to expire on June 30 there are going to be considerable changes requested of the legislative committees.

Dr. MARSTON. Yes, sir.

Mr. MICHEL. How is that treated in the 1972 budget?

DR. MARSTON. What we have done is to project the impact of the administration's proposals for administrative changes in the budget you have before you. The uncertainty here is that since there are a number of bills before the legislative committees, if they choose ways other than the recommendations of the administration, it is possible we would have to relook at the impact on our budget.

Mr. MICHEL. Generally what would it be—more money or less money?

Dr. MARSTON. It is quite a mixture. It depends on which bill you are talking about. In some areas the administration has proposed some things that are not in the other bills. There is a series of bills. I think it would be fair, Dr. Endicott, to say that most of the bills, the two I think of at least, propose the expenditure of more money than the administration's proposal in most areas.

Is that a fair statement?

Dr. ENDICOTT. Yes, sir, that is correct. The thing that would make the greatest difference in the budget would be the level of capitation grants which might require an appropriation per enrolled student. The figures proposed by the administration are roughly $1,500 per student in medicine, for example. The other bill would propose $5,000. These are both entitlement grants which might make a major difference.

In the case of nursing, the administration is proposing to eliminate authority for formula grants and Mr. Rogers has introduced a bill

which would provide $2,000 per nursing student which in itself would require $300-odd million.

So a great deal depends on how the legislation goes as to what the budget requirement would be.

FUNDS FOR NURSING EDUCATION

Mr. MICHEL. I am glad you brought up the matter of nursing because that is what we on this side of the table are getting the most letters on. In view of that partial response I am not altogether sure. Is there anything on the rosy side of the picture I could tell these people who write us? They are interested, of course, in the nursing field and know the act expires and would like to see something on the books extended or something more.

What do I tell them?

Dr. ENDICOTT. I think you might point out to them that the administration's budget proposal requests increased funds in support of the training of teachers, for special projects in schools of nursing, for student aid, but does not contain any proposal to fund formula grants or capitation grants. This is an element which in Mr. Rogers' bill would require more than $300 million for funding.

Mr. MICHEL. Will the student-assist part of that be as much as they are getting today? More or less?

Dr. ENDICOTT. The scholarship fund would be increased, but it is proposed to convert loans from direct loans to guaranteed loans. So that the amount available to them might be substantially larger provided the money market responds properly.

Dr. MARSTON. The budget, based on the administration's proposal for legislation, includes a proposed increase of over $100 million between 1971 and 1972. So you see that the manpower programs have been given very serious consideration.

CANCER CONQUEST PROGRAM

Mr. MICHEL. I notice on this chart which we have here, not altogether an organization chart, but in which the National Cancer Institute is in one box, and then a separate box for the cancer conquest program.

Is the special program really going to be that visible?

Dr. MARSTON. No, sir. This chart reflects what you had in the budget document in which, as you know, the $100 million is shown separately with a special degree of visibility.

In program terms, we think of a budget of $334 million for cancer research.

Mr. MICHEL. As distinguished from what figure last year?

Dr. MARSTON. $230 million for 1971 and $181 million for 1970.

Mr. Richardson's proposal, which he has sent to Senator Kennedy, outlines the organizational arrangement for the cancer conquest program in which the National Cancer Institute would be the core of the program. It would not be something separate. It would all be together, as it would have to be to make good sense.

Mr. MICHEL. We had a question raised here earlier as to whether or not the expenditure level would actually be the amount that you have cited for cancer in 1972. That is a $100 million request, of course, to be expended over a 2-year period.

Dr. MARSTON. The important point on this is that it is the intention to obligate the total amount of $100 million in fiscal 1972. We have come before this committee to request that you let us begin obligating that amount on the first of July rather than its normal time of appropriation.

The reason for the 2-year request is not a belief that we will need 2 years to obligate the money and to get the President's program underway. It is solely due to the fact that some parts of the program, such as construction and the organization of complex centers, require fairly lengthy and thorough negotiations and we simply don't want to be faced with an arbitrary cutoff for that on June 30.

But it is not our purpose to have 2-year authority to be able to spend the money over a 2-year period. We expect to obligate the $100 million in 1972. Actual expenditures will be whatever the expenditures will be. They will be somewhat higher if we get the opportunity to obligate more of the money earlier in the year than if we obligate most of it in April, May and June leaving less time for the institutions to actually spend it.

Mr. MICHEL. Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Casey.

Mr. CASEY. Thank you, Mr. Chairman.

BUDGET CUT FOR GENERAL RESEARCH SUPPORT GRANTS

Doctor, I want to echo the fears of the chairman that these restrictions in the National Institutes don't look too good, and particularly the one for general research support grants. You have been talking about grants to Mr. Michel, but you were talking about all grants by the Institutes were you not?

Dr. MARSTON. Yes, sir.

Mr. CASEY. How much is cut in general research support grants? You have a drop there from $60,700,000 to a request for $49,200,000 if I understand these figures. What is going to happen there?

Dr. MARSTON. This is one of the cases, Mr. Casey, in which the decision on the 1972 budget level had been made prior to the firming up of the 1971 budget.

As you recall, the figure was increased in 1971 over the President's estimates. What the figure before you reflects is a decision that had been made to decrease the program in 1972. We made the decrease from 1970 to 1972 over a 2-year period rather than doing it in 1 year. But it was a programmatic decision. There was a specific decision to decrease it.

Would you like for me to go into specifics?

Mr. CASEY. Yes. I would like to know what is going to happen. I know what you did.

Dr. MARSTON. The overall decrease of $5 million, includes a small decrease for the biomedical sciences support which is a formula program for other than medical schools which we started and carried out for a number of years, and a decrease of $2 million for the health

science advancement awards which we are discontinuing. Of that $5 million, $2 million is for discontinuance of that specific program.

Mr. CASEY. You say there is a reduction of $5 million?

Dr. MARSTON. Yes, sir.

Mr. CASEY. That doesn't jibe with the figures on page 204 of my book which says in 1971 we appropriated $60,700,000. Your estimate this year for 1972 is $49.2 million. That looks like better than $11 million.

Dr. SHERMAN. The decrease in the figure cited there includes four different reductions. A part of the reserve against the 1971 appropriation was used for pay raise purposes. There were also three programmatic reductions—the elimination of the health sciences advancement awards since the program was being phased out and the commitments were running down. Dr. Marston mentioned that this accounts for about $2 million.

There was a small reduction in a companion program to the general research support program itself, the so-called biomedical sciences support grants which are given to graduate schools. That reduction amounts to about $400,000.

Then there is a reduction of $2.6 million in the parent program—that is the general research support grants themselves, a component which unfortunately has the same name as the total formula grant activity covered by this item in the bill. Therefore, these four items, three of which are programmatic and one of which is administrative, make up that reduction.

CHANGES IN GENERAL RESEARCH SUPPORT GRANT LEVELS

Mr. CASEY. You are going to have fewer grants made out of this particular appropriation then are you not?

Dr. SHERMAN. No, sir. This is a formula program and therefore the amount of the individual grants will be affected. The only change in the number of grants awarded would be where an institution loses its eligibility in the program because it has not accumulated enough research grants in open competition.

You may recall that the formula is tied to the amount of regular grant support awarded to the institutions in open competition. Some institutions each year are on the border line of eligibility and some of them drop out.

Mr. CASEY. Will you put in the record just what these reductions are?

Dr. SHERMAN. Yes.

Mr. CASEY. And what you are going to do with the $49.2 million, because it is going to be a little hard to explain to some of these people the grant level is going to be the same when you have $11 million less.

Dr. MARSTON. We would not say that in this instance the grant level is going to be the same. It is going to be decreased and the reason for the decrease is the belief that the dollars will be more beneficially used in project-grant support rather than in the formula grant under the general research support grant program. There is a decrease here. Throughout the budget there are examples of decreases and examples of increases.

(The information follows:)

GENERAL RESEARCH SUPPORT GRANTS

[In thousands of dollars]

	1971 appropriation	Reserve [1]	1971 column of 1972 budget	Program decreases	1972 budget
General research support	48,200	−4,777	43,423	−2,623	40,800
Biomedical sciences support	7,750	−973	6,777	−377	6,400
Health sciences advancement awards	4,750	−750	4,000	−2,000	2,000
Total	60,700	−6,500	54,200	−5,000	49,200

[1] Proposed for transfer to fund increased pay costs.

Mr. CASEY. Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Shriver.

OBLIGATION OF FISCAL YEAR 1971 FUNDS

Mr. SHRIVER. Thank you, Mr. Chairman.

NIH received the fiscal 1971 increase voted by Congress very late in the fiscal year as you mentioned.

Dr. MARSTON. Yes.

Mr. SHRIVER. Aside from the $15 million for health facilities construction grants, will all of this money be obligated before the end of 1971 fiscal year?

Dr. MARSTON. We expect that all of it will be obligated with the exception of a very small amount.

I think that I need to point out that in some instances the pay raise will absorb some of these obligations, and there is thus not an identical match with the purposes for which Congress voted the funds.

One of the particular areas, which I mentioned in my opening statement, is that we have in the training grant area made the decision to hold the dollar level essentially the same until the study is completed. There were dollar increases by Congress in the training grant area which will be obligated for other purposes.

There is a total of about $10 million for which there is not a complete match between what Congress voted and what the dollars will be spent for. We expect that, with the exception of small amounts, we will be obligating all of these dollars by the end of this year.

APPROPRIATIONS AND OBLIGATIONS BY INSTITUTE AND ACTIVITY, 1970–72

Mr. SHRIVER. As indicated, this committee gets letters from time to time about funding levels of the various institutes. Could you furnish for the record a table showing the relationship of the program levels and appropriation levels and requests for the major items? Could you put that in a table in the record?

Dr. MARSTON. Yes. I am not entirely clear.

Mr. SHRIVER. You discussed very effectively the increase of your programs over the past year, and very interestingly. Could we get that put together into a table?

Dr. MARSTON. Yes, sir; 1970, 1971, 1972 on a programmatic basis?

Mr. SHRIVER. Yes. Many times I think people are confused when they write to us and it is difficult for us to find the answer in our offices.

(The information follows:)

1970 APPROPRIATION BY ACTIVITY—ACTUAL OBLIGATIONS IN PARENTHESIS (INCLUDES SUPPLEMENTAL)

	DBS	NCI	NHLI	NIDR	NIAMD	NINDS	NIAID
Research grants		$83,495.0	$104,200.0	$16,147.0	$94,505.0	$60,229.0	$61,195.5
		(78,462.3)	(95,411.0)	(14,515.9)	(86,031.0)	(55,524.1)	(56,166.9)
Fellowships		4,374.0	7,000.0	1,611.5	7,000.0	3,007.0	4,081.0
		(3,609.7)	(6,914.9)	(1,528.7)	(5,482.0)	(2,656.8)	(3,901.4)
Training grants		11,941.0	19,006.0	5,495.0	17,545.0	17,950.0	8,972.0
		(10,774.0)	(16,577.7)	(5,206.0)	(15,072.0)	(14,299.1)	(8,451.9)
Direct operations:							
Labs and clinics		17,254.0	14,004.0	4,922.0	16,191.0	10,100.0	15,272.0
		(18,067.7)	(14,285.6)	(5,072.7)	(16,079.2)	(10,286.5)	(15,863.3)
Collaborative research and development		68,092.5	21,719.0	942.0	7,191.0	9,960.0	12,182.0
		(65,084.9)	(21,642.9)	(833.6)	(5,566.0)	(8,936.3)	(10,715.7)
Biochemistry, epidemiology, and field studies		1,551.0	1,721.0	436.0	1,211.0	3,125.0	
		(1,577.9)	(1,890.4)	(455.3)	(679.9)	(2,808.4)	
International center							
Computer research and technology							
Biologics standards	8,225.0						
	(8,235.3)						
Training activities			204.0			72.0	155.0
			(165.4)			(43.1)	(100.2)
Review and approval		2,582.0	2,810.5	761.0	2,429.0	2,094.0	1,520.0
		(2,624.1)	(2,482.3)	(739.1)	(2,220.3)	(2,130.2)	(1,530.0)
Program direction		1,082.0	592.0	330.0	353.0	441.0	317.0
		(1,144.5)	(888.3)	(364.6)	(323.0)	(479.3)	(325.7)
Supplemental appropriation	14.0	123.6	121.0	164.3	285.0	387.0	
Total, direct operations	8,239.0	90,676.1	41,171.5	7,555.3	27,660.0	26,179.0	29,446.0
	(8,235.3)	(88,499.1)	(41,354.8)	(7,465.3)	(24,868.4)	(24,683.8)	(28,534.9)
Total, Institute/Research Division	8,239.0	190,676.1	171,377.5	30,808.8	146,619.0	107,365.0	103,694.5
	(8,235.3)	(181,345.1)	(160,258.4)	(28,715.9)	(131,453.4)	(97,163.8)	(97,055.1)

	NIGMS	NICHD	NEI	NIEHS	FIC	RR	Total
Research grants	$86,626.0	$45,627.0	$17,810.0	$8,451.0	$150.0	$67,831.0	$646,266.5
	(77,894.0)	(44,357.6)	(16,871.6)	(7,903.1)	(20.0)	(59,195.0)	(592,352.4)
Fellowships	20,126.0	3,616.0	1,018.5	164.0	1,067.0	126.0	53,191.0
	(17,622.3)	(3,615.3)	(890.0)	(255.8)	(1,193.9)	(126.0)	(47,796.8)
Training grants	48,477.0	9,892.0	3,313.0	3,617.0		352.0	146,469.0
	(44,477.0)	(9,392.0)	(2,983.6)	(3,525.0)		(352.0)	(131,110.3)
Direct operations:							
Labs and clinics		6,021.0	800.0	5,316.0			89,871.0
		(6,655.2)	(866.8)	(4,819.1			(91,996.1)
Collaborative research and development	4,788.0	6,818.0	349.0			1,483.0	133,524.5
	(3,477.7)	(6,841.0)	(364.0)			(1,383.2)	(124,845.3)
Biochemistry, epidemiology, and field studies		2,086.0	317.0				10,447.0
		(2,100.7)	(265.5)				(9,769.1)
International center					1,737.0		1,737.0
					(1,516.8)		(1,516.8)
Computer research technology						4,646.0	4,646.0
						(4,359.5)	(4,359.5)
Biologics standards							8,225.0
							(8,235.3)
Training activities	336.0	85.0					852.0
	(360.4)	(70.8)					(739.9)
Review and approval	3,237.0	2,011.0	535.0	442.0		1,580.0	20,001.5
	(3,160.2)	(2,138.6)	(418.6)	(355.0)		(902.1)	(18,700.5)
Program direction	1,054.0	793.0	200.0	338.0		640.0	6,140.0
	(1,098.4)	(790.7)	(153.7)	(395.8)		(614.0)	(6,578.0)
Supplemental appropriation	10.3	243.0					1,348.2
Total, direct operations	9,425.3	18,057.0	2,201.0	6,096.0	1,737.0	8,349.0	276,792.2
	(8,096.7)	(18,597.0)	(2,059.6)	(5,569.9)	(1,516.8)	(7,258.8)	(266,740.6)
Total, Institute Research Division	164,654.3	77,192.0	24,342.5	18,328.0	2,954.0	76,658.0	1,122,718.7
	(148,090.0)	(75,961.9)	(22,804.8)	(17,253.8)	(2,730.7)	(66,931.8)	(1,038,000.0)

1971 APPROPRIATION BY ACTIVITY—ESTIMATED OBLIGATIONS IN PARENTHESIS[1]

	DBS	NCI	NHLI	NIDR	NIAMD	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	FIC	RR	Total
Research grants		$95,605	$116,774	$16,269	$90,003	$61,759	$58,274	88,553	$50,773	$20,972	$9,048	$650	$62,810	$671,490
		(95,411)	(116,774)	(16,625)	(88,858)	(58,802)	(57,877)	(88,321)	(50,223)	(20,754)	(9,480)	(520)	(62,810)	(666,455)
Fellowships		3,798	6,871	1,601	5,740	2,782	3,749	18,454	3,786	1,676	264	1,117	126	49,964
		(3,798)	(6,871)	(1,601)	(5,740)	(2,782)	(3,579)	(18,454)	(3,786)	(1,676)	(264)	(1,247)	(126)	(49,924)
Training grants		11,574	17,643	5,451	15,780	14,972	9,394	46,770	10,142	3,898	3,787		352	139,763
		(10,774)	(17,643)	(5,206)	(15,072)	(14,300)	(8,922)	(43,746)	(10,142)	(2,998)	(3,117)		(352)	(132,272)
Direct operations:														
Labs and clinics		20,658	16,413	5,833	17,548	11,182	17,167		9,102	1,807	6,696			106,406
		(22,012)	(17,125)	(6,229)	(18,741)	(11,926)	(18,175)		(9,600)	(1,886)	(5,420)			(111,114)
Collaborative research and development		94,739	30,491	4,333	5,915	9,300	11,794	7,665	15,350	1,332			1,384	182,303
		(96,432)	(30,590)	(3,862)	(5,948)	(9,517)	(11,647)	(4,667)	(15,406)	(1,332)	(984)		(1,387)	(181,772)
Biochemistry, epidemiology, and field studies			1,807	670	858	3,250			2,145	330				9,060
			(1,906)	(713)	(892)	(3,374)			(2,184)	(347)				(9,416)
International center												1,815		1,815
												(1,899)		(1,899)
Biologic standard	$8,838													8,838
	(9,277)													(9,277)
Training activities			165		62	93	268	73						661
							(299)	(83)						(382)
Review and approval		2,792	2,690	724	2,157	2,014	1,452	3,209	2,178	658	456		909	19,239
		(3,157)	(2,579)	(786)	(2,338)	(2,255)	(1,573)	(3,507)	(2,353)	(704)	(486)		(982)	(20,720)
Program direction		1,217	625	376	338	486	326	1,153	887	313	369		620	6,710
		(1,548)	(1,413)	(408)	(367)	(529)	(564)	(1,200)	(970)	(332)	(400)		(663)	(8,394)
Total, direct operations	8,838	119,406	52,191	11,936	26,816	26,294	30,832	12,295	29,735	4,440	7,521	1,815	2,913	335,032
	(9,277)	(123,149)	(53,613)	(11,998)	(28,286)	(27,601)	(31,959)	(9,673)	(30,596)	(4,601)	(7,290)	(1,899)	(3,032)	(342,974)
Total, Institute/Research Division	8,838	230,383	193,479	35,257	138,339	105,807	102,249	166,072	94,436	30,986	20,620	3,582	66,201	1,196,249
	(9,277)	(233,132)	(194,901)	(35,430)	(137,956)	(103,485)	(102,337)	(160,194)	(94,747)	(30,029)	(20,151)	(3,666)	(66,320)	(1,191,625)

[1] Obligations include anticipated supplemental.

1972 APPROPRIATION AND ESTIMATED OBLIGATIONS BY ACTIVITY

	DBS	NCI	NHLI	NIDR	NIAMD	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	FIC	RR	Total
Research grants		$97,403	$120,981	$18,886	$91,491	$57,492	$56,919	$87,657	$54,229	$23,535	$11,918	$520	$64,310	$685,341
Fellowships		3,348	6,195	1,367	5,094	2,595	3,334	15,142	3,653	876	264	909	126	42,903
Training grants		8,358	13,592	4,285	11,475	11,456	7,280	38,385	9,085	2,225	2,843	.....	352	109,336
Direct operations:														
Labs and clinics		21,529	17,137	6,547	17,958	10,572	17,745	.....	11,571	3,075	7,314	.....	.....	113,394
Collaborative research and development		98,310	31,166	5,408	5,477	7,831	11,729	3,607	18,521	1,332	1,995	.....	1,391	186,758
Biochemistry, epidemiology, and field studies		.....	2,048	938	949	3,476	.....	.....	2,227	385	.....	.....	.....	10,023
International center		.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	1,890	.....	1,890
Biologics standards	$8,956	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	8,956
Training activities		.....	.....	.....	.....	.....	.....	373	93	.....	.....	.....	.....	466
Review and approval		3,636	2,886	929	2,572	2,492	1,714	3,846	2,808	821	524	.....	1,153	23,381
Program direction		1,763	1,487	469	417	607	621	1,390	1,099	390	413	.....	737	9,393
Total, direct operations	8,956	125,229	54,724	14,291	27,373	24,978	31,809	9,216	36,265	6,003	10,246	1,890	3,281	354,261
Total, Institute/Research Divisoin	8,956	234,338	195,492	38,829	135,433	96,521	99,342	150,400	103,232	32,639	25,271	3,319	68,069	1,191,841

CANCER RESEARCH BY DR. SZENT-GYÖRGY

Mr. SHRIVER. On April 29 there was an article in the Washington Evening Star regarding the claims of a Dr. Szent-György, a former Nobel Prize winner, that he has the answer for curing cancer but can't find financing for his project.

Are you familiar with his research?

Dr. MARSTON. I have known of his work in general over the years. He is a man that has contributed to the scientific literature for many, many years.

Mr. SHRIVER. It looks as though there is going to be additional money for cancer research to be administered from NIH. Is it possible his experiments will be funded from NIH?

Dr. MARSTON. It is certainly possible. We seek the best ideas and the best research projects that we can find to achieve the goal of unraveling cancer.

Mr. SHRIVER. I don't know anything about him; I just read the article.

Dr. SHERMAN. He has been a grantee of NIH for many years.

REQUESTED PROGRAM INCREASES

Mr. SHRIVER. You mentioned substantial increases required for genetic research on sickle cell anemia. What other specific areas received increases?

Dr. MARSTON. There is a request for an increase in population and family planning research. I could go down the list of increases.

Mr. SHRIVER. Place it in the record and also the cutbacks.

Dr. MARSTON. Yes, sir. The largest increases that we have, of course, are the cancer program, Sickle cell anemia and population research. There are about two pages that summarize the increases and decreases.

(The requested information follows:)

SPECIAL EMPHASIS PROGRAMS

[In thousands of dollars]

Institute/program	1972 President's budget		
	1971	1972	Increase or decrease
NCI:			
Cancer therapy	31,582	31,881	+299
Special virus cancer research	38,507	41,103	+2,596
Third natjonal cancer survey	2,191	2,190	−1
Cancer research centers	22,453	21,453	−1,000
Cancer task forces	4,068	4,079	+11
Chemical carcinogenesis	10,454	10,579	+125
Smoking and health	3,119	3,122	+3
NHLI:			
Arteriosclerosis	34,447	37,251	+2,804
Heart cooperative drug study	5,330	4,006	−1,324
Artificial heart/myocardial infarction	9,631	7,631	−2,000
Organ transplantation	1,953	2,065	+112
Pulmonary diseases	13,696	13,404	−292
Specialized centers of research	16,442	16,442	
Nutrition	3,388	3,483	+95
Sickle cell anemia	933	5,933	+5,000
Smoking and health	673	945	+272
Genetics research	2,000	2,000	

SPECIAL EMPHASIS PROGRAMS—Continued

[In thousands of dollars]

Institute/program	1972 President's budget		
	1971	1972	Increase or decrease
NIDR:			
Dental research institutes	4,700	6,200	+1,500
National caries program	6,200	9,100	+2,900
Restorative materials	920	[1] 920	
NIAMD:			
Endocrine and diabetes hormone developmental research	559	559	
Artificial kidney/chronic uremia	4,783	4,288	−495
Cystic fibrosis	2,645	2,701	+56
Diabetes	8,511	8,347	−164
Nutrition	6,273	7,254	+981
Sickle cell anemia	805	816	+11
Digestive diseases	13,458	13,131	−327
NINDS:			
Head injury	3,563	3,514	−49
Acute spinal cord injury	300	300	
Cerebral death	490	490	
Parkinsonism	2,552	2,474	−78
Infections of the CNS	1,938	1,744	−194
Epilepsy	3,526	3,358	−168
Sensory prosthesis	400	400	
Stroke	6,004	5,975	−29
Neurological disorders of childhood	14,440	13,356	−1,084
NIAID:			
Transplantation and related immunology	7,977	8,222	+245
Respiratory vaccine	4,836	4,886	+50
Hepatitis research	537	541	+4
NIGMS:			
Automated clinical laboratories and biomedical engineering	14,701	13,623	−1,078
Pharmacology and toxicology	17,440	18,134	+694
Anesthesiology and diagnostic radiology	8,299	9,060	+761
Trauma	3,054	3,615	+561
Nutrition	600	588	−12
Genetics research	37,291	38,828	+1,537
NICHD:			
Population research	28,118	37,718	+9,600
Aging	8,533	7,180	−1,353
Child health	47,048	46,903	−145
NEI: Genetics research	300	318	+18
NIEHS:			
Environmental health sciences centers	3,050	3,550	+500
Alpha emitters	743	920	+177
Smoking and health	650	625	−25
Genetics	225	240	+15
RR:			
Pharmacology-toxicology information	1,000	1,000	
Primate research centers	10,500	10,500	
Genetics	3,801	4,133	+332
Nutrition	20,113	23,121	+3,008
HM: Nutrition	3,003	3,681	+678

[1] Increase of $205,000 in materials is included under national caries program.

PROPOSED CHANGE IN TRAINING GRANT PROGRAM

Mr. SHRIVER. You will be paying funds for faculty salaries in all research training grants in a lump sum directly to the deans of the institutions if I understand your testimony?

Dr. MARSTON. For those institutions that are eligible for support by that mechanism, yes, sir.

Mr. SHRIVER. You said it would give the deans flexibility in the use of the funds?

Dr. MARSTON. Yes, sir.

Mr. SHRIVER. What do you propose to accomplish by this change?

Dr. MARSTON. The goals of this change are modest. We do not expect that there will be major changes in the actual distribution of these funds largely because the requirement is that the same activity—the training of researchers—will be maintained.

The first point is that one should not get the idea there will be major, sweeping changes in the distribution of these dollars. Any given institution will get the same amount of funds it would have gotten if we had not changed the mechanism of giving it to them.

The benefit we would hope—and, quite frankly, I don't think any of us know how well this will—is that by allowing greater flexibility the Federal Government will get somewhat more effective use of the dollars than we would have gotten otherwise.

FUNCTION OF THE NATIONAL LIBRARY OF MEDICINE

Mr. SHRIVER. On page 16 of your statement, you say the National Library of Medicine's role is much broader than is usually meant by the word "library" and it is in fact a national communications center for biomedical information.

Dr. MARSTON. Yes.

Mr. SHRIVER. Why don't you change the name of it then from library to reflect whatever the activity is?

Dr. MARSTON. I hope this is a question you will bring up with Dr. Cummings. One answer is that it is our belief that libraries in general have an appropriate role that goes beyond being a repository of books—and that included in the word "library" is the sense that they are there to facilitate the exchange of information.

Could I ask Dr. Cummings if he wants to comment?

Dr. CUMMINGS. The major reason the change has not taken place is really historical precedent. The institution known as the National Library of Medicine has had this name for 135 years and I think that is an impediment to changing the name.

What I believe would happen, however, in the context of your question, is that someday the Library of Medicine will be a component of the center for biomedical communication, that there will be an inversion of the program so that the communications center will be the parent of the library.

At this point in its history, the center is so small in relationship to the parent library that a change of name wouldn't accomplish much.

Mr. SHRIVER. That is a very good answer. Thank you.

Mr. FLOOD. Mr. Patten.

Mr. PATTEN. Doctor, earlier you said you are happy that things are a little bit better as far as money goes particularly for clinical research involving bed patients. I wonder if you would explain this.

Dr. MARSTON. No. I meant research that involves patients. The problem that we have had under a stable dollar budget is that the cost of taking care of patients has gone up much higher than other costs in our economy. Where our research was dependent on paying hospitalization costs, we had an increase averaging 15 or more percent and with a fixed budget we had particular problems in maintaining the level of research.

Mr. PATTEN. It is not you have some new leads as to taking care of people that have to lie in bed a long time?

Dr. MARSTON. No, sir. Although we have new clues and leads in almost all areas of biomedical science.

PRIORITY OF ARTHRITIS RESEARCH

Mr. PATTEN. One more question, Mr. Chairman. All the fellows my age have arthritis. It looks like you made about 10 transfers out of the arthritis fund. Is it you don't have any real leads on arthritis to inspire you to expand the program? Also, you are the first doctor that mentions the word "liver."

Dr. MARSTON. Yes, sir. I hope this can be pursued when Dr. Whedon is here to talk about the specifics of the problem. Certainly the problems of arthritis constitute one of the major health problems of the American people, and it is a major responsibility of that Institute. There are important and difficult problems that are being worked on in the area of arthritis.

I could mention a number of them. During the past few years the possible relationships between infectious agents, in some form, and arthritis has aroused a lot of interest. There are other examples that I hope Dr. Whedon will have a chance to speak to in this area.

Mr. PATTEN. That is all, Mr. Chairman.

Mr. FLOOD. Mrs. Reid.

Mrs. REID. Thank you, Mr. Chairman.

PHYSICIAN ASSISTANT TRAINING FUNDS

Doctor, last year you indicated that the 2-year program to train physician assistants was quite successful. Do you still feel this is true?

Dr. MARSTON. I would like to get Dr. Endicott to expand on this. While there was that early program, and some other early programs, there are now a number of alternative ways of looking at the general problem of training individuals who can expand the usefulness of physicians.

Dr. Endicott, I think you reviewed that program not long ago. Would you comment on this question?

Dr. ENDICOTT. Up to now the administration has looked upon the physician assistant approach more or less in an experimental framework. This year's budget proposes $15 million specifically for training additional numbers in various facets of physician assistance. So we are clearly moving from an experimental to a production phase.

Dr. MARSTON. Duke is one of the good ones and there are other possibilities we are supporting.

Dr. ENDICOTT. There are probably upwards of 75 different institutions in the country with plans to have physician assistant programs of some sort. The ones at the University of Washington and the Medex program and the program at Duke are pioneer programs, but the idea is catching on all over the country.

PHYSICIAN-POPULATION RATIO IN SOVIET RUSSIA

Mrs. REID. Last year I asked you Doctor, about the number of physicians we have in the United States in proportion to the population, compared with that of other nations of the world, for instance Russia. And you indicated you would better be able to answer such a question this year because you were going to visit Russia.

Dr. MARSTON. Yes.

Mrs. REID. Did you make that visit?

Dr. MARSTON. I made that trip and I learned several things other than just numbers.

The U.S.S.R. has about twice the number of physicians we have in this country.

MALE-FEMALE RATIO AMONG RUSSIAN DOCTORS

Mrs. REID. What about the women physicians in Russia?

Dr. MARSTON. About 70 percent are women, which is a reflection both of the high mortality of men during World War II and also what, I think, was a sense that there are particular opportunities for women in medicine.

The ratio of women to men in the entering classes in medical school has been dropping so it is closer to 50–50 now. When one projects this into the future, one would expect that there will be a lesser predominance of women in the future compared to the immediate past.

While it was not possible to get them to say this was a policy—indeed when I asked about the selection of people for medical school they said women versus men it is the same, it makes no difference, it is a competitive examination.

Yet there has been a change in distribution all over the country, and it undoubtedly reflects some sense of a change in the distribution of women doctors.

Incidentally they feel, although they have something over 600,000 physicians, that they don't have enough physicians and they are planning to expand the number.

THE RUSSIAN FELDSHER

Mrs. REID. You also said that at that time the Russians were re-examining whether they were able to give quality care with relatively independent and unsupervised people.

Dr. ENDICOTT. The point they made is that the Feldsher is not a physician's assistant, the nurse is. The Feldsher is trained specifically to do specific jobs such as in the sanitary area, such as in the first aid stations in industry or such as working in emergency care situations in a remote area, usually with a midwife. They said that our concept that the Feldsher is a physician's assistant or substitute was an erroneous one.

Individuals are trained for specific purposes. Their goal is to replace all of the midwife Feldshers with physician midwife assistants.

If a Feldsher wants to become a physician he has to take additional education and he then stops being a Feldsher and becomes a physician.

FOREIGN M.D.'S IN THE UNITED STATES

Mrs. REID. Is our dependence on foreign medical graduates to provide patient care still on the increase?

Dr. ENDICOTT. Let me say factually that we still have large numbers of graduates of foreign medical schools. They do give patient care and if they didn't, our problems in delivery of patient care would be even greater.

So in that sense, I think, the answer to your question is "Yes"; that we are dependent upon the fact that we have a sizable number of

graduates of foreign medical schools coming into this country to meet our health needs.

ADEQUACY OF FUNDING FOR NLM

Mrs. REID. I recently received a letter from the executive vice president of the Bank of America who serves as regent on the National Library of Medicine. He said he viewed with alarm what he considered to be inadequacy of funding for the library for the 5-year period 1968 through 1972.

Would you comment on this and tell us if there has been any effect on the information services?

Dr. MARSTON. I think it is clear the years you have touched on have been the years of tight budget in the Federal Government both under the past administration and under this administration, and it hasn't been possible to fund at the level that one could justify in looking at program opportunities alone.

I think the problem of the Library of Medicine—I would like to get Dr. Cummings to comment on this—is that they have been caught in the squeeze of having some programs which are absolutely essential in which there has been an unusually rapid escalation of costs.

Those uncontrollable increases put a much tighter squeeze on the so-called controllable parts of the budget, some of which are high priority items from the point of view of national need.

Dr. CUMMINGS. One example of this is reflected in the rising costs of acquiring books and journals. They have gone up at a rate of 13 percent per year during the period that is cited in this letter, which is twice the normal escalation of costs of business.

In addition there are more living physicians, scientists, and educators now than there were years ago and therefore there are greater demands for services. More people are available to ask for more service.

I would say the most direct effect of the stable budget has been a reduction in the number of services that we are able to provide because of the cost escalation. This is reflected specifically, for example, in our having to close the library on Sundays for the first time in many, many years.

Mrs. REID. Have you received adverse response to the closing on Sunday?

Dr. CUMMINGS. I received complaints from the physicians and students who come to the Library on Sunday and find the doors locked. They let me know their displeasure.

RESEARCH INTO PROBLEMS OF THE AGING

Mrs. REID. In view of the increase in life expectancy, what research is being done in regard to special problems of the aging?

Dr. MARSTON. We have a center for aging research in Baltimore. Research in the aging areas is the responsibility of the National Institute of Child Health and Human Development. It is one of the areas Dr. LaVeck will be speaking to specifically when he appears.

I would comment, though, if I may, that the problems of aging go beyond any specific Institute. Just because something is labeled aging

does not assure that is where the needed knwoledge is going to come from.

The best overall chance of improving the prospects for a graceful and dignified and active life is to have a better understanding of the basic life processes which then gives us an opportunity to have a better understanding of where they go wrong and cause premature aging.

Premature deaths of the American male from cardiovascular disease is an aging problem, although the research is being done in the National Heart and Lung Institute. You do have a higher rate of death from a process that occurs to some extent in every one who lives and could be classified as an aging problem, too.

We work on problems where the expertise is. One could say the same thing about essentially all of our Institutes.

CAUSE OF THE RISING CANCER DEATH RATE

Mrs. REID. I read an article a short time ago which I think gives us food for thought in regard to cancer, the increased funds, and the feeling we are on the verge of a breakthrough of the dread disease; that although there are improved methods of treatment which should help to stem the number of annual deaths in cancer, the number of these deaths continues to rise more rapidly than the increase in the size of the population. Why would this be?

Dr. MARSTON. One of the big components is the increase—almost epidemic increase—in death from lung cancer. When you look at the problems in the cancer field generally, this is the one that stands out both in terms of the rate of increase and also the number of deaths.

One has to be sure of what one's goal is in looking at as complex a field as cancer research. We must put a considerable emphasis on preventing premature death and assuring dignified death and comfortable death. But the chances of preventing death is not a realistic goal of research in the biomedical areas.

The concern we have, and the opportunities we have, in cancer is to cure what is a frightening disease and a disease that kills young people as well as old people. I don't think—and the President was cautious not to overpromise—that someday we will wake and cancer will not exist anymore.

TIME FRAME FOR CANCER BREAKTHROUGH

Mrs. REID. But I have felt we are on the verge of important new findings in research on cancer. Isn't this true?

Dr. MARSTON. Yes, and I have spoken enthusiastically about the need to capitalize on the opportunities that have come out in a number of ways. I think there is an urgency about our doing this. But we are probably talking about decades and we are talking about different kinds of cancer. We will make progress in some cancers and we will not make progress at the same rate in other cancers.

At the same time we are improving our ability to diagnose and treat and prevent cancer, we are putting new chemicals out into the environment, many of which undoubtedly will have the ability to cause cancer. We need to be able to identify those hazards. They are being introduced in larger numbers and larger amounts and the problem of

identifying which ones are dangerous, which ones are not, is a major problem.

Mrs. REID. It is a vicious cycle.

Dr. MARSTON. It is. I think—and when Dr. Baker is here this point will come out again and again—that we have immense problems and we have made immense progress, and you can't have one without the other.

Sometimes when a problem is solved it opens up a whole new group of problems we didn't know existed. Sometimes they are encouraging and sometimes they are discouraging. I think it can be said that, as a whole, the field is advancing more rapidly than it has in the past, and there is a need for substantial increases in investment of human effort and financial support in this area at this time.

But we can't guarantee when there is going to be "an answer" or indeed whether there is going to be one answer rather than many answers.

Mrs. REID. Thank you.

Mr. FLOOD. Mr. Conte?

BUDGET DEFICIENCIES

Mr. CONTE. You intimate on page 1 of your statement that the fiscal 1972 budget may not fulfill all your desires. Are there any major deficiencies in the budget requests that you would single out?

Dr. MARSTON. That is a hard question to answer because it depends on how one defines "deficiencies"—or, rather, within what framework one judges the budget requests. I think this is a good budget but, as I said, it doesn't provide for everything we might have liked to see included. But I would not describe these things as major deficiencies.

Solely on the basis of program considerations—that is on the basis of the importance of health research problems and the scientific opportunity to do more about them—there are, of course, a number of areas where more could be done if no limit were set on budget requests, if we didn't have to make choices or weigh priorities.

An obvious example is heart disease. As you know, the American Heart Association feels very strongly that we are not doing enough about heart disease. They are understandably unhappy that the budget request for a major attack on cancer is not matched by a similar request for cardiovascular diseases which, they point out, kill more people than cancer and are a field in which there has already been rapid progress and in which there is a high potential for further significant advances.

The point is that much of medical research is in a dynamic state with real opportunities for progress similar to that which has recently been so effectively publicized for cancer. Examples of such opportunities, disease by disease, will emerge, I am sure, as the Directors of the various Institutes testify.

Mr. CONTE. What major projects will be deferred under your budget requests?

Dr. MARSTON. This budget, like all budgets, has both increases for some programs and decreases for others. There are two general areas in which it would be fair to say that projects—or, at least, additional projects—are being deferred. One is the training grant area in which any budget increases have been deferred until a study of these programs, that is now underway, has been completed. The other is the

construction of health research facilities in which further grants will continue to be deferred partly because of the inflationary effect of construction projects and partly until a decision is made about the future level of Federal support for research which will give a clearer indication of the future need for additional research facilities.

In this connection, I should point out that the additional $100 million requested for the cancer conquest program does include up to $16 million for construction or modification of research facilities and $2 million for training grants.

EFFECT OF LATE AVAILABILITY OF 1971 APPROPRIATIONS

Mr. CONTE. How serious an administrative problem did the unavailability of 1971 appropriations until 2 months ago create for NIH?

Dr. MARSTON. The most serious consequence was that it had the effect of keeping all the programs at their 1970 level during most of 1971. Receiving additional funds so late in the year—especially when program operators had reason to doubt whether the congressional increases would be apportioned and actually be available for expenditure—creates a disproportionately heavy administrative burden during the last few months of the year. This is, of course, especially true of programs for which new funds or proportionately large increases are provided, such as the $10 million increase for genetics research.

In our collaborative programs, the negotiation of research contracts is usually a fairly complex and time-consuming business and having only a few months in which to do it can create serious problems. Sometimes one can anticipate the actual availability of the additional funds by negotiating ahead of time but this isn't always possible, practical or prudent. But even in the regular research grant programs, in which the applications will already have been routinely reviewed, there can be quite a scramble to get all the paperwork done and the award notices in the mail before June 30.

"SEVEN LEAN YEARS"

Mr. CONTE. What programs suffered most as the result of the steady loss of momentum you experienced in your "seven lean years"?

Dr. MARSTON. The effect was felt across-the-board and, I may say, across the Nation and, indeed, the world. I would say that uncertainty and confusion about the Federal Government's attitude to biomedical research and its intent regarding levels of support has been the most serious overall effect.

Its effect on program is illustrated by the progressive decline in the number of research projects supported. Close to half of the funds available to the Institutes are devoted to the funding of research project grants to investigators throughout the United States. This proportion has remained fairly constant. Funds for these grants went up slowly during those lean years but costs, as you well know, went up very rapidly. As a result, the number of research projects we were able to support declined steadily. In 1963 we were able to fund 15,200 research project grants; in 1970 we were able to fund only 11,300. This is a drop of more than 25 percent in the number of projects supported.

In this respect, some Institutes fared better than others. The ones that suffered the most, to answer your question, was the Institute of General Medical Sciences which mainly supports so-called basic

research that is vitally important to future progress in all fields of medical research. The number of projects that Institute was able to support fell from 2,200 to just over 1,100—a drop of just about 50 percent. Similarly, in the Dental Institute grants dropped from 450 in 1963 to 200 in 1970—that's a drop of 55 percent.

Cancer and Heart didn't do so well, either. Cancer research grants dropped by a third from 1,800 to 1,200. Heart research grants dropped almost as much: from 2,400 to 1,700. The experience of the Allergy and Arthritis Institutes was in line with the average for NIH as a whole—that is, a drop of about 25 percent. The Neurology Institute fared better. The number of grants it was able to support dropped by only 10 or 12 percent.

These figures do not tell the whole story, of course, but I think they illustrate the extent of the loss of momentum. The fact that we could support fewer and fewer projects had its greatest impact on new projects and new investigators. The number of new projects we were able to support fell from 2,700 in 1963 to 1,800 in 1970—that is down one-third. We were torn between our desire to assist young investigators just entering the biomedical research field and our reluctance to withdraw support from important ongoing work in order to make this possible. On the whole, we avoided making arbitrary decisions in this respect and let the normal review process take its course. Until this year, at least, the youngsters competed fairly well. One does, however, hear increasingly of talented, dedicated young investigators who have become discouraged. I hope the increases requested in this budget for 1972 will help to restore their confidence.

There is no way to measure the effect of this decline in support on the progress of research or to assess what accomplishments might have resulted if there had not been such a decline. A few of the unsuccessful grant applicants may have found support elsewhere. A few were probably able to continue their work—on a reduced scale or at a slower pace—without additional project support. But there is no doubt that many good projects had to be abandoned or were never started—with what loss to our present or future ability to fight disease no one can say.

IMPACT OF CANCER CONQUEST PROGRAM

Mr. CONTE. How, specifically, will the patterns and directions of the biomedical research program change under the new cancer conquest program?

Dr. MARSTON. The principal impact of the new cancer conquest program will be a really major expansion of research, a heightening of effort and, I hope, an accleration of progress. That is obviously its purpose. The additional funds will make it possible for the Cancer Institute to put into effect some plans that were, heretofore, beyond its means. But much of the added thrust will be in extensions of ongoing activities. The need to expand these activities and, particularly, to take full advantage of the new leads and new research opportunities that have been uncovered led to the decision to add an extra $100 million to the cancer-research effort. I expect that coordinated, managed research programs—by this I mean collaborative research programs and contract research projects—will be significantly expanded. At the same time, we will also give additional support

to investigator-initiated research through the regular research grant program.

Over the years, NIH has developed expertise in the management of large-scale national research programs and has made increasing use of contracts for some types of research and of collaborative programs involving NIH's own scientific staff and a number of investigators and institutions throughout the country. The regular research-grant program has, of course, been outstandingly successful stimulating interest in particular areas of biomedical research and in mobilizing individuals with the best scientific competence.

The directions of cancer research will continue to be dictated by the leads and opportunities that emerge. Making additional funds available will not, of itself, create such leads or opportunities—what it does is to give us the wherewithall to follow them up quickly and vigorously. When Dr. Baker presents the budget justification for the National Cancer Institute, he will elaborate on these features and present in considerably greater detail the scientific aspects of research expansion under the new cancer conquest program.

Mr. CONTE. Some have argued that an all-out attack on cancer could divert scientists from efforts to gain a better understanding of the basic mechanisms of life, turning researchers away from models not directly linked to cancer. How would you answer these arguments?

Dr. MARSTON. I am seriously concerned that unwise handling of the cancer program could have a bad effect both on cancer research and on biomedical research generally. As I said in my opening statement, there is some justification for the fear that putting so much emphasis on cancer—and I had in mind the fact that three-fifths of the budgeted increase for research is for cancer—will detract from research on other serious health problems. It depends on how we go about it and what we do about the other areas of research. The point I was trying to make in my opening statement is that every area of research—in other words, the program of each of the research institutes—should be judged on its own merits. Support should be provided in relation to the magnitude and importance of the health hazards, on the one hand, and the scientific opportunities for doing something, about them on the other.

We propose to add $100 million to cancer research because cancer is a very major health hazard and because the scientific opportunities to use that money effectively do, indeed, exist. This must not be interpreted, however, as meaning that this field is ready for a moon-shot approach—we are very far from being in the position of the Apollo program of merely having to exploit existing scientific knowledge for the accomplishment of a difficult and dramatic task. In cancer, as in most of biomedical research, the even more difficult but less dramatic task is to acquire the basic scientific knowledge which will make dramatic clinical achievements possible. Nor does the request for a major increase for cancer research imply that there is no present need to expand our efforts in other areas of research that are concerned with major health hazards and in which there are similar opportunities for progress.

For the immediate future, the addition of $100 million to cancer research is not of such a magnitude that it will adversely affect other biomedical research. Future additions to the cancer conquest program

could have such an effect if we do not take very deliberate and early steps to guard against it. We must be alert to the fact that the cancer program, from a scientific and professional point of view, is an important part of our overall national biomedical research effort. To sustain an all-out attack on cancer over a period of years—and we are deluding ourselves, and the public, if we do not plan for a long period of years—we must create the necessary resources both for cancer research and for other areas of health research. Part of our initial efforts in an expanding research program must be to train the people and provide the facilities to make further expansion possible. Our plans for the cancer conquest program do, in fact, provide for this.

Finally, I would point out to those who are worried about the diversion of effort that biomedical research is a continuum in which the work done and the results obtained do not necessarily reflect their sources of support. The flow of scientific information from the cancer field to other areas of research and from those other areas to cancer will continue. Virologists, for example, will continue to explore how viruses cause disease and whether that disease is cancer or a muscular debility or a nasty cold does not depend on who supports the research. This indivisibility of so much of medical research, especially the all-important search for basic understanding, is the reason we feel so strongly that the Cancer Institute should not be organizationally divorced from the other Institutes with whose work it is inescapably linked.

PROPOSAL TO CREATE A NATIONAL CANCER AUTHORITY

Mr. CONTE. What is your assessment of proposed legislation that calls for the creation of an independent national cancer authority which would assume all the activities of the National Cancer Institute?

Dr. MARSTON. Separating cancer research from other medical research activities—in a way, putting it in competition with other medical research—would, I think, do real damage to all of medical research including cancer research itself. To put it bluntly, from a scientific point of view, it makes no sense.

Moreover, I foresee that the separation of the Cancer Institute from NIH could lead to the dismantling of not merely NIH as an institution, but of the whole, integrated biomedical research structure which NIH support has built up throughout the country. Pressure is already beginning to build up for the creation of an independent heart authority if a national cancer authority comes into being. Heart disease and the related cardiovascular and renal diseases kill more people and cause more disability than cancer. A good case can be made for giving the heart people the same status and support as the cancer people—a case which the Congress and, indeed, the administration will find it difficult to resist. If there are separate heart and cancer authorities, people will ask what we are going to do about strokes, about the very seriously debilitating neurological and muscular diseases, about mental retardation and birth defects, and so on. They, too, will want separate and independent authorities because they will feel that this is the only way to get Federal support for research in these areas.

The recommendations of the panel of consultants for a greatly strengthened and expanded cancer research program rest on solid

ground. Both the need and the opportunity are unmistakably here. The plans for the cancer conquest program recognize this and this program will, in fact, meet every major recommendation in the panel's report except the proposal to transfer cancer research to a separate authority. As I pointed out in this committee's hearings on the supplemental appropriations bill a week ago, there is no substantive difference between the aims of the cancer conquest program and the aims of the proponents of a National Cancer Authority. There is disagreement only over the organizational mechanism for implementing an expanded cancer research program. I firmly believe that an expanded cancer research program can flourish within NIH and will also greatly strengthen the whole operation of its diverse medical research activities. And I feel just as strongly that separating cancer research from NIH will do a great deal of damage to the effectiveness of NIH and to the whole biomedical research structure that has been painstakingly built up during the past 15 years.

LEADS IN CANCER RESEARCH

Mr. CONTE. You said in your opening statement that directions of research are often determined by the presence or absence of enticing leads for further exploration. Is this the case with the cancer program? If so, what are these enticing leads that need further exploration?

Dr. MARSTON. It is very much the case in the cancer program. There are many leads for further exploration—and they are now being generated at a faster pace than ever before—in the virus causation of cancer, in the chemical causation of cancer, and in the treatment of cancer. Dr. Baker, I am sure, will go into considerable detail on this when he testifies for the Cancer Institute.

As you know, there is now a great deal of excitement about the relationship of viruses to cancer. They have been definitely linked to various forms of cancer in animals and one of the most active fields in cancer research today is to follow up the leads from those animal studies in human cancers. If a specific virus can be identified as the cause of a particular form of cancer and if that virus can then be isolated and reproduced, the way would be open for the development of a vaccine.

The prevention of any cancer depends, of course, on finding its cause. That is why the work being done in chemical carcinogenesis is so very important. In our complex technological way of life, we are being assaulted by an increasing number of chemicals. Already about 1,000 chemicals have been identified that can cause cancer in animals. They need to be tested to see whether they also cause cancer in man—we know that something like two dozen do. This is a tremendously difficult, tedious and long-drawn-out job. We also need to do much more research to see if it is possible to block the steps by which environmental chemicals transform normal cells into cancerous ones.

There are many leads in the drug treatment of cancer. Some forms of cancer can now be cured by combinations of drugs but this cannot yet be done for the more common tumors. The techniques that have been developed thus far do, however, point the way for trying various combinations of drugs on the more common tumors.

There is no shortage of leads. In fact, there is a staggering amount of work to be done in cancer research.

CANCER RESEARCH RELATIONSHIP WITH OTHER INSTITUTES

Mr. CONTE. What are some of the research missions of the other Institutes with which cancer research is linked?

Dr. MARSTON. For many years there has been close collaboration between scientists in the National Institute of Allergy and Infectious Diseases and the National Cancer Institute in studies of virology and immunology. Many of the early leads on the relationship of viruses to cancer came from the work of virologists who were concerned with the structure and behavior of viruses and really were not doing cancer research at all. As a matter of fact, Dr. Robert Huebner, now one of the leading investigators in the cancer virology field, began his work in the Allergy Institute. In time, the work he was doing became more and more relevant to cancer so, about 4 years ago, he actually transferred to the Cancer Institute staff. Much of the work being done by virologists on the Allergy Institute's staff—or by grantees supported by that Institute—continues to be highly relevant to cancer research.

Important developments in tissue culture and virology have also resulted from collaborative studies between scientists in the Division of Biologics Standards and in the National Cancer Institute.

Research on the so-called slow viruses, which are thought to be responsible for a number of neurological and muscular diseases is conducted and supported by the National Institute of Neurological Diseases and Stroke. These viruses may also be responsible for some cancers and they are thus of great interest to the Cancer Institute. The two Institutes keep in close tough and collaborate on some of this work.

Research in the basic medical sciences, supported by the National Institute of General Medical Sciences, makes constant contributions to all aspects of disease-related research. The blossoming of research on fundamental genetic processes is of particular importance to cancer research as it may well provide the key to the mechanism by which normal cells become malignant cells.

Fundamental work is being done in molecular biology, the study of how cells are constructed and how they behave; in immunology, which is concerned with how the body protects itself against disease; and in biochemistry, which tries to get a better understanding of the chemistry of living things. These fields are important to all disease problems. All the Institutes have programs in them. The research done by the staff and grantees of each Institute will initially have a different focus, depending on the mission of the Institute, but there is no telling where work in these fundamental fields will lead. This is why it is so important to do everything possible to maintain close relationships and a free flow of information between the various areas of research. This is why we think it so important to keep the Cancer Institute as part of the NIH family.

GENETICS RESEARCH

Mr. CONTE. How great a backlog of genetics applications do you have at present?

Dr. MARSTON. We have just funded 160 grant applications with the funds made available for the special genetics program. This takes us down to a priority score which is not quite half-way down the priority

scale. As I said in my opening statement, all the highest priority projects have now been funded. There are probably about an equal number of applications of lesser priority that have not been funded. I doubt that we would think it prudent to fund all of these. I would say, therefore, that for practical purposes we have a backlog of over 100 applications but they are all of lesser priority than those we have funded. New grant applications are, of course, coming in all the time.

Mr. CONTE. What will the major thrust of genetics research be in the near future?

Dr. MARSTON. In terms of scientific objectives, the major thrust of genetic research must be the accumulation of the basic knowledge and understanding of the genetic defects to cause or are predisposing to disease. Only as we accumulate this knowledge can we make any significant strides toward the cure and, ultimately, the prevention of these diseases—of which more than 3,000 have been identified.

Progress during the past 15 years in genetics research has been so dramatic—I should say, revolutionary—that an ability to do something about hereditary diseases has become a real, if still somewhat distant, possibility. In fact, it is now a very exciting field.

In terms of program, the major thrust during the next few years can best be described for you by Dr. Stetten when he appears to testify for the National Institute of General Medical Sciences which provides most of the NIH support for genetics research. I know he has given a great deal of thought to what needs to be done during the next 5 years and how it can best be accomplished.

RESEARCH ON SICKLE CELL ANEMIA

Mr. CONTE. How is the work of the four Institutes presently engaged in sickle cell anemia research coordinated? What provisions have been made for maintaining communication and for avoiding duplication of effort?

Dr. MARSTON. A coordinator for the sickle cell anemia program has been appointed in the National Heart and Lung Institute. He will be responsible for coordinating the overall program both at the NIH and with the Health Services and Mental Health Administration. He will appoint a working committee, with representation from each of the concerned Institutes and HSMHA, which will be responsible for maintaining communication and for avoiding duplication of effort.

Mr. CONTE. You said in your opening statement that an encouraging advance has been made recently in the management of acute crises of sickle cell anemia. What is this advance?

Dr. MARSTON. I had two new treatments for acute crises in mind. One is the use of alkalyzing agents—for example, sodium citrate; the other involves the use of urea in invert sugar. Both of these treatments have so far been used in only a relatively small number of patients but with some success in the relief of symptoms. However, controlled clinical tests have not yet been done. The Heart and Lung Institute expects to start the first phase of a controlled clinical trial to evaluate therapy for sickle cell crisis within the next few weeks.

MONITORING BLOOD RESOURCES

Mr. CONTE. What new technologies are being developed to insure the safe use of blood resources?

Dr. MARSTON. Several new technologies and procedures are under development to insure safer use of blood resources.

Considerable work is being done to develop more sensitive methods of identifying the Australian Antigen in blood and blood products which, in turn, will lead to a decreased incidence of transfusion hepatitis. New methods are also under study for removing or inactivating the hepatitis virus from blood and blood products.

There is work on machine-monitored procedures to identify the blood type of blood donors and recipients so as to lessen the chance of a patient receiving the wrong blood and having a dangerous transfusion reaction.

New techniques are being developed to remove histocompatibility antigens—mostly white blood cells—from blood given to transplant recipients in order to decrease the likelihood of transplant rejection.

New techniques are also being developed to standardize the potency of cryoprecipitate which is the mainstay in the treatment of hemophiliacs in this country today.

Work is being done on more effective methods of platelet preservation.

There are a number of studies of the oxygen-carrying capacity of blood so that eventually we will be able to select blood with an optimum oxygen-carrying capacity for use in transfusions.

Mr. CONTE. What logistical and legal problems will be involved in eliminating the hepatitis risk in blood transfusions?

Dr. MARSTON. The logistical problem in completely eliminating the hepatitis risk in blood transfusions involves making available to all blood banks an inexpensive, rapid, highly sensitive method of detecting the infectious agent of hepatitis in blood. This becomes very important because a recent court decision in Illinois, based on the concept of strict liability, implies that because of the hepatitis risk, blood transfusion, no matter what the precautions, is unreasonably dangerous. The development of more sensitive and reliable tests for hepatitis detection should constitute adequate and reasonable protection and the concept of strict liability would then probably no longer be applicable.

RESEARCH ON AGING

Mr. CONTE. Though a net increase of $9.6 million is being requested for the National Institute of Child Health and Human Development, research on aging is being cut back from $8 million to $6.7 million. What is the reason for this cut?

Dr. MARSTON. The appropriation requested for the National Institute of Child Health and Human Development in the President's budget for fiscal year 1972 is $103.2 million, of which $7.2 million is allocated for the aging program. This represents a $1.4 million reduction compared to funds spent in fiscal year 1971 for this program. Its effect will be a moratorium on new aging research grant awards during fiscal year 1972. This reduction reflects decisions on research priorities under the budget ceiling for health research in 1972. Although special emphasis will be given in 1972 to research on population control and reproductive biology, we certainly have not decided that research on aging is of low priority. It is, in fact, a very important field. Research on the problems of aging are not confined to the aging program of this one Institute but are part and parcel of the programs of all of the Institutes as older people are particularly susceptible to

arteriosclerosis and other cardiovascular diseases, to arthritis, to degenerative diseases of the muscles and nervous system, and so forth.

PROPOSED PHASEOUT OF PREDOCTORAL FELLOWSHIP PROGRAM

Mr. CONTE. Why is the predoctoral fellowship program being phased out?

Dr. MARSTON. The award of predoctoral fellowships has always presented problems because it is difficult to select suitable candidates on the basis of a national competition. The candidates are young men and women who have done well in their undergraduate studies. There are very many of them and we can support only relatively few. It is very difficult to select the most deserving candidates from so large a group solely on the basis of their quite similar undergraduate records. It is certainly impossible to do so with complete fairness. This is a major reason for deciding to limit our fellowships to post-doctoral students whose performance and aptitude for research can be much more easily and fairly judged on the basis of the research they have already done, the theses they have written, and the assessment of their preceptors with whom they worked quite closely.

We believe that decisions on support for predoctoral students can best be made by the institutions which are prepared to accept them as graduate students. Federal funds for their support should therefore be made available to these institutions rather than directly to the student in the form of a fellowship.

STUDY OF TRAINING PROGRAMS

Mr. CONTE. When will the training study now underway be completed?

Dr. MARSTON. We expect to have it by the end of this year—this calendar year. The survey of students, department chairmen, and deans is nearing completion. We expect to have the raw data by the end of the academic year—say by the end of June—and the contractor's report shortly thereafter. Our own staff will then have to analyze the data, explore its significance, interpret it, and draw conclusions. On the basis of past experience, it is reasonable to suppose that some of the field data will have to be checked. In other words, there is still a lot of work to be done which may well take about 6 months.

Mr. CONTE. Will a decision on the future of the training grant program be made on the basis of this study?

Dr. MARSTON. I am sure the results of the study will be of major help in the decisionmaking. That, of course, was the reason for undertaking the study. There were a lot of conflicting opinions about the need for the training programs, about their impact, and about their effectiveness, but no one had the facts to resolve these conflicts, to confirm or deny whether something someone thought was really so. We hope the study will give us at least some of those facts. But, of course, policy decisions and, I suppose, what might be called ideological considerations, will also play a part in deciding the future of these programs. It may well be possible—and some people may prefer—to achieve some of the purposes of the research training programs by using other support mechanisms.

We do, however, expect the study to throw more light than we have now on the need for and effect of the research training programs, and particularly on the desirability and validity of having the categorical research institutes administer them.

Mr. CONTE. Thank you, Dr. Martson.

Mr. FLOOD. Thank you, Dr. Marston.

As we have for the last several years, we will place in the record at this point the overall tables and statements that you have prepared at the committee's request.

(The material referred to follows:)

National Support for Performance of Medical and Health-Related Research
by Source of Funds, Fiscal Years, 1965-1971[1]
(millions of dollars)

Source of funds	1965	1966	1967	1968	1969	1970	1971[2]
	actual					estimate	
Total	$1,837	$2,053	$2,266	$2,440	$2,593	$2,685	$3,035
Government	1,229	1,377	1,524	1,640	1,728	1,740	2,010
Federal	1,174	1,316	1,459	1,571	1,656	1,664	1,933
State and local	55	61	65	69	72	76	77
Industry	450	510	565	615	675	750	825
Private support	158	166	177	185	190	195	200
Foundations and health agencies	88	91	100	106	108	110	113
Other private contributions	25	28	29	30	32	32	33
Endowment	19	19	19	19	19	19	19
Institutions' own funds	26	28	29	30	32	34	35

Note:

The estimates for medical and health-related research shown above update the series extending back to 1947 published in Resources for Medical Research, Report No. 10, "Dollars for Medical Research, Sources and Performers, 1947-1966" (PHS Publication No. 1612), and Resources Analysis Memo No. 10, "Biomedical Research, 1966-68".

Current data for the Federal Government were obtained through the annual survey, conducted by the National Institutes of Health, of Federal agencies' support for medical and health-related research. Estimates for state and local governments include appropriations made to educational institutions and hospitals for the performance of medical and health-related research. The industry sector includes data for the pharmaceutical, medical supply and biomedical engineering industries. The non-industrial private sector covers the funds provided by philanthropic foundations, voluntary health agencies, and other private contributors to the support of medical and health-related research. Resources for Medical Research Report No. 10 also presents a detailed discussion of the definitions and statistical methodology underlying the time series.

1/ Coverage is limited to conduct and support of medical and health-related research. Support of other activities such as research training or capital outlays for research facilities is not included in this series.

2/ Data on Federal obligations are available at the beginning of the fiscal year. Firm data on non-Federal support cannot be obtained until after the end of the fiscal year; the estimates for 1971 may, therefore, overstate the Federal share.

Office of Resources Analysis
National Institutes of Health
February, 1971

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FEDERAL SUPPORT FOR PERFORMANCE OF MEDICAL AND HEALTH-RELATED RESEARCH, FY 1969-1971[1]
(millions of dollars)

Agency	1969 actual			1970 actual			1971 estimate		
	Total	Budgeted	Directly Related	Total	Budgeted	Directly Related	Total	Budgeted	Directly Related
Total	$1,656.1	$1,305.7	$350.4	$1,664.0	$1,324.2	$339.7	$1,932.9	$1,567.7	$365.3
Atomic Energy Commission	97.9	8.1	89.8	104.2	9.9	94.3	105.1	10.7	94.4
Environmental Protection Agency	-	-	-	-	-	-	85.0	85.0	-
National Aeronautics and Space Administration	116.8	-	116.8	85.9	-	85.9	102.9	-	102.9
National Science Foundation	25.6	-	25.6	28.0	-	28.0	29.9	-	29.9
Tennessee Valley Authority	2.4	-	2.4	1.9	-	1.9	2.2	-	2.2
Veterans Administration	50.3	50.3	-	58.7	58.7	-	61.7	61.7	-
Department of Agriculture	48.2	-	48.2	50.1	-	50.1	54.7	-	54.7
Department of Commerce	2.9	-	2.9	.6	-	.6	.5	-	.5
Department of Defense	117.5	72.0	45.6	124.9	68.2	56.6	117.0	65.5	51.5
Department of Health, Education, and Welfare[2]	1,174.1	1,169.8	4.3	1,176.9	1,173.9	3.0	1,324.2[3]	1,321.2	3.0
National Institutes of Health	889.9	889.9	-	873.3	873.3	-	1,038.5	1,038.5	-
Health Services and Mental Health Administration	173.8	173.8	-	174.8	174.8	-	209.5	209.5	-
Food and Drug Administration	15.5	15.5	-	21.8	21.8	-	25.9	25.9	-
Other DHEW agencies[2]	94.9	90.6	4.3	107.0	104.0	3.0	50.3[3]	47.3	3.0
Department of Interior	4.4	2.6	1.8	12.4	10.9	1.4	22.5	20.8	1.7
Department of State	8.7	-	8.7	10.8	-	10.8	11.1	-	11.1
Department of Transportation	7.3	2.9	4.4	9.7	2.6	7.1	16.2	2.8	13.4

Note on Coverage and Sources:

The statistics shown above -- actual obligations for fiscal years 1969, 1970, and estimates for 1971 -- 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 (life, psychology, physical, mathematics, engineering, environmental, and social) distinguishing between (1) funds separately budgeted for medical and health-related research, specifically identified, programmed and justified as such, and supported for the purpose of improving human health (all of the research activities of agencies or sub-agencies whose sole mission is advancement of human health through research may thus be included); and (2) funds for research directly related to health in terms of substance or probable application, but which derive from funds budgeted, justified or supported for purposes other than medical or health objectives (for example, the general support of science, the promotion of agriculture, the achievement of the Nation's strategic objectives in outer space). As the table shows, about 20 percent of the total represents this latter category of research directly related to health but supported for other purposes. These data up-date and continue the time series presented in Resources for Medical Research "Federal Support for Medical and Health-Related Research, 1947-1964", Report No. 4, (PHS publication No. 1068) and Resources for Medical Research "Dollars for Medical Research, 1965-67", Report No. 12; and Resources Analysis Memo No. 10, "Biomedical Research, 1966-68". These publications together with data shown above constitute the definitive time series on Federal support for the performance of medical and health-related research in the post-War era.

[1] Coverage is limited to conduct and support of medical and health-related research, training and capital outlays are not included.

[2] Data for fiscal year 1971 exclude environmental research programs transferred, on December 2, 1970, to the Environmental Protection Agency.

Office of Resources Analysis
National Institutes of Health
February, 1971

TABLE 6.—Health and medical care: Private expenditures and expenditures under public programs, selected fiscal years, 1928–29 through 1969–70

[Amounts in millions]

Type of expenditure	1928–29	1939–40	1949–50	1954–55	1959–60	1964–65	1966–67	1967–68	1968–69	1969–70 [1]
Total	$3,589.1	$3,804.6	$12,129.5	$17,923.6	$26,366.7	$38,911.6	$47,902.3	$53,650.9	$59,905.0	$67,240.1
Private expenditures	3,112.0	3,021.0	9,064.0	13,503.0	19,971.5	29,366.0	32,185.0	33,728.0	37,125.0	42,258.0
Health and medical services	3,010.0	2,921.0	8,812.0	13,123.0	19,326.5	28,036.0	30,789.0	32,218.0	35,382.0	39,647.0
Direct payments	[2] 2,900.0	[2] 2,909.0	7,146.0	9,448.0	13,087.0	17,590.5	18,904.0	19,100.0	20,278.0	22,909.0
Insurance benefits	----	----	879.0	2,344.0	4,897.5	8,280.5	9,343.0	10,444.0	12,333.0	13,813.0
Expenses for prepayment	----	----	274.0	596.0	792.0	1,211.5	1,491.0	1,556.0	1,581.0	1,667.0
Other [3]	110.0	92.0	513.0	735.0	750.0	953.5	1,051.0	1,116.0	1,190.0	1,258.0
Medical research	----	----	37.0	55.0	121.0	162.0	177.0	185.0	192.0	195.0
Medical-facilities construction	102.0	81.0	215.0	325.0	524.0	1,168.0	1,219.0	1,325.0	1,581.0	2,416.0
Public expenditures	477.1	781.6	3,065.3	4,420.6	6,395.2	9,545.6	15,717.3	19,922.9	22,780.0	24,982.1
Health and medical services	372.5	679.5	2,470.2	3,862.3	5,346.3	7,647.3	13,577.4	17,468.5	20,231.4	22,274.6
OASDHI (health insurance for the aged)	----	----	----	----	----	----	3,394.6	5,347.2	6,597.7	7,145.2
Temporary disability insurance (medical benefits [4]	----	----	2.2	20.0	40.2	50.9	53.7	54.6	57.7	60.0
Workmen's compensation (medical benefits) [4]	75.0	90.0	193.0	315.0	420.0	580.0	715.0	790.0	875.0	970.0
Public assistance (vendor medical payments)	----	----	51.3	211.9	492.7	1,367.1	2,382.6	3,580.8	4,423.2	5,042.4
General hospital and medical care	117.1	297.6	886.1	1,297.6	1,973.2	2,515.5	2,808.3	2,927.7	3,009.6	3,132.1
Defense Department hospital and medical care (Armed Forces)	29.2	45.4	336.2	744.8	820.1	858.5	1,323.4	1,482.9	1,531.1	1,650.2
Military dependents' medical care	----	----	----	----	60.1	78.3	108.3	165.4	218.4	260.0
Maternal and child health programs	6.2	13.8	29.8	92.7	140.7	223.0	309.9	336.8	408.6	428.6
School health (educational agencies)	9.4	16.4	30.6	65.9	101.0	142.2	177.9	204.6	231.0	263.0
Other public health activities	88.8	154.5	350.8	383.7	401.2	671.0	883.8	1,000.6	1,194.7	1,429.0
Veterans' hospital and medical care	46.7	61.8	582.8	721.8	879.4	1,120.9	1,249.5	1,372.3	1,433.9	1,399.2
Medical vocational rehabilitation	.1	.3	7.4	9.1	17.7	34.2	67.4	102.0	124.6	152.0
OEO health and medical care	----	----	----	----	----	5.6	103.5	105.5	126.0	148.9
Medical research	----	2.6	72.9	138.9	471.2	1,228.8	1,428.7	1,615.5	1,599.7	1,694.7
Medical-facilities construction	104.7	99.6	522.3	419.4	577.7	669.5	711.2	838.9	948.9	1,012.7
Defense Department	[5]	[5]	1.1	33.0	40.0	31.1	49.7	26.8	71.8	52.1
Veterans Administration	4.2	14.3	161.5	34.1	59.6	81.2	49.4	46.0	53.9	77.5
Other	100.4	85.2	359.8	352.4	478.1	557.2	612.1	766.1	823.2	883.1
Total expenditures as a percent of gross national product	3.6	4.0	4.6	4.7	5.3	5.9	6.2	6.5	6.7	7.0
Public expenditures as a percent of total expenditures	13.3	20.5	25.3	24.7	24.3	24.5	32.8	37.1	38.0	37.2
Personal care expenditures [6]	3,272.2	3,501.7	10,549.4	15,855.0	23,236.2	33,505.4	41,456.9	46,552.0	52,148.7	58,048.5
Private expenditures	2,960.0	2,979.0	8,447.0	12,396.0	18,306.5	26,551.0	29,000.0	30,319.0	33,425.0	37,586.0
Public expenditures	282.2	522.7	2,102.4	3,459.0	4,929.7	6,954.4	12,456.9	16,233.0	18,723.7	20,462.5
Percent from:										
Private expenditures	91.4	85.1	80.1	78.1	78.8	79.2	70.0	65.1	64.1	64.7
Direct payments	88.6	82.8	67.7	59.6	56.3	52.5	45.6	41.0	38.9	39.5
Insurance benefits	----	----	8.3	14.8	20.2	24.7	22.5	22.4	23.6	23.8
Public expenditures	8.6	14.9	19.9	21.9	21.2	20.8	30.0	34.9	35.9	35.3

[1] Preliminary estimates.
[2] Includes any insurance benefits and expenses for prepayment (insurance premiums less insurance benefits).
[3] Industrial in-plant services and philanthropy.
[4] Includes medical benefits paid under public law by private insurance carriers and self-insurers.
[5] Data not available.
[6] Includes all items shown under "health and medical services" except (1) "expenses for prepayment;" (2) expenditures of private philanthropic agencies under "other health and medical services;" (3) "other public health activities;" and (4) administrative expenses for: "health insurance for the aged," "maternal and child health programs," and "veterans' hospital and medical care."

62-645 O - 71 - pt. 3 - 5

TABLE 7.—Health and medical care: Expenditures under public programs, by source of funds, selected fiscal years, 1928–29 through 1969–70

[In millions]

Type of expenditure	1928–29	1939–40	1949–50	1954–55	1959–60	1964–65	1966–67	1967–68	1968–69	1969–70 [1]
	Federal expenditures									
Total	$98.3	$177.7	$1,361.8	$1,947.6	$2,917.6	$4,635.1	$9,772.7	$13,021.5	$15,148.3	$16,666.9
Health and medical services	93.1	158.1	1,059.6	1,657.3	2,174.8	3,080.8	8,075.8	11,097.2	13,132.7	14,502.5
OASDHI (health insurance for the aged)							3,394.6	5,347.2	6,597.7	7,149.2
Workmen's compensation (medical benefits)	.6	5.2	5.2	6.9	9.0	11.3	13.9	15.3	16.7	19.0
Public assistance (vendor medical payments)				23.3	190.8	555.0	1,157.0	1,760.0	2,208.0	2,515.0
General hospital and medical care	8.5	15.5	46.4	66.7	103.4	137.9	163.8	186.6	193.2	216.4
Defense Department hospital and medical care (Armed Forces)	29.2	45.4	336.2	744.8	820.1	858.5	1,323.4	1,482.9	1,531.1	1,650.2
Military dependents' medical care					60.0	78.3	108.3	165.4	218.4	250.0
Maternal and child health services	1.2	7.8	20.1	23.5	34.7	69.1	139.0	160.6	189.6	214.0
Other public health activities	6.9	22.7	63.8	65.0	57.3	222.9	372.7	426.8	524.7	626.6
Veterans' hospital and medical care	46.7	61.5	582.8	721.5	879.4	1,120.9	1,240.5	1,372.3	1,433.9	1,599.2
Medical vocational rehabilitation	.1	.1	5.1	5.7	11.2	21.2	50.6	76.5	93.4	114.0
OEO health and medical care						5.6	103.0	103.5	126.0	148.9
Medical research		2.6	72.9	138.9	448.2	1,173.8	1,363.7	1,546.5	1,527.7	1,621.7
Medical-facilities construction	5.2	17.1	229.3	151.4	294.7	380.5	333.2	377.9	487.9	542.7
Defense Department	[2]	[2]	1.1	33.0	40.0	31.1	49.7	26.8	71.8	52.1
Veterans Administration	4.2	14.3	161.5	34.1	59.6	81.2	49.4	46.0	53.9	77.5
Other	.9	2.7	66.8	84.4	195.1	268.2	234.1	305.1	362.2	413.1
	State and local expenditures									
Total	$378.8	$603.8	$1,703.6	$2,472.9	$3,477.5	$4,910.5	$5,944.7	$6,901.4	$7,631.7	$8,315.1
Health and medical services	279.3	521.3	1,410.6	2,204.9	3,171.5	4,566.5	5,501.7	6,371.4	7,098.7	7,772.1
Temporary disability insurance (medical benefits) [3]			2.2	20.0	40.2	50.9	53.7	54.6	57.7	60.0
Workmen's compensation (medical benefits) [3]	74.4	84.8	187.8	308.1	411.0	568.7	701.1	774.7	858.3	951.0
Public assistance (vendor medical payments)			51.3	188.6	292.9	812.1	1,225.6	1,820.8	2,215.2	2,527.4
General hospital and medical care	108.6	282.1	839.7	1,230.9	1,869.8	2,377.6	2,644.5	2,741.1	2,816.4	2,915.7
Maternal and child health services	5.0	5.0	9.7	69.2	106.1	153.9	170.9	176.2	219.0	214.6
School health (educational activities)	9.4	15.4	30.6	65.9	101.0	142.2	177.9	204.6	231.0	263.0
Other public health activities	81.9	131.9	287.0	318.8	343.9	448.1	511.1	573.8	670.0	802.4
Medical vocational rehabilitation	.1	.1	2.3	3.5	6.6	13.0	16.9	25.5	31.1	38.0
Medical research					23.0	55.0	65.0	69.0	72.0	73.0
Medical-facilities construction	99.5	82.5	293.0	268.0	283.0	289.0	378.0	461.0	461.0	470.0

[1] Preliminary estimates.
[2] Data not available.
[3] Includes medical benefits paid under public law by private insurance carriers and self-insurers.

HISTORY OF CONGRESSIONAL ACTION ON BUDGET REQUESTS FOR NIH INSTITUTES AND DIVISIONS

Year	Budget request			Appropriation		
	Obligational cash	Liquidating cash	Contract authority	Obligational cash	Liquidating cash	Contract authority
1933	$48,000	----------	----------	$48,000	----------	----------
1934	54,775	----------	----------	54,775	----------	----------
1935	50,000	----------	----------	50,000	----------	----------
1936	64,000	----------	----------	64,000	----------	----------
1937	64,000	----------	----------	64,000	----------	----------
1938	464,000	----------	----------	464,000	----------	----------
1939	515,000	----------	----------	515,000	----------	----------
1940	587,750	----------	----------	707,000	----------	----------
1941	712,120	----------	----------	711,000	----------	----------
1942	705,000	----------	----------	700,000	----------	----------
1943	1,278,270	----------	----------	1,278,270	----------	----------
1944	1,291,000	----------	----------	2,555,020	----------	----------
1945	2,835,000	----------	----------	2,835,000	----------	----------
1946	2,078,000	----------	----------	3,414,700	----------	----------
1947	10,799,500	----------	----------	8,125,448[1]	----------	----------
1948	22,403,000	----------	----------	28,876,000	----------	----------
1949	45,701,460	----------	$2,300,000	37,668,000	----------	$10,300,000
1950	40,567,000	$3,900,000	3,595,000	50,167,000	$4,925,000[2]	15,425,000
1951	49,845,000	12,725,000	----------	47,334,750[3]	12,725,000	----------
1952	53,386,000	5,648,000	----------	52,477,291	5,198,000	----------
1953	55,005,000	----------	----------	59,030,750	----------	----------
1954	56,340,000	----------	----------	71,153,000	----------	----------
1955 [4]	71,128,000	----------	----------	81,268,000	----------	----------
1956 [5][6]	90,023,000	----------	----------	98,458,000	----------	----------
1957 [5]	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	----------	----------	560,000,000[8]	----------	----------
1962	583,000,000	----------	----------	738,335,000[9]	----------	----------
1963	780,400,000	----------	----------	880,800,000	----------	----------
1964	930,454,000	----------	----------	918,454,000	----------	----------
1965 [10]	956,492,000	----------	----------	965,992,000	----------	----------
1966 [10]	1,105,006,000	----------	----------	1,138,406,000	----------	----------
1967 [11]	1,231,764,000	----------	----------	1,306,983,000	----------	----------
1968 [11]	1,152,250,000	----------	----------	1,143,424,000[12]	----------	----------
1969	1,188,293,000[13]	----------	----------	1,100,092,000	----------	----------
1970	1,064,870,000[14]	----------	----------	1,122,718,700[15]	----------	----------
1971	1,035,548,000	----------	----------	1,196,249,000		
1972	1,183,309,000	----------	----------			

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, Montana.
10/ Includes $25,000,000 for Regional Medical Programs, $19,700,000 for Mental Health Staffing, and $20,250,000 for Heart Disease, Cancer and Stroke Program.
11/ Excludes $246,741,000 for National Institute of Mental Health. Includes $20,615,000 for Environmental Health Sciences.
12/ Excludes $21,000,000 unobligated balance available, start of year, for Regional Medical Programs.
13/ Excludes $30,928,000 unobligated balance available, start of year, for Regional Medical Programs.
14/ Excludes $7,093,000 for Office of the Director, NIH.
15/ Includes $1,348,200 supplemental.

NOTE: Not all amounts on 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.

NATIONAL INSTITUTES OF HEALTH

YEAR END STATUS OF EXTRAMURAL PROGRAMS

RESEARCH GRANTS-REGULAR PROGRAM[1]

(Dollar amounts in thousands)

	1969		1970		1971 estimate		1972 estimate	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Cancer:								
Funded	1,100	58,622	1,004	58,358	936	68,005	954	69,123
Unfunded	132	5,069	245	15,184	334	13,554	421	26,037
Heart:								
Funded	1,633	81,553	1,512	78,089	1,454	87,463	1,440	93,854
Unfunded	57	7,130	154	12,076	238	14,970	216	13,700
Dental:								
Funded	271	10,525	189	9,618	209	10,751	202	11,398
Unfunded	64	2,975	119	6,102	133	4,753	68	2,614
Arthritis:								
Funded	2,266	80,768	2,062	75,768	1,959	79,335	1,823	82,848
Unfunded	296	16,043	463	28,054	377	21,813	612	34,507
Neurology:								
Funded	1,437	50,290	1,314	46,929	1,267	49,651	1,166	48,887
Unfunded	93	4,850	120	11,573	255	14,832	374	17,940
Allergy:								
Funded	1,222	50,178	1,258	47,049	1,175	48,462	1,239	48,856
Unfunded	174	5,187	207	11,267	253	13,081	208	13,724
NIGMS:								
Funded	1,436	69,154	1,109	64,579	1,076	75,313	948	75,415
Unfunded	371	15,598	819	37,661	664	27,339	677	31,921
NICHD:								
Funded	867	35,231	799	37,910	732	41,890	760	45,279
Unfunded	328	11,399	414	17,455	583	24,281	678	30,600
NEI:								
Funded	355	13,436	353	14,487	427	18,492	500	21,443
Unfunded			53	4,664	24	2,100	64	3,264
NIEHS:								
Funded	103	5,094	88	4,525	87	5,445	131	7,937
Unfunded	17	1,138	42	2,482	85	4,052	25	1,253
Fogarty:								
Funded	49	111						
Unfunded								
Subtotal:								
Funded	10,739	454,962	9,688	437,312	9,322	484,807	9,163	505,040
Unfunded	1,532	69,389	2,636	146,518	2,946	140,775	3,343	175,560
NLM:								
Funded	46	1,321	34	990	20	590	17	600
Unfunded	6	154	9	404	2	310	5	500
BHM:								
Funded	98	4,754	78	4,251	81	4,611	69	4,214
Unfunded	7	358	3	151	8	255	8	228
Total NIH:								
Funded	10,883	461,037	9,800	442,553	9,423	490,008	9,249	509,854
Unfunded	1,545	69,901	2,648	147,073	2,956	141,340	3,356	176,288

[1] Excludes special research grant programs with unfunded applications $34,714 in 1970, $36,596 in 1971, $45,641 in 1972.

YEAR END STATUS OF EXTRAMURAL PROGRAMS-Continued

TRAINING GRANTS

(Dollar amounts in thousands)

	1969		1970		1971 estimate		1972 estimate	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Cancer:								
Funded	201	11,641	185	10,774	155	10,774	125	8,358
Unfunded	3	153	19	3,839	41	5,309	46	5,980
Heart:								
Funded	386	18,815	360	16,577	370	17,643	359	13,592
Unfunded	1	36	2	81	5	1,208	12	1,352
Dental:								
Funded	97	5,609	88	5,206	88	5,206	81	4,285
Unfunded			4	407	10	869	7	325
Arthritis:								
Funded	302	16,109	288	15,072	264	15,072	249	11,475
Unfunded	9	398	23	1,857	34	2,342	35	2,020
Neurology:								
Funded	545	19,504	445	14,299	365	14,300	351	11,456
Unfunded	53	4,201	84	7,067	202	8,563	239	12,600
Allergy:								
Funded	173	9,488	151	8,452	152	8,822	157	7,280
Unfunded	3	68	24	1,113	33	1,869	36	1,800
NIGMS:								
Funded	616	46,901	544	44,477	514	43,746	487	38,385
Unfunded	77	3,678	125	9,999	104	12,346	106	12,554
NICHD:								
Funded	153	10,012	131	9,392	116	10,142	100	9,085
Unfunded	23	1,280	57	4,831	78	5,955	90	7,000
NEI:								
Funded			52	2,984	47	2,998	41	2,225
Unfunded			10	1,153	5	1,023	9	1,907
NIEHS:								
Funded	45	3,652	41	3,525	42	3,103	34	2,843
Unfunded			1	380	1	102	6	586
DRR:[1]								
Funded			9	352	9	352	8	352
Unfunded			3	429	11	318	11	300
Subtotal:								
Funded	2,518	141,731	2,294	131,110	2,122	132,158	1,992	109,336
Unfunded	169	9,814	352	31,156	524	39,904	597	46,424
NLM:								
Funded	17	1,310	10	983	12	1,000	11	1,000
Unfunded	2	89	6	333	3	183	6	380
BHM:								
Funded	878	27,734	678	21,659	690	23,970	698	24,906
Unfunded	127	7,995	99	7,376	86	8,380	95	8,273
Total NIH:								
Funded	3,413	170,775	2,982	153,752	2,824	157,128	2,701	135,242
Unfunded	298	17,898	457	38,865	613	48,467	698	55,077

[1] In FY 1969 DRR was included with BHM.

YEAR END STATUS OF EXTRAMURAL PROGRAMS-Continued

FELLOWSHIPS

(Dollar amounts in thousands)

	1969		1970		1971 estimate		1972 estimate	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Cancer:								
Funded	319	4,366	254	3,610	242	3,798	216	3,348
Unfunded	8	96	167	1,980	135	1,525	155	1,938
Heart:								
Funded	405	6,933	363	6,915	339	6,871	255	6,195
Unfunded			32	325	6	129	48	1,155
Dental:								
Funded	121	1,765	102	1,529	97	1,601	82	1,367
Unfunded	8	73	20	199	--	--	3	28
Arthritis:								
Funded	459	6,737	371	5,482	343	5,740	280	5,094
Unfunded	31	291	177	1,735	130	1,515	171	2,000
Neurology:								
Funded	244	3,630	169	2,657	135	2,782	123	2,595
Unfunded	44	615	121	1,358	105	1,200	175	1,861
Allergy:								
Funded	280	4,035	238	3,864	203	3,579	186	3,334
Unfunded	28	205			76	725	35	646
NIGMS:								
Funded	2,449	21,373	1,800	17,624	1,619	18,454	1,140	15,142
Unfunded	824	6,227	1,492	10,536	551	6,280	403	5,353
NICHD:								
Funded	273	4,192	199	3,615	191	3,786	173	3,653
Unfunded	2	31	160	1,500	152	1,416	170	1,600
NEI:								
Funded			57	890	123	1,676	52	876
Unfunded			81	943	5	60	38	432
NIEHS:								
Funded	20	194	20	256	19	264	18	264
Unfunded	5	33	2	15	11	128	5	72
Fogarty:								
Funded	180	1,602	145	1,193	128	1,247	85	909
Unfunded			32	302	31	310	49	490
DRR:[1]								
Funded			14	126	14	126	14	126
Unfunded			7	79			3	25
Subtotal:								
Funded	4,750	54,827	3,732	47,761	3,453	49,924	2,624	42,903
Unfunded	950	7,571	2,529	18,972	1,202	13,288	1,255	15,600
BHM:								
Funded	168	931	147	799	138	800	135	800
Unfunded	16	133	26	194	51	267	102	539
Total NIH:								
Funded	4,918	55,758	3,879	48,560	3,591	50,724	2,759	43,703
Unfunded	966	7,704	2,555	19,166	1,253	13,555	1,357	16,139

[1] In FY 1969 DRR was included with BHM.

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. It does not include the activities of the Bureau of Health Manpower Education and the National Library of Medicine, although they became components of NIH in 1970.

REGULAR RESEARCH GRANTS

1. Purpose of program

To provide grant support of research in health, medicine, and allied fields with the major objectives (1) of continuing existing programs of research, (2) of expanding medical and biological research activities in universities, hospitals, laboratories, and other public or private institutions and (3) of stimulating new investigations in fields needing exploration. The grants range from support of smaller, discrete, and circumscribed projects, which are defined as project grants, to support of broad programs which integrate the research interests of several investigators, and which are called program project grants.

2. Funds

1963 obligations	$353,102,000
1964 obligations	401,868,000
1965 obligations	425,516,000
1966 obligations	461,756,000
1967 obligations	448,431,000
1968 obligations	461,327,000
1969 obligations	454,949,000
1970 obligations	442,118,000
1971 estimates	483,169,000
1972 estimates	497,217,000

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 1971 program of about $663,000,000 in regular and special research grant programs. In order to maintain a stable number of research grants and investigators, NIH began in 1969 to negotiate individual competing projects downward by an average of approximately 10% below the 1968 level. This action was necessary because of the cutback required in the Revenue and Expenditure Control act of 1968. Reductions were necessary in 1970 and are again in 1971. Although the above table reflects an increase in 1971 funds these are largely for new programs and it will be necessary to continue downward negotiations of ongoing projects. 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. NIH plans to significantly reduce negotiation of grants for fiscal reasons in FY 1972 with hopeful complete elimination in FY 1973.

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).

1963 obligations	$30,000,000
1964 obligations	35,000,000
1965 obligations	45,000,000
1966 obligations	45,200,000
1967 obligations	1/ 51,700,000
1968 obligations	1/ 59,674,445
1969 obligations	1/ 60,700,000
1970 obligations	1/ 57,677,000
1971 estimates	1/ 54,200,000
1972 estimates	1/ 49,200,000

1/ An amount for NIMH is included here (1967--$6,434,000; 1968--$5,483,000; 1969--$7,755,000; 1970--$7,367,000; 1971--$8,027,000; 1972--$8,027,000) inasmuch as the total is obligated through NIH.

3. Present stage of development

In 1971 general research support grants will provide support for 326 health professional schools, hospitals, research institutes, laboratories, centers and certain other nonprofit research organizations heavily engaged in health related research. In addition approximately 112 academic institutions other than health professional schools will be supported. Approximately 9 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 1972 President's budget represents a decrease of $5,000,000 from the 1971 level. It provides support for 333 institutions or organizations under the basic program, 116 biomedical sciences support grants to academic institutions and 4 Health-Sciences Advancement Awards. The reduction was made on the basis that overall medical research efforts would be best served by programming available funds toward well-defined Institute research programs rather than on the more generalized basis effected through this program.

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 to take advantage of unique biomedical problems in foreign countries which are of vital concern to the USA.

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. In 1969 this activity was transferred to the NIAID and is the responsibility of the National Institute of Allergy and Infectious Diseases.

1963 obligations	$2,483,000
1964 obligations	2,484,000
1965 obligations	2,511,000
1966 obligations	2,473,000
1967 obligations	2,360,000
1968 obligations	2,314,000
1969 obligations	2,300,000
1970 obligations	2,070,000
1971 estimates	2,263,000
1972 estimates	2,263,000

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 has an effective training program for U. S. citizens at both the domestic and overseas sites. During 1971 the program was broadened to offer scientific opportunities for investigators from all U. S. medical schools and schools of public health.

The cooperating institutions of the four International Centers now in operation are as follows:

U. S. University	Foreign Cooperating Institutions
John Hopkins University----------	All India Institute of Hygiene and Calcutta School of Tropical Medicine, Calcutta, India
University of California----------	Institute of Medical Research, Kuala Lumpur, Federation of Malaysia
Tulane University----------	Universidad del Valle, Cali, Colombia
University of Maryland----------	Institute of Hygiene and Lahore General Hospital, Lahore, West Pakistan

4. Plans for the future

The 1972 President's budget will permit the continuation of the existing four centers

SCIENTIFIC EVALUATION AND PLANNING GRANTS (CHAIRMAN'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

1963 obligations----------	$1,516,000
1964 obligations----------	1,847,000
1965 obligations----------	2,030,000
1966 obligations----------	2,163,000
1967 obligations----------	2,040,000
1968 obligations----------	2,134,000
1969 obligations----------	2,235,000
1970 obligations----------	2,077,000
1971 estimates----------	2,393,000
1972 estimates----------	2,393,000

3. Present stage of development

Research grant applications are reviewed prior to submission to the advisory councils by the appropriate initial review group. Each of these more than 60 panels 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.

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 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 pre-clinical 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 1969 awards had been made to 93 general clinical research centers. During 1970, because of increasing hospital costs 13 centers were notified of phase out and 80 general clinical centers are currently being funded in 1971.

Seventy-eight categorical center grants will be funded in fiscal year 1971. Five new awards will be made in 1971 for allergic disease centers. As with the general clinical research centers program, the categorical programs have yielded important scientific accomplishments.

4. Plans for the future

The 1972 President's budget will provide continued support of 80 general clinical research centers, including research on ambulatory patients, as well as support of 81 categorical clinical research centers. The feasibility of funding 2 new spinal cord centers is being studied by Neurology and there will be a continuation of the 5 allergic disease centers newly funded in 1971.

FUNDING OF CLINICAL RESEARCH CENTERS PROGRAM

Research center grants and physical resource component of program project grants

(In thousands)

	Obligations, 1963	Obligations, 1964	Obligations, 1965	Obligations, 1966	Obligations, 1967	Obligations, 1968	Obligations, 1969	Obligations, 1970	Estimates 1971	Estimates 1972
Research Resources	$17,374	$27,057	$26,906	$28,500	$28,463	$30,443	$35,004	$35,004	$38,004	$39,004
Child Health	-------	-------	209	198	112	330	302	-------	-------	-------
Cancer	4,437	4,849	4,898	7,283	1/	1/	1/	1/	1/	1/
Mental	781	1,604	1,379	1,292	-------	-------	-------	-------	-------	-------
Heart	2,048	1,597	1,580	4,500	4,500	4,500	4,500	3/	3/	3/
Dental	-------	-------	212	344	212	327	276	337	380	380
Arthritis	1,119	1,202	1,249	1,500	1,500	1,500	1,500	1,380	1,380	1,380
Allergy	237	852	949	881	1,099	869	1,066	1,034	1,266	1,266
Neurology	1,353	1,200	1,200	3,000	3,150	3,005	3,150	2,255 2/	3,154	3,454
Eye	-------	-------	-------	-------	-------	-------	-------	686	686	686
Total	27,349	38,361	38,582	47,498	39,036	40,974	45,798	40,696	44,870	46,170

1/ Beginning with 1967 the Cancer Institute funds are included in the table for specialized research centers.

2/ Excludes funds for the "National Eye Institute" established as a separate institute in 1970.

3/ Beginning with 1970, the Heart Institute funds are included in the table for specialized research centers.

BIOTECHNOLOGY RESOURCES*

1. Purpose of program

To provide grants to non-Federal research institutions for the support of specialized resources concerned with the technology and expertise vital to modern biomedical research and patient care. The primary emphasis is on computers (including those used in diagnosis of heart disease and monitoring of the critically ill); molecular spectroscopy (used for determining the molecular structure of chemical substances that comprise or interact with living organisms); biological materials preparation (such as enzymes or cultures otherwise unobtainable); and electron microscopy (which provides biomedical scientists with information about the detailed structure of living material which has not been available before). The mode of support makes it economically feasible to provide biomedical scientists supported by the NIH with both (a) urgently needed scientific capabilities that could not be justified or fully utilized on an individual basis and (b) the expertise necessary for the most efficient and effective utilization of such expensive and advanced research tools.

2. Funds

1963 obligations	$6,117,000
1964 obligations	5,077,000
1965 obligations	8,169,000
1966 obligations	10,618,000
1967 obligations	10,850,000
1968 obligations	10,529,000
1969 obligations	10,494,000
1970 obligations	9,867,000
1971 estimates	9,617,000
1972 estimates	10,117,000

3. Present stage of development

Program plans for 1971 call for the continuation of support of 47 resources: 33 biomedical computer resources, ten biochemical instrumentation resources, three biological materials preparation resources, and one high voltage electron microscopy resource.

4. Plans for the future

The 1972 President's budget will provide for the funding of 46 resources.

* In prior years shown as "Special Research Resources".

ANIMAL RESOURCES

(Includes Primate Research Centers)

1. Purpose of program

This program assists institutions in providing animal resources required for medical research and education through grants for special animal colonies that support research related to improving animal health and care, disease diagnosis and control studies directed to enhancing the usefulness of animal models for research, and general improvement of management and accomodation for institutional animal resources.

The program also provides support for the operation of seven primate centers which provide a unique research environment where scientists can conduct biomedical and behavioral research using the nonhuman primate as an experimental animal. The nonhuman primate is biologically and behaviorally closer to man than any other animal, and is effected with many diseases similar to man. Therefore, the possibility of successfully applying information gained from nonhuman primates to man is higher than that obtainable with any other animal.

2. Funds

1963 obligations	$4,444,000
1964 obligations	6,194,000
1965 obligations	7,819,000
1966 obligations	8,527,000
1967 obligations	12,100,000
1968 obligations	15,600,000
1969 obligations	15,068,000
1970 obligations	14,224,000
1971 estimates	14,974,000
1972 estimates	14,974,000

3. Present stage of development

Plans call for the support of 71 animal resources including the 7 primate centers in 1971.

4. Plans for the future

The 1972 President's budget will support approximately 71 animal resources including the primate centers.

LEUKEMIA RESEARCH SUPPORT CENTERS

1. Purpose of the program

Leukemia research support centers are utilized to make platelet transfusions and domiciliary care available to children under treatment of leukemia, as well as to do research on other forms of therapy. Platelet transfusions are an essential factor in the modern treatment of childhood leukemia. Marked improvement in the results of anti-leukemic therapy have followed upon the use of this technique. The massive platelet transfusions required have not been widely available and this program provides for the preparation, administration and evaluation of platelet transfusions in institutions across the country responsible for the care of leukemic children.

2. Funds

1966 obligations	$824,000
1967 obligations	1,425,000
1968 obligations	1,257,000
1969 obligations	1,491,000
1970 obligations	1,401,000
1971 estimates	1,851,000
1972 estimates	1,851,000

3. Present stage of development

In 1971 approximately 27 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 1971 level for 1972. Emphasis will continue to be placed upon accumulating evidence regarding platelet replacement therapy and its use as an effective device in connection with the use of control drugs.

HEART COOPERATIVE DRUG STUDY

1. Purpose of program

This program is designed and organized as a national cooperative study to determine whether several lipid-lowering drugs will, over prolonged periods of use, reduce the mortality or morbidity of coronary heart disease.

2. Funds

1965 obligations	$447,000
1966 obligations	1,770,000
1967 obligations	3,433,000
1968 obligations	3,820,000
1969 obligations	3,812,000
1970 obligations	3,967,000
1971 estimates	4,579,000
1972 estimates	3,255,000

(Some additional funds for the study are included in direct operations amounts.)

3. Present stage of development

The study is underway at 53 participating clinics. Patient recruitment was completed in June 1969 (over 8,300 patients are enrolled).

4. Plans for the future

The 1972 President's budget continues support for the project's clinical phase, which will be completed in 1974. By then all patients will have completed a five-year period of drug testing. The continued analysis and interpretation of the data will follow that date.

PHARMACOLOGY-TOXICOLOGY RESEARCH CENTERS

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 of large scale projects for research in areas of pharmacology and toxicology related to the use of drugs and chemical intoxication. These programs are university based and located in appropriate academic and scientific environments.

2. Funds

1966 obligations	$1,000,000
1967 obligations	3,358,617
1968 obligations	3,500,000
1969 obligations	3,500,000
1970 obligations	3,325,000
1971 estimates	3,593,000
1972 estimates	3,593,000

3. Present stage of development

The program was initiated in 1966. Ten centers are presently being supported. Greater emphasis is being placed on clinical pharmacology and implications of new knowledge as it relates to medical therapy in man.

4. Plans for the future

The President's budget will provide continuing support for the program. Emphasis will continue to be placed on development of the clinical aspects of the program.

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 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 offer a unique environment for the training of researchers and academicians.

2. Funds

1967 obligations	$2,996,000
1968 obligations	3,000,000
1969 obligations	3,000,000
1970 obligations	3,400,000
1971 estimates	4,700,000
1972 estimates	5,200,000

3. Present stage of development

Currently, five dental research institutes are in operation at the following universities: Alabama, Michigan, North Carolina, Pennsylvania, and Washington.

4. Plans for the future

The President's budget provides continuing support for the five institutes initially established.

ANESTHESIOLOGY AND DIAGNOSTIC RADIOLOGY CENTERS

1. Purpose of program

The purpose of the anesthesiology and diagnostic radiology centers program is to provide research support for clinical and laboratory investigation related to teaching and patient care in these fields. One aspect of the program will be concerned with research leading to the development and evaluation of new techniques, bringing the fruits of biomedical engineering to the improvement of these specialties which are essential to all branches of health care.

2. Funds

1967 obligations	$500,000
1968 obligations	1,000,000
1969 obligations	1,000,000
1970 obligations	950,000
1971 estimates	950,000
1972 estimates	950,000

3. Present stage of development

The program was initiated in 1967. Four centers have been established to date.

4. Plans for the future

The amounts in the President's budget provide for the continuing support of the established 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.

2. Funds

	Obligations			
	1969 Actual	1970 Actual	1971 Estimate	1972 Estimate
Heart and Lung	$270,000	$148,000	$16,442,000	$16,442,000
Cancer	12,950,000	12,122,000	19,453,000	21,453,000
Neurology	850,000	790,000	840,000	540,000
Total	14,070,000	13,060,000	36,735,000	38,435,000

3. Present stage of development

In 1971 the Heart and Lung Institute was appropriated funds for the operational support of 25-30 centers in arteriosclerosis, thrombosis, hypertension, and pulmonary diseases. Applications for these awards are currently under intensive review. Cancer Institute now supports 33 specialized research centers which are performing intensive, highly specialized clinical research or laboratory research relating to prevention, diagnosis, and treatment of cancer in man. Neurology currently has 14 centers in operation.

4. Plans for the future

The Heart and Lung Institute will continue the support of 25-30 centers in four targeted research areas. Cancer Institute plans to continue the same number of centers in 1972 and will initiate one or two new centers in geographic areas where no center currently exists. Neurology will continue 8 centers and make a funding shift of $300,000 to categorical centers program for study of the feasibility of financing two spinal cord injury centers.

ENVIRONMENTAL HEALTH SCIENCE CENTERS

1. Purpose of program

The purpose of the environmental health science centers is to support programs utilizing university-based resources for both research and training programs designed to concentrate research skills and efforts on the complex and challenging problems in environmental health. 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. University-based 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 obligations	$2,529,000
1968 obligations	3,000,000
1969 obligations	2,993,000
1970 obligations	2,850,000
1971 estimates	3,050,000
1972 estimates	3,550,000

3. Present stage of development

In 1971 the Institute is supporting six university-based centers that have operational status.

4. Plans for the future

The President's budget provides for the continued development of the six ongoing centers and the initiation of one additional center grant.

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 postdoctoral 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
1963 obligations	893	$14,224,000
1964 obligations	1,078	19,811,000
1965 obligations	3,659	22,448,000
1966 obligations	4,192	25,937,000
1967 obligations	1,159	25,292,000
1968 obligations	1,157	26,840,000
1969 obligations	1,177	27,987,000
1970 obligations	1,129	27,708,000
1971 estimates	1,146	29,706,000
1972 estimates	1,077	28,675,000

3. Present stage of development

Approximately 1,146 fellows will be supported in 1971. This is the sum of 140 Research Career Awards, and 1,006 Research Career Development Awards. No new Research Career Awards have been made since 1964.

4. Plans for the future

During 1972 about 1,077 career fellowships will be supported. This represents a decrease of 66 Research Career Development Awards and a decrease of 3 Research Career Awards over the number supported in 1971.

FOGARTY SCHOLARSHIPS

1. Purpose of program

This program is designed to facilitate the discussion, expansion and evolution of ideas between distinguished leaders in science, scholars in other disciplines and other creative individuals. The program proposes to select outstanding scientists and scholars from the international biomedical community, provide for their residence at the Fogarty International Center and have them focus their attention on broad aspects of important issues raised by the findings of modern biomedical research.

2. Funds

1969 obligations	$192,000
1970 obligations	167,000
1971 estimates	170,000
1972 estimates	170,000

3. Present stage of development

Several scholars engaged in studies under the program are currently in residence in Stone House, at the Center.

4. Plans for the future

Funds in the President's budget will provide continuing support at the same level as in 1971.

REGULAR RESEARCH FELLOWSHIPS

NOTE: In this, and the following sections on Fellowships and Training grants, data through 1966 include amounts for the National Institute of Mental Health. Beginning with 1967, pursuant to the reorganization of the Public Health Service, the tables omit NIHM but include the Division of Environmental Health Sciences. The principal effects of this change are in Predoctoral Fellowships and in Training grants where there are reductions in 1967 over the amounts shown for 1966. It does not include data for the Bureau of Health Manpower and the National Library of Medicine, although they became components of NIH in 1970.

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 in science. 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
1963 obligations	$7,869,000	$8,626,000	$3,642,000	$20,137,000
1964 obligations	8,522,000	8,460,000	4,233,000	21,215,000
1965 obligations	10,638,000	8,312,000	5,053,000	24,003,000
1966 obligations	12,368,000	8,493,000	5,818,000	26,679,000
1967 obligations	8,234,000	7,999,000	5,920,000	22,153,000
1968 obligations	7,875,000	8,790,000	7,124,000	23,789,000
1969 obligations	7,457,000	10,856,000	8,469,000	26,782,000
1970 obligations	5,117,000	6,761,000	7,017,000	18,895,000
1971 estimates	3,478,000	7,647,000	7,846,000	18,971,000
1972 estimates	2,461,000	5,152,000	5,706,000	13,319,000

3. Number of awards

	Predoctoral	Postdoctoral	Special	Total
1963 actual	1,533	1,210	386	3,129
1964 actual	1,665	1,181	422	3,268
1965 actual	1,964	1,194	501	3,659
1966 actual	2,323	1,287	582	4,192
1967 actual	1,586	1,086	522	3,194
1968 actual	1,556	1,058	579	3,193
1969 actual	1,508	1,389	684	3,581
1970 actual	1,042	824	561	2,427
1971 estimates	661	909	590	2,160
1972 estimates	442	608	412	1,462

4. Present stage of development

There is a decrease in the total number of fellowships in this program in 1971 related to the planned phase out of the predoctoral program.

5. Plans for the future

The number of fellowships supported in 1972 will decrease by 698 from the number supported in 1971. There is a corresponding decrease in funds available for 1972.

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
1963 obligations	172	$1,198,000
1964 obligations	177	1,199,000
1965 obligations	184	1,177,000
1966 obligations	166	1,199,000
1967 obligations	155	1,200,000
1968 obligations	159	1,378,000
1969 obligations	173	1,419,000
1970 obligations	142	1,027,000
1971 estimates	122	1,077,000
1972 estimates	79	739,000

3. Present stage of development

This program was established in Western Europe in 1958 with 15 countries participating. Plans were made at that time for an orderly increase in the number of participating countries based on research potential and likelihood that returning fellows would use training in the United States. The increase in the number of countries participating has progressed according to schedule as follows: 1959, 30; 1960, 36; 1961, 40; 1962 and 1963, 41; 1964 and 1965, 42; 1966 through 1968, 43; 1969 through 1970, 44; 1971, 43.

4. Plans for the future

In 1972 approximately 79 fellows will be supported. This is a decrease of 43 over the number supported in 1971.

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) providing 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. The following table does not include data for the Bureau of Health Manpower and the National Library of Medicine.

2. Funds

1963 obligations	$135,502,000
1964 obligations	164,895,000
1965 obligations	178,617,000
1966 obligations	208,784,000
1967 obligations	134,403,000
1968 obligations	134,951,000
1969 obligations	141,941,000
1970 obligations	131,110,000
1971 estimates	109,336,000
1972 estimates	109,336,000

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. The reduction of approximately $23 million reflects a shift of medical research training grant funds from the NIH research Institutes to the Bureau of Health Manpower Education, NIH. This is reflected as a comparative transfer in 1971.

In 1971 about 2,113 training grants will be supported.

4. Plans for the future

Emphasis will continue in areas where current and projected manpower shortages can be identified. Examples of such program areas to be supported by NIGMS include pharmacology and toxicology, the behavioral sciences, genetics, biophysics, biomedical engineering, and biostatistics. Areas of manpower shortages in programs supported by other Institutes include mental retardation, developmental and clinical pharmacology, aging, congenital malformations, virology, epidemiology, immunology and organ transplantation, artificial organs, orthopedics, urology and kidney disease, and neurology. Approximately 1,992 training grants will be supported in 1972, a decrease of 121 from the number supported in 1971. The funds reflect a continuation of the shift to the Bureau of Health Manpower Education.

MORTALITY AND MORBIDITY FROM CANCER

Department of Health, Education and Welfare
National Cancer Institute

Statistics on 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 1969 (Estimated data in Provisional Report of the National Center for Health Statistics, Division of Vital Statistics):

Mouth and Pharynx	7,300
Digestive system	93,710
Respiratory system	66,100
Breast	29,290
Genital organs	40,520
Urinary organs	14,710
Leukemias	14,480
Other neoplasms of lymphatic and hemopoetic tissues	18,060
All Other Sites	39,160
Total, All forms of cancer	323,330

II. Cancer disability in 1969 (estimated on the basis of data supplied by the National Cancer Institute and the National Center for Health Statistics):

(a) Estimated cases under treatment 964,000
(b) Estimated person-days of disability (these estimates have a large margin of error):

Restricted activity	64,945,000
Sick in bed	36,535,000

III. Estimated cancer's cost to the Nation in 1969 (based on 1963 costs given in -- Estimating Cost of Illness - Health Economics Series-No.6. These figures refer to all neoplasms - benign, malignant and unspecified. No more recent analyses are available and current costs are undoubtedly higher. The 3rd National Cancer Survey being conducted in 1970-1972 is designed to include some information of this kind).

(a) $1.8 billion were spent in 1969 for direct costs, hospital care, nursing home care, physicians' services and nursing services for neoplasms.

(b) A total of 175,000 man-years of productivity, amounting to $1.2 billion in current dollars, were lost in 1969 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 $12.3 billion.

CARDIOVASCULAR AND CHRONIC PULMONARY DISEASES

I. Deaths from cardiovascular and pulmonary diseases during 1968 [1]
(Division of Vital Statistics, National Center for Health Statistics):

	Total, Males and Females		
	Under 65	65 & Over [2]	Total
Cardiovascular diseases:			
Ischemic heart and hypertensive disease:			
Acute ischemic heart disease (includes "heart attack")	125,101	249,200	374,301
Other ischemic heart and hypertensive disease	57,847	269,360	327,207
Stroke	38,353	173,037	211,390
Rheumatic fever and rheumatic heart disease	9,810	6,548	16,358
Congenital heart disease	7,856	165	8,021
Other cardiovascular diseases	27,133	83,903	111,036
Subtotal, cardiovascular diseases	266,100	782,213	1,048,313
Chronic obstructive pulmonary diseases:			
Chronic and unqualified bronchitis	2,093	4,112	6,205
Emphysema	7,592	16,593	24,185
Asthma	1,701	987	2,688
Subtotal, chronic obstructive pulmonary diseases	11,386	21,692	33,078
Total, Cardiovascular and Pulmonary	277,486	803,905	1,081,391

	Males		
	Under 65	65 & Over [2]	Total
Cardiovascular diseases:			
Ischemic heart and hypertensive disease:			
Acute ischemic heart disease (includes "heart attack")	97,108	141,854	238,962
Other ischemic heart and hypertensive disease	39,256	125,112	164,368
Stroke	20,683	76,018	96,701
Rheumatic fever and rheumatic heart disease	4,803	2,720	7,523
Congenital heart disease	4,431	66	4,497
Other cardiovascular diseases	17,003	41,217	58,220
Subtotal, cardiovascular diseases	183,284	386,987	570,271
Chronic obstructive pulmonary diseases:			
Chronic and unqualified bronchitis	1,473	3,121	4,594
Emphysema	6,157	14,277	20,434
Asthma	747	487	1,234
Subtotal, chronic obstructive pulmonary diseases	8,377	17,885	26,262
Total, Cardiovascular and Pulmonary	191,661	404,872	596,533

Cardiovascular and Chronic Pulmonary Diseases (continued)

	Females		
	Under 65	65 & Over 2/	Total
Cardiovascular diseases:			
Ischemic heart and hypertensive disease:			
Acute ischemic heart disease (includes "heart attack")	27,993	107,346	135,339
Other ischemic heart and hypertensive disease	18,591	144,248	162,839
Stroke	17,670	97,019	114,689
Rheumatic fever and rheumatic heart disease	5,007	3,828	8,835
Congenital heart disease	3,425	99	3,524
Other cardiovascular diseases	10,130	42,686	52,816
Subtotal, cardiovascular diseases	82,816	395,226	478,042
Chronic obstructive pulmonary diseases:			
Chronic and unqualified bronchitis	620	991	1,611
Emphysema	1,435	2,316	3,751
Asthma	954	500	1,454
Subtotal, chronic obstructive pulmonary diseases	3,009	3,807	6,816
Total, Cardiovascular and Pulmonary	85,825	399,033	484,858

1/ Final 1968 mortality statistics (unpublished)
2/ Includes age not stated

II. Disabilities from cardiovascular and pulmonary diseases (unpublished figures from Division of Health Interview Statistics, National Center for Health Statistics, based on data collected during the period from July 1967 to June 1968).

	Disability Category					
	Restricted activity			Bed disability		
	Total	Under 65	65 & Over	Total	Under 65	65 & Over
Average annual number of disability-days (in millions):						
Cardiovascular conditions	493	262	231	185	91	94
Heart conditions	252	130	122	98	48	50
High blood pressure 1/	69	43	26	22	14	7
Other cardiovascular conditions	172	89	83	65	29	37
Chronic bronchitis and emphysema	172	127	44	66	50	16
Total	665	389	275	251	141	110
Average number of persons (in thousands): 2/						
Cardiovascular conditions	1,351	717	633	506	249	257
Heart conditions	689	355	335	269	132	137
High blood pressure 1/	190	118	71	59	38	20
Other cardiovascular conditions	472	244	228	178	79	100
Chronic bronchitis and emphysema	470	349	121	181	137	43
Total	1,821	1,066	755	687	386	300

III. Estimated national health expenditures for the cardiovascular diseases in 1969 (computed from data published by PHS)

Type of Expenditure	Amount
Hospital care	$2,800,000,000
Nursing home care	1,200,000,000
Physicians' and other professional services	1,800,000,000
Drugs and other health services and supplies	600,000,000
Research and medical facilities construction	600,000,000
Total	7,000,000,000

1/ Without heart involvement
2/ Disability days/365

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

National Institute of Dental Research

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the Dental Institute, and the estimated annual cost to the Nation.

1. Deaths related to oral disease

Oral cancer causes the death of more than 7,000 Americans each year.

2. Disabilities related to oral diseases

Proper functioning and the state of health of the oral cavity contribute greatly to the individual's physical, mental, and social well-being. Not only are they indispensable to nutrition and communication, but they exercise tremendous influence on the general health of the body. Early manifestations of systemic illnesses frequently appear first in the mouth, so periodic oral examinations serve a broad purpose in the preservation of of total health.

Oral diseases range from tooth decay and gum infections to malignancies. They are the most universal afflictions of mankind and very few persons escape one or another of these disorders in the course of a lifetime.

Dental caries affects 98 percent of the population and is the most prevalent affliction of children. By the time the average child reaches school age, he has three decayed teeth, and the average 15-year old has eleven decayed teeth.

The neglect of dental caries represents the major cause of tooth loss during the first three decades of life. Further, the physical trauma incident to the extraction of decayed teeth can have severe consequences in individuals suffering from certain kinds of heart diseases as a result of harmful bacteria entering into the bloodstream. In addition, the early loss of teeth from decay contributes significantly to impaired speech and mastication, as well as malocclusion that may eventually predispose to destructive diseases of the supporting tissues.

Periodontal (gum) disease affects two out of three middle-aged Americans. Destruction of the tissues and structures that hold teeth fast in their sockets accounts for 75 percent of tooth loss after age 40. It is a worldwide problem that dates back to antiquity, and troubles rich and poor alike. In the United States, an estimated 75 million adults have this disease. In addition, more than 20 million adults have lost all their teeth because of it. Although the disease usually has its onset in adolescence, it is not generally noticed until after age 30. Without care it tends to increase in severity with age. Gingivitis, the early reversible form of gum disease, is present in four out of five persons by the time they are 15 years of age. A more advanced stage is already evident in about 4 percent of these.

Clefts of lip and palate are one of the most common birth defects, affecting 6,000 to 7,000 babies each year. There are more than one-quarter million persons in the United States with this deformity. Cleft lip/palate accounts for 13 percent of all reported birth annomalies.

Without proper therapy, these afflicted persons go through life with deformed noses, scarred lips, mutilated palates, and incoherent speech. In addition to appropriate surgical, prosthetic, and speech help, the cleft palate child also needs psychosocial attention. The psychosocial impact also, sometimes leads to complete disruption of family life. Therefore, it is important that informed long-range counseling be given to the family for its own well-being as well as for the rehabilitation of the infant.

Cancer of the mouth accounts for approximately 3 to 4 percent of all cancers occurring annually in the United States, and unlike most oral diseases it can be fatal. Readily visible oral cancers often are ignored because of the absence of early warning pain. Oral cancer can strike men and women of any age, but most frequently is found in men after age 40. The most common site is the lip, which accounts for 25 to 30 percent of all oral cancers. The tongue and floor of the mouth are the next most common sites. Others are gums, cheek, palate, tonsils, lower jaw, and salivery glands. With early detection and therapy more than half of all mouth-cancer patients are alive five years after treatment. In fact, 89 percent of all males treated for lip cancer are alive five years later. A significant, though lesser, percent of 5-year cures has been reported for oral cancer in other sites, such as the tongue.

The control and prevention of oral diseases is dependent upon basic research, the bedrock of all scientific and technological progress, and thus, dental research has frequently made contributions to other branches of medicine and science. For example, isolation of the collagen-destroying enzyme collagenase in the human body resulted from research into the causes of periodontal disease. Collagen is the major structural protein of the body. Isolation of collagenase has contributed to the study of other connective tissue disorders.

3. Estimated annual cost to the nation

The cost of private dental care in this country approximates $4 billion dollars a year, or less than 10 percent of the $50 billion spent annualy on all private health care. Less than half of the population visits a a dentist each year, and estimated three-fifths of our citizens receive no dental care in the course of a year. Because of its human and economic burden in terms of suffering, inability to eat properly, loss of productivity, and restriction of job opportunity, tooth decay exacts a far greater cost than the approximately two billion dollars spent each year for its treatment by the 40 percent of the population who seek dental care. If all cavities incurred each year could be filled, the annual cost would reach about 10 billion dollars.

Impact of the problem is demonstrated in experience of the military. The U.S. Army currently finds that every 100 inductees require 600 fillings, 112 extractions, 40 bridges, 21 crowns, 18 partial dentures, and one full denture. Oral problems are responsible for the loss each year of approximately 100 million man-hours of productive work.

Rehabilitation of a cleft patient requires coordinated efforts of a team of specialists and costs about $14,000 through the 18th year. Annual expenditure for those receiving treatment and rehabilitative services is estimated at $100 million.

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 (Source: National Center for Health Statistics, PHS)

Category:	
Diabetes mellitus (1969)----------	37,400
Gastrointestinal diseases (ulcer of stomach and duodenum, cirrhosis of the liver, gastritis, duodenitis, enteritis, and colitis) (1968)---------	53,000
Total----------	90,400

II. Disabilities
(Source: National Center for Health Statistics, PHS, 1969.)

Number of persons in U.S. reporting chronic activity limitation due to arthritis (excluding gout and bursitis): $3,373,000.

III. Estimated annual economic cost to the Nation
(Source: The Arthritis Foundation, 1970.)

Arthritis and rheumatism, $4 billion.

Prepared February 10, 1971

Neurological and Sensory Disabilities: Estimated Numbers and Cost

Introduction

The mission of the National Institute of Neurological Diseases and Stroke (NINDS) is to conduct and support research and professional training on the problems of neurological and sensory disabilities. These are a leading cause of chronic human suffering and economic burden in the United States.

As much as 10 percent of the total population of the Nation may be suffering from one of the approximately 200 disabling neurological or sensory disorders. An estimated 20 percent of hospital admissions are related to these neurological and sensory ailments.

Impairments range from speech defects and hearing problems to nervous-system disorders which cause crippling and death. Multiple handicaps are common.

Such conditions include cerebral palsy, mental retardation, strokes, epilepsy, multiple sclerosis, muscular dystrophy, Huntington's disease, and spinal cord injury, also loss of hearing and speech. The vast majority of these problems are still incurable.

Mortality Statistics

Neurological ailments have been causing about 12 percent of the total U.S. deaths. A Pennsylvania study has shown that 2 of every 1,000 live newborns die of neurological conditions before they are one year old. Although certain chronic neurological conditions contribute to death, they often are not listed as cause of death. Mortality statistics, therefore, do not portray the full magnitude of the neurological and sensory disease problem.

Prevalence

Exact figures on prevalence are not available for various reasons:
Case finding is difficult because neurological and sensory diseases are not reportable. Many conditions become evident to the individual only after they have progressed to a point of disability. Or, persons affected by some neurological disorders conceal their handicap, as in epilepsy, because of job discrimination and other forms of social non-acceptance. Moreover, medical diagnosis of neurological problems is still difficult in certain disorders; many cases are incorrectly diagnosed or missed for long periods.

NINDS's Estimate of the Problem

NINDS can only estimate the range of neurological and sensory disability. In doing this, it has drawn on figures from various voluntary health organizations, the Department of Health, Education, and Welfare's National Center for Health Statistics, and other sources.

Voluntary and Government agencies recognize the need for more reliable data on chronic impairments among our population. Such information has decided importance in promoting a solution to the vast problems raised by chronic illness.

Estimated Numbers and Cost of Major Chronic Neurological and Sensory Disorders

Disability	Mortality 1/	Estimated Total Cases 2/	Estimated Annual Cost of Care 3/	Remarks
NEUROLOGICAL				
Amyotrophic lateral sclerosis (ALS)	1,410	6,000	$ 12,000,000	An NINDS research study showed ALS deaths were underreported by about 30 percent. This appears to be typical of many neurological ailments.
Cerebral palsy (CP)	1,376	750,000	750,000,000	National Health Education Committee (NHEC) estimates one-third of the patients are under 21 years old. United Cerebral Palsy estimates 25,000 born each year with CP.
Epilepsy	1,972	2,000,000	800,000,000	About 80 percent of children and adults with epilepsy might have their seizures substantially or completely controlled by prescribed anticonvulsants. (Epilepsy, HTR, NINDS)
Head injuries	50,000(est.)	3,053,000	150,000,000	Over 700,000 persons are bed-disabled for 1 day or more as a result of injury to the head. (National Center for Health Statistics)
Huntington's disease (chorea)	198	14,000	25,000,000	Committee to Combat Huntington's Disease believes about 50,000 Americans have the HD gene and now have or will have symptoms if they live to the age where HD symptoms appear.
Mental retardation		6,000,000	3.5 billion	(President's Committee on Mental Retardation)
Multiple sclerosis (MS) and related diseases	1,647	500,000	500,000,000	MS is a long-term progressive disease usually starting between the ages of 20 and 40 years.
Muscular dystrophy (MD) and related neuromuscular disorders	530	1,000,000	625,000,000	Muscular Dystrophy Associations of America, Inc., believes this is a conservative estimate of all neuromuscular disorders including the various dystrophies and myositis; muscular dystrophy, mostly in children, accounts for 200,000.
Myasthenia gravis (MG)	267	30,000	40,000,000	Again reported deaths do not reflect estimated total cases. (MG Fact Sheet, NINDS)
Parkinson's disease (paralysis agitans)	3,193	1,000,000	800,000,000	Parkinson deaths may be 5 times higher than cited, as an indirect cause. (Parkinson's Disease Foundation)

Estimated Numbers and Cost of Major Chronic Neurological and Sensory Disorders

Disability	Mortality 1/	Estimated Total Cases 2/	Estimated Annual Cost of Care 3/	Remarks
NEUROLOGICAL (con't)				
Reading disabilities		8,000,000	$800,000,000	Of the estimated 15 percent of all school children having some type of reading disability, about one-third may have a slight brain dysfunction. (NINDS)
Spina bifida	932	27,500	55,000,000	An estimated 11,000 babies are born annually with spina. bifida or related birth defects (often incurable). (Spina Bifida, HTR, NINDS)
Spinal cord injury	2,500(est.)	100,000	2.4 billion	Economic loss to patient and society of 10,000 traumatic paraplegia and quadriplegia patients is estimated by an insurance company.
Strokes (cerebrovascular accidents--CVA)	211,390	2,000,000	440,000,000	One-third of patients with strokes (CVA) are wage earners under age 65 made unemployable by the residuals of a stroke. (NHEC and President's Commission on Heart Disease, Cancer, and Stroke)
Tumors of the brain and other parts of the nervous system	10,240	140,000	272,000,000	Brain tumors cause about 40 percent of the deaths from diseases of the central nervous system exclusive of strokes.
SENSORY				
Hearing disorders				In 1970, 46,997 pupils were enrolled in 1,375 American schools and classes for the deaf. The last German measles (rubella) epidemic resulted in many deaf or deaf-blind children whose education poses a serious national problem. Rubella vaccine may lower the number damaged in the future. (American Annals of the Deaf)
totally deaf		236,000		
other hearing impairments		8,500,000		
Speech impairments		10,000,000	500,000,000	Hearing and speech impairments frequently occur together, making it difficult, statistically, to separate them. (Report of the Subcommittee on Human Communication and Its Disorders, 1969; NINDS)

REFERENCES

1/ Deaths during 1968 from Division of Vital Statistics, National Center for Health Statistics, Department of Health, Education, and Welfare.

2/ Morbidity estimates obtained from the respective voluntary associations.

3/ Costs calculated on these assumptions per year for maintenance:

a. Partially disabled individual: $500 drugs, physicians' fees, and special management.

b. Totally disabled individual cared for at home: $2,000.

c. Totally disabled individual cared for in public and private institutions: $2,500 to $7,500.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Statistics covering the annual number of deaths and reported illnesses caused by selected diseases dealt with in the National Institute of Allergy and Infectious Diseases are presented in Table I. Only those deaths and new cases reported by professional health personnel are included. Table II reports annual disability and estimated cost to the Nation of infectious and parasitic, and respiratory diseases.

Table I

Category	Morbidity 1969	Mortality 1968
I. Parasitic Infections		
Amebiasis	2,915	51
Malaria	3,102	7
Trichinosis	215	0
Schistosomiasis	205 (3) 1/	0
Ascariasis	418 (6)	7
Toxoplasmosis	63 (7)	0
II. Bacterial Diseases		
Brucellosis	235	1
Diphtheria	241	30
Leptospirosis	89	9
Meningococcal Infections	2,951	741
Pertussis (whooping cough)	3,285	36
Salmonellosis (excluding typhoid)	18,419	70
Tularemia	149	1
Tetanus	192	86
Tuberculosis	38,650	6,292
Typhoid Fever	364	7
Strep sore throat and scarlet fever	450,008	28
Rheumatic fever	3,229 (37)	363
Septicemia (Blood Infections)	Unreported 2/	2,991
Shigellosis	11,946	0
Venereal Disease (new cases)		
Syphilis	92,162	586
Gonorrhea	534,872	1
Other	1,778	6
III. Rickettsial Diseases		
Typhus (including Rocky Mountain Spotted Fever)	534	2
IV. Viral Diseases		
Chickenpox	97,329 (43)	99
Encephalitis (Acute)	1,613	744
Hepatitis	54,325	877
Influenza	Unreported	7,062
Measles (Rubeola)	25,826	24
Mumps	90,918	25
Mononucleosis	10,059 (33)	14
Poliomyelitis	20	130 3/
German Measles (Rubella)	57,686	24

1/ Figures in parenthesis indicate number of states reporting, if less than complete.

2/ Though widespread, some diseases must be listed as "unreported" because accurate diagnosis depends on laboratory tests generally not carried out. However, in the period July 1967-June 1968, an estimated 80.2 million conditions were reported as "influenza-like illnesses".

3/ Many of these deaths occurred at least 1 year after the disease was contracted.

Table I. (Continued)

Category	Morbidity 1969	Mortality 1968
V. Fungal Diseases		
Actinomycosis	13 (9)	16 3/
Coccidiodomycosis	903 (12)	58
Blastomycosis	30 (10)	111 3/
Histoplasmosis	158 (14)	58
VI. Multiple or Unspecified		
Acute Respiratory Infections	447,498 (18)	784
Bronchitis	Unreported	7,637
Pneumonia	Unreported	66,430
Gastroenteritis (in persons 4 weeks of age and over)	Unreported	2,219
VII. Allergic Disorders		
Asthma	Unreported	3,862 4/
All Others	Unreported	51
TOTALS	1,952,400	98,549

4/ Adjusted to reflect changes in International Classification of Diseases.

Morbidity statistics taken from Annual Supplement, Summary 1969, MORBIDITY and MORTALITY Weekly Report, Vol. 18, No. 54, Center for Disease Control, Atlanta, Georgia.

Mortality Statistics were furnished by the Mortality Statistics Branch, Division of Vital Statistics, National Center for Health Statistics, Rockville, Maryland.

Table II

Cost to the Nation's Populace - 1968

ITEM	Combined Total: Infectious, Parasitic & Respiratory Diseases		Infectious & Parasitic	Respiratory
	Number	Percent of all Acute Conditions		
Number of cases	280,067,000	70.1	41,592,000	238,475,000
Restricted activity (days)	1,032,716,000	60.9	164,025,000	868,691,000
School loss (days)	155,892,000	81.3	33,209,000	122,683,000
Work loss (days)	167,257,000	59.3	18,119,000	149,138,000
Work loss (cost)	$4,348,682,000	59.3	$471,094,000	$3,877,588,000

From VITAL AND HEALTH STATISTICS Data from the National Health Survey, Series 10, Number 56, Current Estimates from the Health Interview Survey -- United States -- 1968. National Center for Health Statistics, Health Services and Mental Health Administration, PHS, DHEW.

Work loss cost based on average income of full-time workers, all industries, 1968, $6,454 annually or approximately $26 per day for 256 working days. Department of Commerce, National Income Division, Personal Income Section.

Morbidity from Visual Disorders

Department of Health, Education, and Welfare

National Eye Institute

Statistics on the number of disabilities caused by the major diseases dealt with in the National Eye Institute, and the estimated annual cost of visual disorders to the nation.

Range and Cost of Major Vision Disorders, U.S.

Disability Category	Estimated Total Cases	Estimated Annual Cost of Care	Remarks
Eye Disorders		$2.4 billion (est.)	An estimated 77 percent of legally blind population in the U.S. is 40 years old or over. (National Society for the Prevention of Blindness, 1966) Estimate of the partially seeing: National Center for Health Statistics.
Legally blind	446,500		
Partially blind	13,620,000		

HIGHLIGHTS OF PROGRESS IN RESEARCH
Conducted and Supported
by the
NATIONAL INSTITUTES OF HEALTH
1970

CANCER

Several milestone discoveries of 1970, achieved by scientists working with the aid of National Cancer Institute funds, offer the hope of understanding and eventually controlling cancers in man.

FIRST SYNTHESIS OF A GENE

The first complete synthesis of a gene was announced in June 1970 by Dr. H. Gobind Khorana at the University of Wisconsin after 10 years of grant support from the NIH National Cancer Institute. A Nobel prize winner in 1968, Dr. Khorana had worked out with Dr. T. Mathai Jacob a method of building, step by step, nucleotide chains which are sub-units of DNA, the master chemical of cells. In the more recent achievement he had duplicated the structure of yeast DNA which in turn synthesizes alanine transfer RNA. His feat in creating this first complete gene offers hope of eventual synthesis of other more complex genetic chemicals. If, as many scientists believe, cancer is a disease of cells caused by a faulty gene or genes, Dr. Khorana's findings may eventually permit the replacement or alteration of such genes, thus correcting the genetic error that is cancer.

GENES IN ACTION

A "candid camera" view of bacterial genes in action was reported in July 1970 by scientists financed in part by the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, the U.S. Atomic Energy Commission, and the National Science Foundation. Using the electron microscope, a team of investigators headed by Dr. Oscar L. Miller, Jr. of the Oak Ridge National Laboratory were able for the first time to directly observe the production of proteins -- an essential life process. Viewing the electron micrographs, the scientists were able to distinguish genes, enzymes, and other components of the cells' production line for proteins. Such observations will prove useful if and when correction of genetic errors associated with human cancer and other diseases comes within reach.

CENTRAL DOGMA MODIFIED

In June 1970, NCI grantees Drs. Howard M. Temin and Satoshi Mizutani at the University of Wisconsin's McArdle Laboratory for Cancer Research electrified the scientific world with findings, published in the scientific journal Nature, that seemed a reversal of a central dogma of molecular biology. Until that time, the cell chemical called DNA or deoxyribonucleic acid was generally regarded

as the unique and only gene material of cells. RNA or ribonucleic acid was considered to be a servant chemical in the cell, usually formed from a DNA blueprint to carry out instructions coded in the DNA. Instead, said the scientists, in some instances at least, RNA is the blueprint from which DNA is formed, and in those instances controls the cell's heredity.

VIRUS-CANCER RESEARCH

The astonishing report by Drs. Temin and Mizutani had particular impact on the cancer research community since the revolutionary events they had documented were occurring in cells infected with a cancer-causing RNA virus. This was the Rous sarcoma virus that causes cancer in chickens. Drs. Temin and Mizutani reported that the Rous virus contains an enzyme or catalyst called RNA-dependent DNA polymerase that uses RNA as a blueprint to make DNA.

In the same issue of Nature (June 27, 1970), Dr. David Baltimore of the Massachusetts Institute of Technology, supported by the National Institute of Allergy and Infectious Diseases as well as by the National Cancer Institute, also reported the presence of the new-found enzyme in the Rauscher virus that causes leukemia in mice as well as in the Rous virus of chickens.

With these findings cancer scientists for the first time can explain how RNA tumor viruses, after penetrating a cell, take over its reproductive machinery and produce new generations of altered or cancerous cells from an RNA virus blueprint.

CONFIRMATION OF NEW ENZYME

In August 1970, Dr. Sol Spiegelman of Columbia University's College of Physicians and Surgeons provided quick confirmation of the Temin/Mizutani/Baltimore results and extended their findings to other species. In research supported by the NCI's Special Virus Cancer Program, he reported the presence of the RNA-dependent DNA polymerase in seven RNA viruses associated with tumors of mice, cats, monkeys, and birds.

In October 1970 Dr. Brenda Gerwin of the U.S. Atomic Energy Commission laboratories in Rockville, Maryland, working with Dr. George J. Todaro and his colleagues at NCI, characterized the enzyme's activity in two strains of mouse leukemia viruses. Using detergents to separate the enzyme from virus particles, they found its activity associated chiefly with the nucleus. Moreover, they were able to inhibit the enzyme's activity almost completely in the nucleus and soluble portions of the virus by the use of blood serum obtained from rats bearing antibodies to a cancer-causing virus of mice.

LINK TO HUMAN LEUKEMIA

In November 1970 Dr. Robert C. Gallo of NCI's Human Tumor Cell Biology Branch, with colleagues at Bionetics Research Laboratories under contract to NCI, reported the discovery of the RNA-dependent

DNA polymerase enzyme in white blood cells from 3 patients with acute leukemia. The enzyme was not detected in white blood cells from 48 normal blood donors. Because this enzyme seems always present in RNA tumor viruses of animals, its discovery in cells from leukemia patients is considered good supportive evidence that viruses are associated with cancers in man. Moreover, Dr. Gallo reported that in test tube experiments with white blood cells from leukemia patients an antibiotic called n-demethyl rifampicin was able to inhibit completely the enzyme's activity. Previously Dr. Maurice Green of St. Louis University, with contract support from NCI's Special Virus Cancer Program, had discovered that the compound was able to inhibit the enzyme in cells from animals.

NEW THEORY OF INHERITED CANCER GENE

In September 1970 Dr. Robert J. Huebner of NCI and his colleagues proposed in the Proceedings of the National Academy of Sciences that an inherited cancer gene present even before birth could also be a growth factor in the developing embryo. The inherited genetic material, which is common to a group of RNA viruses that cause cancers in mice, chickens, hamsters and cats, was detected through its "footprints" in healthy embryos of both laboratory-bred and wild mice.

In 1969 Dr. Heubner and Dr. George J. Todaro, also of NCI, had first presented their theory of the oncogene (tumor gene), suggesting that an inherited cancer gene is present from conception throughout life, even though inactive as a cancer-causing agent. According to the concept, its genetic activity is somehow "switched off" for cancer at an early age; it lies dormant until it may be "switched on" again by the ageing process or environmental agents.

In December 1970 Dr. Huebner received the prestigious Rockefeller Public Service Award in science and technology, presented annually to an American career civil servant. Early in 1970 he had accepted the National Medal of Science from President Nixon, and in October shared the 1970 Kimble Methodology Award with Dr. Janet W. Hartley of the National Institute of Allergy and Infectious Diseases for significantly advancing methodology and knowledge in virus and tumor studies.

Late in December Dr. George J. Todaro was selected by the U. S. Jaycees as one of America's Ten Outstanding Young Men of 1970, an honor he received at ceremonies in Memphis on January 16, 1971. Dr. Todaro was cited for his 12-year career in cancer research.

In May 1970 two other NIH scientists made a finding that offers support for the oncogene theory proposed by Drs. Huebner and Todaro in 1969. Dr. Robert Stern of the National Institute of Dental Research and Dr. Robert M. Friedman of the National Cancer Institute reported in Nature that double-stranded RNA, previously believed unique to viruses, is present in apparently normal uninfected cells as well as infected cells. Small amounts of double-stranded RNA (2% of the total RNA) were found in cells from normal and diseased humans and even in cells from germfree chick embryos. The

scientists suggested that the double-stranded RNA, because it was found in all cells examined, may be part of the cell's normal machinery or it may be a latent "RNA gene" that if activated can cause disease.

CANCERS OF BREAST AND CONNECTIVE TISSUE

In April 1970 Dr. Harish C. Chopra of the John L. Smith Memorial for Cancer Research, Chas. Pfizer & Co., under contract to the National Cancer Institute, reported observing large numbers of viruses in breast tissues obtained from an unbred, middle-aged female rhesus monkey with breast cancer. The viruses, seen under the electron microscope, were similar in size and shape to RNA viruses that cause cancer in other species, and like particles found occasionally in the milk and breast tissue of women with breast cancer. The report on the monkey, one of an NCI-supported monkey colony at Mason Research Institute in Worcester, Massachusetts, was presented at the annual meeting of the American Association for Cancer Research.

At the same meeting, Dr. William F. Feller of Georgetown University and his colleagues at Sloan-Kettering Institute for Cancer Research reported on NCI-supported studies in which type-C RNA viruses have been continually obtained from a tissue culture of human breast cancer cells. (Establishment of the human breast cancer cell line, designated BeLev, was described in the "Highlights of NIH Research during 1969".)

In May 1970 Dr. Donald L. Morton of NCI reported at the 10th International Cancer Congress that a virus is associated with a wide variety of human cancers of connective tissue. Dr. Morton described immunologic and electron microscopic evidence that suggests a possible viral cause of such cancers of bone, cartilage, muscle, tendons, joints and fatty tissue. A type-C RNA virus was implicated through electron microscopic studies reported earlier by Dr. William T. Hall of NCI.

DNA VIRUSES

In April 1970 a team of NCI scientists headed by Dr. Paul H. Levine presented evidence suggesting that a virus of the DNA type may play a role in Hodgkin's disease, a cancer of the lymph system that usually affects young adults. Dr. Levine and his colleagues found high levels of antibody to a DNA herpes-type virus called the Epstein-Barr (EB) virus in these patients. This is the same virus that is associated with Burkitt's lymphoma, a cancer of the lymph system that occurs most often among African children. Presence of the virus antibody was demonstrated by indirect immunofluorescence tests of blood samples from the Hodgkin's disease patients. There was no significant difference in antibody levels between the normal controls and a group of patients with non-cancerous diseases.

Also in April, Dr. Werner Henle of Children's Hospital, Philadelphia, addressing the American Association for Cancer Research on "Burkitt's Lymphoma, Carcinoma of the Nasopharynx and Infectious Mononucleosis," described research in which he and Dr. Gertrude Henle

found an association of the Epstein-Barr virus with those diseases. Their research was supported in part by a contract with the National Cancer Institute.

Cellular effects of two other DNA viruses, the simian virus 40 (SV40) and polyoma virus, both of which cause tumors in rodents, were described by NIH investigators in the October 1970 Proceedings of the National Academy of Sciences. A team led by Dr. Roscoe O. Brady of the National Institute of Neurological Diseases and Dr. Peter T. Mora of the National Cancer Institute discovered that cells transformed by these viruses have a greatly reduced amount, if any, of an enzyme called amino sugar transferase. Lack of this key enzyme prevents the synthesis of gangliosides, complex fat-like substances that normally are concentrated in cell walls. In the virus-transformed cells, lack of ganglioside synthesis coincides with a profound alteration in the surface properties of the cells, permitting them to grow against each other, pile up and over-run one another, with disregard for the normal behavior pattern of "contact inhibition." In normal cells contact inhibition causes cells to stop growing when they bump into each other, prevents their invading or overrunning one another.

Another DNA virus, the type 2 herpes virus, was shown in 1968 to be associated with human cancer of the uterine cervix. As reported in "Highlights of NIH Research" for that year, NIH-supported scientists at the Emory University and Baylor University Schools of Medicine reported that clinical, laboratory, epidemiologic and immunologic evidence suggested that type 2 herpes virus was a prime suspect in the cause of this third (now forth) most deadly form of cancer in U.S. women. (The number of deaths due to this cancer is declining in the U.S. as a result of wider use of the "Pap test" which detects the disease in its early, usually curable stages.)

In the September 1970 issue of the Journal of the National Cancer Institute, Dr. Laure Aurelian and her colleagues at The Johns Hopkins School of Medicine provided further evidence of the implication of type 2 herpes virus in cervical cancer. She presented immunologic evidence that the virus was present in cells obtained from 95% of women with very early, pre-cancerous "atypical" cells of the cervix studied, as well as in 100% of the cells from women with advanced, invasive cancer of the cervix. (Control populations gave evidence of the virus in 44% and 67% of cervical cells, respectively.)

CANCER DRUGS

During 1970 research on cancer chemotherapy, or drug treatment of cancer, continued to be a major thrust in the Institute's effort to control cancer. Development of new drugs--and of techniques to use established drugs more effectively--were goals actively sought.

Almost 14,800 compounds, including approximately 8,500 synthetic chemicals and 6,300 natural products from fermentation, plant, and animal sources, were tested by NCI as potential anti-cancer agents during 1970.

The compounds were evaluated against mouse leukemia L-1210, a tumor model found to be the most reliable test system for predicting the response of human cancer to drug therapy. In addition, some of the natural products were given a second test, this time against tumor P-388, a mouse leukemia similar to L-1210 but able to detect the activity of smaller quantities of crude material.

As a result of such initial screening against rodent cancers, six materials showed sufficient anti-tumor activity to be selected by NCI scientists for pharmacology-toxicology studies in large animals. Such studies are a prerequisite to drug evaluations in human cancer, in order to assure that the test compounds will be relatively non-toxic and safe to use. Moreover, they help to determine the starting dose for human drug administration, which usually begins in NCI-sponsored drug evaluations at one-tenth the dose tolerated by dog or monkey (whichever is less).

During 1970 six compounds passed the NCI's stringent tests in animals for pharmacologic evidence of activity and safety, and were accepted for study against human cancer. The materials selected for these important tests are guanazole (NSC-1,895); beta-deoxythioguanosine (NSC-71,261); 5-hydroxy-picolinaldehyde thiosemicarbazone (NSC-107,392); adriamycin (NSC-123,127); bleomycin (NSC-125,066); and acronycine (NSC-403,169). During 1970 the National Cancer Institute filed for Investigational New Drug applications with the Food and Drug Administration to conduct clinical studies of all of the foregoing compounds. Then the painstaking, long-term clinical studies were begun to determine whether or not the materials will offer cancer patients therapeutic benefits not now available through conventional methods of treatment.

Three major conferences were sponsored during 1970 by the NCI Chemotherapy Program to communicate to practicing physicians the latest research results achieved with several anti-cancer drugs.

BCNU and 5-FU were the anti-cancer drugs reported on at a conference held January 29-30, 1970 at the Washington Hilton Hotel.

BCNU or 1,3-bis (2-chloroethyl)-1-nitrosourea is one of a class of compounds remarkable for their ability to cross the blood-brain barrier. Reports presented at the January meeting on NCI-sponsored clinical studies of BCNU showed it to be useful in the treatment of advanced Hodgkin's disease (a cancer of the lymph system). Some degree of anti-cancer activity was also reported for BCNU in treating gastrointestinal cancer, melanoma, lung cancer and brain tumors.

5-FU or 5-fluorouracil is an antimetabolite that is erroneously accepted as a metabolite or nutrient by cells, particularly cancer cells, subsequently blocking their growth. 5-FU's temporary usefulness in some cases of gastrointestinal cancer and breast cancer has been known since the early '60's. At the January 1970 meeting, new evidence was presented on longer, symptom-free periods achieved in cancer of the large intestine when the drug is given after surgery, in contrast to results achieved by surgical treatment alone. New information on the optimum scheduling of 5-FU doses -- without

the conventional "loading dose" so widely prescribed--was presented, as well as several reports on the use of 5-FU in combination with other drugs or radiotherapy.

Procarbazine (Matulane R), a new drug that is a close chemical relative of a rocket fuel component, was the subject of NCI's second chemotherapy conference of 1970, held at NIH on March 13. Originally called methyl hydrazine derivative, procarbazine has been found useful in advanced Hodgkin's disease when used as a single agent or in combination with other cancer drugs. Procarbazine is also active against two other cancers of the lymph system, reticulum cell sarcoma and lymphosarcoma, although to a lesser extent than against Hodgkin's disease. A key report at the March 13 conference concerned procarbazine's use in a 4-drug combination effective in advanced Hodgkin's disease.

Ortho para'-DDD and mithramycin were the anti-cancer drugs reported on at NCI's November 5-6 meeting, held at NIH and attended by physicians from 20 States and the District of Columbia.

Ortho para'-DDD, a drug related to the insecticide DDT, was reported as helpful in some patients with advanced cancer of the adrenal cortex. Also described was its usefulness in some cases of Cushing's disease, a rare disease of abnormal growth characteristics sometimes due to an adrenal tumor. Ortho para'-DDD was marketed as "Lysodren" by Calbiochem in 1970 after its approval as a prescription drug by the Food and Drug Administration.

Mithramycin, an antibiotic useful in some cases of inoperable cancer of the testes, was marketed by Chas. Pfizer & Co. under the trade name "Mithracin" after FDA approval earlier in the year. At the November 1970 conference, its use in Paget's disease of bone and in problems of calcium imbalance as well as in testicular cancers was described.

In August 1970 National Cancer Institute scientists reported that a 4-drug treatment developed in 1964 for use in advanced Hodgkin's disease is more than doubling the survival time of patients who respond to treatment. Thirty-five of 43 patients (81 percent) treated at the beginning of the study with the four drugs (vincristine, procarbazine, prednisone, and an alkylating agent) responded with a complete remission. This is 4 times the rate of complete remission usually achieved in advanced Hodgkin's disease. As of August 1970 the median duration of the complete remissions was between 29+ and 42+ months after the end of therapy. The longest continuing complete remission was then lasting 52+ months. Seventeen patients among the 35 complete responders (48 percent) remained free of all evidence of cancer.

A potential treatment for some patients with a rare cancer called melanoma that sometimes develops on the skin from a mole was described in April 1970 in an NCI-sponsored journal called Cancer Chemotherapy Reports. NCI grantees, cooperating in the Southwest Cancer Chemotherapy Study Group, reported results of an initial study of a new drug, imidazole carboxamide (NSC-45388), developed by the NCI

Chemotherapy Program. In this preliminary study, the optimum daily dose was found to range from 200 to 500 milligrams per square meter of body surface. Most patients received 250 milligrams per square meter per day for five days every three weeks. Of 110 patients with advanced melanoma no longer responsive to conventional therapy, 21 (19 percent) achieved objective tumor response, that is, they experienced a temporary remission of their disease that lasted from 1 to 8 months. The median duration of response was 3 months. Of the 21 patients, 5 patients achieved complete responses, the temporary disappearance of all evidence of disease. The other 16 patients had partial responses, that is, their tumors were reduced more than 50 percent, but did not completely disappear. Although early stages of melanoma are sometimes cured by surgery, previous attempts to treat advanced melanoma with cancer drugs have been largely unsuccessful.

In December 1970 the NCI Clinical Investigations Branch organized a 2-day meeting for scientists cooperating in the evaluation of anti-cancer drugs and in the surgical and radiation treatment of cancer at 250 medical centers. Workshops and group discussions were aimed at improving the design and therefore the effectiveness of prospective randomized controlled studies of cancer therapy. With the cooperation of statisticians, chemotherapists, surgeons and radiation therapists, improvements in drug and other treatment protocols were arrived at, for application against various forms of cancer.

The value of estrogen in treating advanced cancer of the prostate was established in 1941, and the hormone had been used widely by physicians until 1967 when scientists of the NCI and Veterans Administration reported a higher-than-normal rate of heart attacks and strokes among estrogen-treated patients. In August 1970 Dr. John Bailar and colleagues at the NCI and VA reported preliminary findings of a study of the effects of various estrogen doses. They discovered that a 1 milligram daily dose, which was substantially lower than that previously used, appeared to have as great an anti-cancer effect as the higher dose, yet spared patients from the excess risk of cardiovascular damage. The study will be continued but preliminary findings were reported because of their therapeutic implications.

Choriocarcinoma, a rare cancer of the uterus that sometimes occurs following pregnancy, was found curable over a decade ago in a majority of patients given anti-cancer drugs. Since many of the drugs are known to produce malformations in the offspring of animals that receive them early in pregnancy, NCI scientists examined the reproductive experience of women treated for choriocarcinoma and closely related disease. The study group consisted of 91 such women treated successfully at NIH between January 1956 and January 1969, and for whom pregnancy was proscribed for one year following drug treatment. In the subsequent years, NCI scientists reported in 1970, there was no evidence of increased incidence of fetal mortality, congenital abnormality nor complicated pregnancy among the patients who received drug treatment for rare cancers of this type.

NEW LEADS IN CANCER CHEMOTHERAPY

In November 1970 Dr. Robert C. Gallo of NCI reported on test tube experiments in which a derivative of an antibiotic called rifampicin was able to inhibit completely an enzyme found in the white blood cells of leukemia patients. The enzyme, called RNA-dependent DNA polymerase, had been reported earlier in the year to be associated with certain viruses that cause cancer in animals. (See above.) In laboratory experiments with human leukemia cells, Dr. Gallo and his colleagues found that although the antibiotic rifampicin was able to block the enzyme's activity only to a small degree, a related compound, n-demethyl rifampicin, was able to inhibit it completely. During 1971, n-demethyl rifampicin and other closely related compounds will be evaluated by NCI scientists for possible effectiveness against cancers in animals. If found active against animal cancers, they will then have to be demonstrated to be relatively non-toxic before they could be evaluated against human leukemia or other forms of human cancer.

Also in November 1970 Drs. Max M. Burger and Kenneth D. Noonan of Princeton University, working with NCI grant support, reported in the journal Nature on experiments with trypsinized Concanavalin A (Con A), a protein obtained from the jackbean plant. The NCI-grantee scientists found that this protein agglutinates, adheres to and clumps malignant cells of the mouse growing in tissue culture. By so doing, it covers up an exposed layer of surface receptors on these cells, mimicking the surface pattern of normal cells and restoring their growth pattern to the normal state of "contact inhibition." Con A's effectiveness in returning malignant cells to a normal growth pattern continues until the cover layer is removed. These findings have aroused the interest of NCI scientists engaged in chemotherapy research, and during 1971 they will evaluate Concanavalin A's effects on the growth of cancer in animals.

CHEMICAL CAUSES OF CANCER

A 100-page report, "Progress Against Cancer 1970," (PAC '70)was released in December 1970 by the National Advisory Cancer Council as its fourth annual report to the public on the state of cancer research. Prepared with the assistance of National Cancer Institute staff, PAC '70 describes various types of chemical pollution that are known to cause cancer. Environmental agents, occupational chemicals, and carcinogens in air, food, drugs, and especially in cigarette smoke, are discussed.

Pinpointing cigarette smoking as a "private pollutant," PAC '70 cites the more than 60,000 deaths a year in the United States from an "epidemic" of lung cancer attributed mainly to cigarette smoking. In its publication, the Council spells out the scientific bases for the new Federal restriction on cigarette advertising, which went into effect January 2, 1971.

In early 1970 the National Cancer Institute issued Supplement 2 to "Survey of Compounds Which Have Been Tested for Carcinogenic Activity," covering the years 1954 through 1960. It will be followed

by three additional supplements to cover 1968-69, 1961-64, and 1965-67, respectively, the first of these to be published by the end of FY 1971.

Another National Cancer Institute publication, "Carcinogenesis Abstracts," was issued regularly during 1970 to bring together information about work being done in all fields of carcinogenesis and encourage interdisciplinary communication. Accordingly, "Carcinogenesis Abstracts" provides a central source for accurate summaries of carcinogenesis literature published throughout the world

To improve the efficiency of research for the identification of cancercausing substances in the human environment, in November 1970 the NCI initiated a special study at the Stanford Research Institute of Menlo Park, California. The study was designed to establish priorities for screening in laboratory animals of the countless new compounds introduced into the environment each year, in addition to those already in existence. Researchers are engaging in a broad assessment of the environment. Industrial chemicals, foodstuffs, air and water pollutants are among the thousands of materials being considered.

The NCI continues to test and retest environmental chemical pollutants including agricultural chemicals such as pesticides, artificial sweeteners such as cyclamates and saccharin, food preservatives, hormonal compounds generally used as oral contraceptives, and natural products of various molds and fungi. Substitutes for those compounds found to be carcinogenic are also being tested.

Scientists continue to investigate the cancer-causing potential of nitrosamines, a class of compounds known to induce tumors in many animal models. As there is no evidence that man is immune to their action, nitrosamines are being tested alone and in combination with other elements. Sometimes nitrosamines are formed when foodstuffs combine with chemicals in the digestive system. Others are preformed as in tobacco smoke, grains and alcoholic beverages, where they are present in concentrations of less than five parts per million. Higher concentrations of nitrosamines have been found in some nitrite-preserved fish meal intended for animal feeds.

A report in the March 1970 issue of the Journal of the National Cancer Institute by Dr. Sidney S. Mirvish of the Weizmann Institute of Science in Isreal, partially supported by a Public Health Service contract with the NCI, suggests that nitrosamines may be formed in foods stored under mildly acidic conditions.

Drs. Roger W. O'Gara and Richard H. Adamson of NCI, with Dr. Dan W. Dalgard of Hazleton Laboratories, reported in April 1970 that two chemicals of the nitrosamine family, diethylnitrosamine and 1-nitrosopiperidine, are potent inducers of liver cancer in four species of primates. Moreover, an abnormal protein called alpha-fetoprotein, a specific marker for liver cancer in monkeys and man, was found in the blood of 60 percent of the monkeys with cancers induced by nitrosamine given orally, and in 97 percent of those whose cancers were induced by injections of nitrosamine.

In May 1970 National Institutes of Health scientists reported in Science that a commonly used herbicide called 2,4,5-T produced deformities and death in a high proportion of mouse and rat fetuses tested. The investigations by Drs. K. Diane Courtney and associates of the National Institute of Environmental Health Sciences and Drs. Richard R. Bates and Ian A. Mitchell of the NCI, are being extended to determine the possible role of a contaminant, tetrachloro dioxin.

Other ongoing studies at the NCI, with expanding cooperation from the Food and Drug Administration and the Department of Agriculture, include investigation of tobacco carcinogens, certain anti-cancer drugs, polyurethanes, asbestos, and a wide range of food additives.

IMMUNOLOGIC APPROACHES TO CANCER

A promising new approach to cancer therapy, application to the skin of small quantities of chemicals that produce an inflammatory reaction of the delayed hypersensitivity type, was described by NCI grantees Drs. Ashbel C. Williams and Edmund Klein of the Roswell Park Memorial Institute in Buffalo, New York. In the February 1970 issue of Cancer, they described the use of weak concentrations of of DNCB (dinitrochlorobenzene) and TEIB (2,3,5-triethylene-iminobenzoquinone) to treat more than 2,000 skin cancers and pre-cancerous skin conditions in more than 50 patients for more than 5 years. Minimal or no effects on the adjacent normal tissues were produced. The immunotherapy resulted in resolution of more than 95 percent of multiple superficial basal cell cancers tested for observation periods lasting up to 5 years. More than 90 percent of localized squamous cell cancers underwent regressions. Deeper lesions responded less favorable. Further research with this immunotherapy technique may, it is hoped, result in a useful extension of these principles to treating other forms of cancer. Dr. Klein receives support from the National Cancer Institute, the Albert and Mary Lasker Foundation, Hoffmann-LaRoche, Inc., the American Cancer Society, and other groups.

In May 1970, NCI grantee Dr. John A. Cavins of the Children's Cancer Research Foundation in Boston confirmed the pioneering results of Dr. Edmund Klein and his colleagues. At the Tenth International Cancer Congress in Houston, Dr. Cavins reported that TEIB and DNCB had been shown effective in the treatment of pre-cancerous skin conditions (keratoses), superficial basal cell cancers and localized squamous cell cancers in a series of 80+ patients. They also described the use of chemotherapy with a 5-fluorouracil ointment in combination with DNCB as an immunotherapeutic agent to treat a patient with a 20-year history of multiple skin cancers.

Two ways to transfer tumor immunity from one animal to another were reported in 1970 by two groups of NCI scientists.

Drs. Harold T. Wepsic and Herbert J. Rapp of the Biology Branch, NCI, reported at the April 1970 meeting of the American Association for Cancer Research a technique that permits the transfer of tumor immunity among animals of an inbred strain of guinea pigs. By

injecting white blood cells from immunized animals into the hearts of animals not yet immune, they were able to confer immunity. The technique of cardiac injection was usually well tolerated; mortality from the injection was rare. The line of guinea pigs used, like human beings and unlike other laboratory animals, was able to develop vigorous and prolonged delayed hypersensitivity reactions which could be observed on the skin. Results could be read in 24 hours, contrasted with weeks and months for other types of tests. The investigators said that the success of the intra-cardiac technique in these animals indicates that similar techniques might be adopted for use in treating cancer patients by introducing tumor-immune cell fractions into the arteries surrounding human tumors.

Drs. Kenneth P. Ramming and Yosef H. Pilch of the Surgery Branch, NCI, won an award for research excellence in June 1970 from the Student American Medical Association at the AMA meeting in Chicago, for their studies demonstrating another way of transferring cancer immunity from one animal to another. Drs. Ramming and Pilch demonstrated that non-immune rodent spleen cells incubated with RNA from animals immunized against tumors were able to produce immunity in a significant percentage of previously non-immune animals that received injections of these cells. (As discussed earlier, RNA or ribonucleic acid is one of the key chemicals that direct the life processes of all cells.) Furthermore, the NCI scientists demonstrated that transfer of tumor immunity mediated by RNA, which is believed to be chemically similar in all animal cells, takes place between different animal species. This is significant because any future application of this or similar forms of therapy in human cancer would require large amounts of RNA, necessitating the use of animal RNA donors.

In December 1970 NCI scientists Dr. Berton Zbar, Irwin Bernstein, Tomiko Tanaka and Herbert J. Rapp reported in the journal Science on an immunizing technique utilizing a vaccine against tuberculosis called BCG. In their research, tumor cells obtained from guinea pigs were mixed with TB vaccine (living Mycobacterium bovis of strain BCG), and the mixture was injected into the skin of unimmunized guinea pigs. An inflammatory response to the BCG occurred, and there was no progressive tumor growth. Without BCG, the tumors grew progressively, spread through the animals bodies and killed them. Moreover, Drs. Zbar and his colleagues reported that animals immunized in this way were subsequently capable of suppressing the intradermal growth of tumor cells even when inoculated with ten times the usually lethal dose. The scientists conclude that improved immunity to tumors may be possible by mixing some of an individual's own tumor cells with BCG and then re-inoculating them into the individual.

In July 1970 a NCI surgeon, Dr. Donald L. Morton, reported in the journal Surgery on his studies of BCG in the treatment of melanoma, an often fatal cancer that may develop on the skin from a pre-existing mole. Dr. Morton reported that during the past two and one-half years he had treated eight patients with widespread melanoma that was incurable by surgery with inoculations of BCG directly into the melanoma nodules. This therapy produced a rise in

antimelanoma antibody and temporary tumor regressions in five patients. One of the patients had a complete remission and remained free of disease at the time of the report, two years following treatment. Dr. Morton suggested that active immunotherapy with BCG or other agents will be most useful in those melanoma patients who are immunologically competent and have localized disease that can be treated surgically.

HEART AND LUNG DISORDERS

ARTERIOSCLEROSIS

Nearly one-fourth of initial non-fatal heart attacks may not be recognized by the patient or his physician, data from the NHLI Framingham Study indicate. However, these "silent" heart attacks appear to pose the same threat of recurrent attacks and death as do those with more dramatic onset.

Of 188 documented first heart attacks occurring in the Framingham Study population during 14 years of surveillance, 44 were unrecognized at the time they occurred. The attack was verified only when the unsuspecting victim subsequently reported for his routine biennial examination and ECG.

About half of these unrecognized attacks produced no pain or other symptoms that the patients could recall. The remainder produced such mild or atypical symptoms that the patients ascribed them to other ailments, such as gallbladder disease, hiatus hernia, or stomach ulcers.

The outlook for "silent" heart attack victims was no better than that of survivors of overt first heart attacks, the study revealed. Within five years, one-third of the patients experienced recurrent attacks, half of which were fatal.

Dr. William B. Kannel and co-workers state that frequent periodic use of the ECG is presently the only practical means of detecting the "surprisingly common" silent heart attack. They urge its routine use especially in those persons with diabetes, hypertension, ECG abnormalities and other conditions known to increase the threat of coronary heart disease and acute heart attacks.

Evidence that sustained lowering of blood lipid levels may benefit patients with angina pectoris is provided by Dr. Henry Buchwald and co-workers, of the University of Minnesota, as an incidental finding of a seven-year study of ileal bypass. This is a heroic procedure for lowering blood lipids by surgically detouring the upper part of the small intestine around its ileal section and thereby decreasing the absorption of dietary fat. In 70 patients, the procedure reduced blood cholesterol and/or triglyceride levels by an average of 45%.

Of 42 patients with angina prior to operation, 36 (85%) had

reported subjective improvement. Improvement has been rated moderate in 8 patients, who have experienced reductions in the frequency and severity of angina episodes and in their requirement for nitroglycerine. Marked improvement has been noted in 28 others, as evidenced by substantial increases in exercise tolerance or complete remission of angina episodes. Only 6 have reported no improvement, 2 of whom have been followed for only 3 months.

None of the 28 patients without angina before operation have subsequently developed symptoms.

The reasons for this improvement are not clear, although preliminary studies have ruled out decreased blood viscosity as a factor. It is tempting to speculate that the blood-lipid reductions may have caused some regression of the coronary atherosclerotic lesions and improved coronary bloodflow, but objective evidence of this is lacking.

Type II hyperlipoproteinemia is characterized by abnormally high blood concentrations of low-density (beta) lipoproteins, the major transport vehicles for plasma cholesterol, and by elevated blood cholesterol levels. It is a common disorder, very often familial, and carries high risk of premature atherosclerosis. Familial Type II is transmitted as a Mendelian dominant trait, and hence occurs with high frequency among the children and kindred of affected individuals.

Studies by Dr. Peter O. Kwiterovich and co-workers, of the NHLI Molecular Diseases Branch, indicate that familial Type II can be diagnosed from birth and the blood lipid abnormality improved or corrected during childhood with therapeutic diets supplemented, as necessary, with the lipid-lowering drug cholestyramine.

The scientists studied 265 children under 20, one or both of whose parents were Type II heterozygotes. Determinations were made of 1) total blood cholesterol and 2) cholesterol bound to beta lipoproteins.

Of the children tested, 138 were normal while ten of the children were Type II homozygotes, with gross cholesterol elevations. Nine of the homozygous abnormal children had xanthomas and 6 had evidence of blood-vessel disease. Combined therapy with the Type II lipid-lowering diet and cholestyramine improved, but did not correct the blood-lipid abnormality.

The rest of the children were found to be heterozygous with moderate elevations of cholesterols. Only 6 had xanthomas and only 1 had evidence of blood-vessel disease. In a group who were treated as outpatients with the Type II therapeutic diet, cholesterols fell by 12 to 14%. In 6 others, treated as inpatients with the Type II diet plus cholestyramine, cholesterols were lowered well into the normal range.

Dr. Richard E. Green and co-workers, of the New York University Medical Center, report excellent results of microsurgery to improve

the blood supply to the hearts of 32 patients with severe coronary artery disease. All of the patients had incapacitating angina; 31 had severe atherosclerosis affecting more than one of the major coronary arteries; and 21 had already experienced one or more acute heart attacks.

In 26 patients, the internal mammary artery (which normally supplies blood to the left side of the chest) was mobilized and spliced end-to-side into the left anterior descending coronary artery at a point "downstream" from any major atherosclerotic obstruction. Eleven of these also received venous grafts that conveyed blood from the ascending aorta into the right coronary branch.

Five patients received branched venous grafts from the ascending aorta into two coronary branches. The remaining patient had such extensive coronary atherosclerosis that no suitable site could be found for splicing the internal mammary artery directly into the coronary circulation, so the artery was implanted into the heart muscle.

There were 5 postoperative deaths, only 2 of which appeared to be due to cardiac causes. All except 3 of the survivors have remained free of angina and have experienced marked increases in exercise tolerance.

After an acute heart attack, an increase in left ventricular cavity size that either does not subside or else is augmented during the recovery period bodes ill for the patient, according to findings reported by Dr. John Ross, Jr. and co-workers at the University of California, San Diego.

Earlier, the scientists had developed a technique for determining left ventricular cavity size from ECG-synchronized X-rays of the chest. The method was reliable and permitted serial determinations even in critically ill patients.

Using the technique for serial determinations of left ventricular cavity size in 28 patients who had experienced acute heart attacks, the scientists found that

- 18 patients experienced increases in left ventricular cavity size that subsequently returned to normal during the recovery period. All of these patients survived.
- the other 10 patients experienced increases that did not subside or else were augmented during the period of followup. All but 1 died within 6 months.

The scientists conclude that their X-ray technique is a useful means of assessing responses to therapy in heart-attack patients and that abnormalities in left ventricular cavity size appears to have important prognostic implications.

Drs. K.T. Lee and W.A. Thomas, of Albany Medical College, have

developed a model of advanced coronary heart disease in pigs strikingly similar to that occurring in man and commonly attended by such clinical manifestations of the naturally occurring disease as heart attacks and sudden death.

Their research promises to fill a need that has long hampered research on acute heart attacks and their potentially lethal consequences: an animal model that closely duplicates the heart-muscle damage, circulatory alterations, physiological consequences, and potential complications of advanced coronary heart disease and acute heart attacks in man.

The technique combines various elements of several techniques developed previously: 1) a high-cholesterol diet to raise blood lipid levels; 2) blockage of normal thyroid function to drive blood lipids still higher; 3) excess calciferol (a vitamin D derivative) to raise blood calcium levels and to produce the calcified deposits characteristic of advanced atherosclerotic deposits in humans; and 4) tissue-damaging doses of X-rays to the coronary arteries to facilitate invasion of the arterial walls by lipids from the blood.

Pigs subjected to this regimen characteristically developed advanced coronary artery disease within 2 months and an extremely high incidence of heart attacks and sudden death soon thereafter. Both the coronary arterial lesions and the heart damage resulting from the induced heart attacks closely resembled in extent, severity, and location, that commonly encountered in clinical situations.

HYPERTENSION

Norepinephrine, released into the blood from the adrenal glands during exertion or emotional stress, is a powerful heart stimulant and blood vessel constrictor. It is the chemical messenger, or neurohormone, of the sympathetic nervous system, released by sympathetic nerve impulses from its storage sites at peripheral nerve endings to convey their messages to target organs. In the cardiovascular system, increased sympathetic activity results in stimulation of the heart, blood-vessel constriction, and increases in blood pressure.

Some derangement in norepinephrine metabolism causing a surfeit of the neurohormone and excessive sympathetic activity has long been suspected of being a factor in essential hypertension, but has never been convincingly demonstrated. Recent studies by NHLI scientists, conducted in a strain of rat that spontaneously develops hypertension closely resembling the disease in humans, suggest instead that a deficiency of norepinephrine in the hypothalmus and lower brain stem may underlie the hypertension in these animals.

The hypothalamus and brain stem are thought to be the control centers of the autonomic nervous system. Drs. Yukie Yamori, Walter Lovenberg, and Albert Sjoerdsma, of the NHLI Experimental Therapeutics Branch, found that spontaneously hypertensive rats had significantly lower norepinephrine concentrations and slower rates of norepinephrine synthesis in these brain regions than did normal rats.

When brain norepinephrine synthesis was stimulated in the hypertensive rats by administering a norepinephrine precursor, the blood pressure of these animals fell.

The findings raise the possibility that norepinephrine, although acting as a stimulant at peripheral sympathetic nerve endings, may have some quite different function in the hypothalamus and brain stem, possibly as a neurohormone in a regulatory mechanism acting to curb sympathetic activity.

Cadmium, a metal with no known biologic function, is found in trace amounts in a wide variety of foods and beverages. When ingested, it tends to accumulate in the kidneys. Earlier studies by Schroeder and co-workers, of Dartmouth, showed that introducing trace quantities of cadmium into the drinking water of rats from birth resulted later on in hypertension that strikingly resembled essential hypertension in humans. Autopsy studies also indicated that kidneys from previously hypertensive humans consistently contained higher cadmium concentrations than did those from previously normotensive subjects, suggesting that this trace metal might somehow operate in the development of the disease.

Recently, the studies of Drs. H. M. Perry, Jr. and M. W. Erlanger, of Washington University of St. Louis, have provided a possible explanation for the hypertension induced in the rat by cadmium. They found that small acute doses of cadmium, whether administered by injection or orally in the animals' drinking water, produced substantial and sustained increases in the renin activity of plasma. Renin is an enzyme thought to be produced and stored in a type of cell, called juxtaglomerular, from its position adjacent to the glomeruli, the plasma filtration units of the kidney. A drop in renal blood pressure or bloodflow is believed to cause these cells to produce and release into the blood increased quantities of renin. In the blood, renin catalyzes the production of angiotensin II, a powerful blood-vessel constrictor. Angiotensin appears to be the initiator of the hypertension resulting from certain kidney diseases or renal arterial obstructions. It appears from these studies that cadmium may serve as a trigger for the renin-angiotensin system.

Plasma renin activity became elevated within 1 minute after peritoneal cadmium injection, reached peak levels after 1-8 hours, but was still nearly twice normal control levels after one month. After oral cadmium administration, the increases in plasma renin activity were neither so rapid nor quite so pronounced as following cadmium injection, but were substantially elevated from the first week on.

Dr. William B. Kannel and co-workers, of the NHLI Framingham Study, report that hypertension appears to be the most common and most potent factor increasing risk of stroke and that control of hypertension--whether labile or fixed, systolic or diastolic, and whatever the patient's age or sex--appears to be central to stroke prevention.

In this study, hypertensive subjects (blood pressures of 165/95 or greater) had about 4 times the stroke risk of normotensive subjects (blood pressures less than 140/90). Subjects with intermediate or borderline blood pressures, had about twice the stroke risk of normotensives. Of the 65 men and 70 women who suffered strokes during the 14-year followup period, only 15% were normotensive.

As expected, the risk of stroke increased with age; but within any given age group, the incidence of stroke was similar in both sexes. If anything, women in the older age groups appeared somewhat more vulnerable than did men.

Although the diastolic pressure tends to be the more closely watched of the two blood-pressure readings, systolic blood pressure appeared to be as accurate in predicting stroke risk. Systolic pressure tends to increase with age, and, in elderly subjects, an elevated systolic pressure is sometimes considered an innocuous consequence of reduced blood-vessel elasticity. The study results indicate that it is far from innocuous, since there is no diminution of the impact of systolic blood pressure on stroke risk with advancing age.

The scientists recommend that any blood-pressure level of 160/90 or greater justifies antihypertensive therapy, since this level carries a roughly threefold increase in risk of both stroke and coronary heart disease.

CARDIAC DISEASE

The majority of drugs currently used to prevent or correct abnormalities in heart rhythm also depress heart function. Unfortunately, this may limit their application in certain clinical situations, such as after an acute heart attack, when the threat of serious arrhythmias is great but the presence or threat of heart failure makes the use of any cardiac depressant hazardous.

Recently, a new antiarrhythmic drug, alprenolol, has become available for clinical investigation. The new drug appears to be effective against a variety of atrial and ventricular arrhythmias, but, unlike most antiarrhythmic drugs, also mildly stimulates heart-muscle contractility.

Dr. Louis Lemberg and co-workers of the University of Miami School of Medicine, studied alprenolol in episodes of arrhythmia occurring in heart-attack patients, most of whom had some degree of heart failure. Depending upon the type of arrhythmia, the drug was effective in restoring normal rhythm in from 50% (for atrial flutter) to 100% (premature ventricular beats) of the episodes. In no instance was the patient's heart failure worsened by the drug.

Dr. Robert F. Batey and co-workers, of the University of Florida and the Veterans Administration Hospital, Gainesville, report that alprenolol was effective in controlling arrhythmias resulting from digitalis in heart-failure patients as well as

arrhythmias with other causes. The drug either abolished the arrhythmia or brought it under control in most instances.

In the two studies, side effects of alprenolol therapy included mild hypotension, bronchospasm, and transient heart block.

Dr. W. Gerald Austen and co-workers, of Harvard Medical School and Massachusetts General Hospital, report that advanced age need not preclude replacement of a severely diseased aortic valve if the patient's general health status warrants it. They cite their experience with 40 patients over 70 years old who underwent aortic valve surgery, 38 of whom received artificial aortic valves.

The initial complication of the aortic valvular disease was congestive heart failure, angina, and fainting spells. Severe coronary artery disease was frequently present in addition to aortic valve disease and nearly all had evidence of varying degrees of peripheral vascular disease.

In nearly all patients, the valve orifice was narrowed and the leaflets stiffened by fibrous, densely calcified atherosclerotic lesions on what had previously been a normal valve. Only 5 of the diseased valves showed evidence of prior rheumatic-fever inflammation, the most frequent cause of aortic stenosis in younger patients.

As might be expected in patients whose average age was 74.6 years, there were more operative problems and postsurgical complications than are usually encountered in younger patients and mortality was higher: there were 8 hospital deaths and 3 late deaths. But all 29 survivors showed substantial clinical improvement and, in many cases, the improvement was spectacular.

Although aortic valve replacement carries definite risk for the elderly patient, the authors feel that it is an acceptable risk in many patients. They state that their experience has made them more aggressive in recommending valve replacement in symptomatic patients whose general status warrants it.

Dr. Norman E. Shumway and co-workers, of Stanford, report that heart transplants can prolong survival and restore recipients to normal physical activity in selected cases.

Since January 1968, twenty-six patients have received heart transplants at Stanford. Thirteen survived longer than 3 months; and 9, including 8 who have had their transplanted hearts for a year or more, are out of the hospital and able to lend relatively normal lives. The longest survivor has lived over two years with his transplanted heart.

In contrast, of 12 patients selected to receive transplants but for whom no suitable donors became available, half died within 30 days and all were dead within 90 days.

Exercise testing in long-term survivors indicates that the transplanted hearts are able to cope with the increased circulatory

demands of significant and prolonged exercise, approximately doubling their output during maximal exertion. The resting heart rate of the transplant is somewhat higher than that of the normal heart. During exercise, its rate rises more slowly and the post-exercise decrease in rate is also more gradual. The transplanted heart is also more dependent upon anaerobic metabolic processes to meet the increased energy expenditure resulting from exercise. The resulting metabolites can substantially increase blood acidity (metabolic acidosis) if exercise is very vigorous and prolonged, but this is unlikely to occur during normal, daily activities, including such sports as golf, bicycling, or tennis.

PULMONARY DISEASE

A hereditary deficiency of the plasma protein alpha-1-anti-trypsin appears to predispose affected individuals to the development of emphysema and to make them extremely susceptible to the harmful effects of cigarette smoking. The deficiency is most pronounced and the risk highest in homozygotes (inheriting the genetic trait from both parents), but is still substantial in heterozygotes (inheriting the genetic trait from only one parent) who are estimated to comprise some 5% of the total population. Hence screening programs to identify the very large group of heterozygous individuals may have great potential in preventive medicine.

Drs. Jack Lieberman and Charles Mittman, of the City of Hope Medical Center, Duarte, California, conducted studies to determine whether screening procedures to detect heterozygotes might be thrown off by the presence of other acute or chronic conditions, especially those resulting in serum protein abnormalities. The 400 patients studied did not have pulmonary disease, but were suffering from a variety of other conditions, including cirrhosis of the liver, nephrosis, diabetes, and various hematologic or neoplastic diseases that often affect protein metabolism.

Only 17 of the 400 patients exhibited antitrypsin deficiencies indicative of the heterozygous state. Only 3 of these, in whom family studies could not be carried out, were not subsequently established to be heterozygous for the antitrypsin deficiency.

The scientists conclude that screening procedures to identify heterozygotes are likely to be accurate even in the presence of other acute or chronic illnesses since none of those studied resulted in falsely low antitrypsin levels.

Dr. George Gregory and co-workers, of the University of California, San Francisco, report that the application of a constant, slight positive pressure (6-12 millimeters of mercury) to the lungs via a tube in the trachea prevents collapse of the air sacs (alveoli) of the lungs and greatly facilitates breathing in newborn infants with hyaline membrane disease. Premature infants are especially susceptible to this disorder, which causes an estimated 25,000 infant deaths each year in the United States.

A major factor in the development of hyaline membrane disease

appears to be lack of the pulmonary surfactant, produced by cells lining the airway passages and alveoli of the fully developed lung, that prevents them from collapsing when the air pressure in these passages is low or negative. In the absence of this surfactant, collapse of these structures prevents normal expansion and contraction of the lungs and compromises oxygen-carbon dioxide exchange that normally occurs in the alveoli, leading to potentially lethal oxygen deficiencies.

The positive-pressure technique keeps the airways and alveoli open and functioning during the first few days until the lungs of the infant begin to produce the surfactant, the pressure being gradually reduced as lung function improves. The technique also reduces the oxygen concentrations required to sustain respiration in affected infants and decreases the risk of toxic effects of excess oxygen.

Narcotics addicts have been observed to develop severe acute pulmonary edema (accumulation of fluid in the lung) following overdoses of heroin, but the causes of this complication have been unclear.

Dr. Richard Spears and co-workers, of the State University of New York Downstate Medical Center, Brooklyn, report the results of studies performed in eight such patients within 24 hours of the onset of symptoms.

All patients exhibited abnormally low blood-oxygen levels, elevated heart outputs, and moderately elevated blood pressure in the pulmonary artery and precapillary branches. Blood pressure in the pulmonary capillary bed was normal, but the volume of blood in the capillary bed was nearly twice normal.

The scientists state that the pulmonary edema resulting from overdoses of heroin appears to come about through a mechanism similar to that which sometimes occurs in subjects acclimatized to low altitudes when they move to the more rarefied atmospheric conditions of higher altitudes. In both instances the initiating factor is hypoxia, which triggers an increased heart output and increased blood volume in the pulmonary circulation. This plus constriction of the pulmonary arterioles raises lung perfusion pressure and increases the permeability of the lung capillaries. The passage of protein-free plasma out of the proximal portion of capillaries is facilitated to a greater degree than its return into the distal portion, hence leading to fluid accumulation in the lung.

Correcting the hypoxia with 100 percent oxygen plus bed rest usually leads to prompt clearance of the edema.

THROMBOSIS AND HEMORRHAGIC DISEASE

NHLI scientists have isolated from immature red blood cells (reticulocytes) of rabbits three initiation factors that "turn on" the hemoglobin assembly machinery in the red cell and also appear to limit the rate at which hemoglobin is made. The three factors

were isolated from intracellular structures called ribosomes, where proteins are assembled by linking together amino acids in the sequence dictated by the messenger RNA "blueprints". Also required in protein synthesis are 1) elongation factors, which "read" the genetic blueprint and 2) transfer RNA, which picks up amino acids from the cell sap and delivers them to the ribosomal assembly line. This mechanism and the interacting factors have been shown in bacterial systems.

Now Dr. W. French Anderson and co-workers, of the NHLI Molecular Disease Branch, used the immature mammalian red cell in these studies because its genetic translation machinery is geared primarily to the production of only one protein: hemoglobin. When this machinery was extracted from reticulocytes, placed in the test tube, and primed with all the factors required for hemoglobin synthesis, this protein was made at a rapid rate. When any one or all three initiation factors were withheld, no hemoglobin was made; and when one of all three were supplied in less than optimal amounts, the rate of hemoglobin synthesis was considerably slower than in the fully primed system. Thus the system previously shown in bacteria is demonstrated to be operant in humans as well.

The scientists also found that when one specific group of transfer RNA molecules was withheld, the two subassemblies of the hemoglobin molecule--the alpha and beta chains--were made at different rates.

These findings suggest that hemoglobin synthesis may be regulated in the cell through either of two mechanisms: one controlling the amount of one or more of the newly discovered initiation factors; the other controlling the amount or type of transfer RNA. They also raise the possibility that some derangement in either or both mechanisms may be involved in certain hereditary anemias characterized by deficient or defective hemoglobin synthesis.

The clot-dissolving agent urokinase plus anticoagulants outperformed anticoagulants alone in relieving pulmonary blood-vessel obstruction and improving bloodflow to the lungs in patients with pulmonary embolism, according to results of the recently completed Urokinase Pulmonary Embolism Trial.

The study involved a total of 160 patients at 16 co-operating institutions. Approximately half received anticoagulants alone; the other half received anticoagulants plus urokinase during the first 12 hours, then anticoagulants alone. The study found that

- clinical improvement was the rule rather than the exception in both groups, but was more pronounced in the urokinase-treated group during the first 24 hours.

- objective evidence of clot dissolution, a resultant improvement in lung perfusion as well as improvement in various indices of heart performance were all marked in the urokinase-treated group during the first 24 hours.

. however, bleeding complications were also more common and more severe among urokinase-treated patients.

. mortality rates were about the same in both groups.

On balance, the study findings indicate the urokinase plus anticoagulants produced only slightly better results than did anticoagulants alone; the differences in terms of clinical improvement were seldom dramatic. The investigators feel that urokinase plus anticoagulants may eventually prove to be the favored therapy for massive pulmonary embolism with shock, but conclude that further evaluation will be needed to establish the value of clot-dissolving agents in this and other thromboembolic disorders.

BIOENGINEERING

Intra-aortic balloons, inflated and deflated in synchrony with heartbeat, have been clinically tested by a number of investigators as a means of providing circulatory assistance in patients with cardiogenic shock, a dreaded complication of acute heart attacks.

The balloon, threaded into the aorta via a catheter, is synchronized with the electrocardiogram to inflate while the heart is refilling between beats and to deflate as the heart contracts. Inflation raises systemic blood pressure and coronary-artery perfusion pressure between heartbeats; deflation leaves in its wake a lower pressure for the heart to work against in expelling blood.

Dr. R. C. Leinbach and co-workers, of Massachusetts General Hospital, report that intra-aortic balloon pumping produced striking clinical and hemodynamic improvement in myocordial infarction patients and was usually successful in stabilizing the threatened circulatory collapse often precipitated by cardiogenic shock. However, they report that the resultant effects on coronary flow and cardiac metabolism, while generally beneficial, were seldom consistent from patient to patient.

Dr. Hiltrud Mueller and co-workers, of St. Vincent's Hospital and Medical Center, New York, report that balloon pumping improved peripheral and coronary perfusion while reducing heart work and favorable affected heart-muscle metabolism in patients with cardiogenic shock. The periods of circulatory assistance ranged from 20-120 hours.

Only 5 of the 12 patients survived the shock state for more than 1 week, and only 1 was discharged alive. The investigators conclude that intra-aortic balloon pumping is indeed effective in sustaining the circulation over the short haul, but that the resulting improvement may be insufficient to reverse the generalized circulatory failure characteristic of cardiogenic shock.

Dr. Sidney Levitsky and co-workers, of the NHLI Surgery Branch, report that radar kymography provides a simple, non-invasive method of measuring variations in heart-muscle contractility.

In radar kymography, the heart is first visualized by fluoroscopy, employing an image intensifier to reduce the X-ray dosage required. The intensified image is scanned by special television equipment that converts the image of the heart border into a distinct energy peak that appears on the TV screen as a very bright outline of the beating heart. Finally, a video tracker is positioned to scan any portion of the outlined heart border. The tracker has a feedback loop system similar to that employed in radar systems that automatically track moving targets. This enables the tracter to "lock on" to the image of the heart border and move in synchrony with it. The movements of the tracker are then converted into a linear tracing on the strip chart of a standard recorder.

The accuracy of the system in determining heart-muscle contractility was evaluated in experimental animals, comparing the results obtained with this technique with those obtained by techniques requiring heart catheterization and other invasive procedures. Contractility was varied over a wide range by means of cardiac stimulants or depressants. In all instances, the results obtained by radar kymography accorded well with those obtained by more complex techniques.

The scientists feel that the technique shows promise in the clinical evaluation of heart-muscle contractility both in health and various congenital or acquired heart conditions.

CARIES

Through research, the National Institute of Dental Research seeks solutions to the oral health problems that plague essentially every American at some time in his life. Only two percent of the population escapes the discomfort of tooth decay, also called dental caries, one of the Institute's chief concerns. Rampant caries in childhood can produce permanent dental crippling. Another major concern is periodontal (gum) disease, which causes most of the tooth loss seen in adults. The NIDR also is looking for better ways to treat, and ultimately prevent, malocclusion or faulty bite, cleft lip and cleft palate, and other conditions ranging from canker sores to oral cancer.

ADVANCES IN THERAPY

Preliminary success with a new plastic coating for the tooth's grinding surface has been reported by Dr. Michael Buonocore, Eastman Dental Center, Rochester, New York. Treated surfaces of children's teeth remained free of decay for one year after the plastic sealant was applied. If clinical tests now underway bear out its initial promise, the coating could take a place beside water fluoridation, which mainly protects the tooth's smooth surfaces, as a preventive of decay on chewing areas.

Plastic materials now marketed for filling decayed front teeth are based on formulations developed by Dr. R. L. Bowen, American Dental Association Research Section, National Bureau of Standards.

Dr. Bowen reports a new composite filling that incorporates four improvements on his earlier material. Small-scale clinical testing is underway.

Dr. Leonard Shulman, Harvard School of Dental Medicine, reports progress in extending the life of dental transplants. His animal and human studies show transplants survive longest when mature teeth are used and cleaned of all soft tissue. Even though transplanted teeth are eventually rejected, Dr. Shulman believes they could be practical replacements if they could be made to last for an average of eight years instead of the approximate four-year survival period now expected.

After ten years of experimentation in baboons, Dr. Milton Hodosh, Brown University, will test plastic tooth replicas in humans. While the plastic tooth is not rejected, gum tissues do not attach to it in the same way they do to natural teeth. Dr. Hodosh encourages bone growth through the plastic roots by drilling holes into them and making the root portions more porous. If the plastic proves as acceptable in humans as it does in rats and baboons, dentistry will have an excellent tooth replacement.

Scientists studying saliva may soon help physicians determine which patients with high blood pressure have adrenal gland tumors and would therefore profit from surgery. Dr. S. Wotman and associates at Columbia-Presbyterian Hospital suggest a way to identify before surgery those patients who have adrenal gland tumors. Their studies show that the amount of potassium in the saliva from the submaxillary glands, one of the major pairs of salivary glands, is significantly higher in patients with high blood pressure due to adrenal gland tumors than in those who have no tumors. Another chemical test on saliva discovered by the same group is helpful in recognizing digitalis overdosage in cardiac patients.

Some five percent of our population seek dental care only in painful emergencies because of irrational fears. Studies now show that these phobias can be relieved through psychological desensitization requiring less than a dozen hours. E. N. Gale and W. A. Ayer, State University of New York, Buffalo, demonstrated that a trained therapist can teach a fearful person to associate dental situations with relaxation instead of anxiety.

Experiments on monkeys suggest more effective techniques for surgery to correct severely protruding or receding upper jaws in adults. Dr. W. H. Bell, University of Texas Dental Science Institute, Houston, reports that the operation can be safely performed in one rather than two stages, provided that no cut is made too close to the tips of tooth roots. Jaws need not be wired together for immobility, and blood vessels grow so rapidly after surgery that orthodontic treatment can begin within weeks.

General anesthesia is increasingly used in dentistry. Frequently it causes irregular heartbeats among adults. This condition can be prevented by the drug propranolol, according to Drs. A. G. Tolas and G. D. Allen, University of Washington in Seattle. Since the

drug is administered one hour before the anesthetic, occasional adverse effects can be observed in time to postpone the operation until the patient's body can eliminate the drug.

ORTHODONTICS

Contrary to the long-held view that the fibers holding teeth in their bony sockets extend only from each tooth to just beneath the surface of the supporting bone, two scientists have independently found that the fibers in laboratory animals cross through the entire thickness of the bone and extend to the neighboring tooth. If this suspension-bridge system of tooth support exists in man, it may explain why the loss of one tooth can affect the alignment of the entire arch, and suggest new treatment approaches. Also, it may help orthodontists combat the natural tendency of teeth to relapse toward undesirable pre-treatment positions after braces are removed. Drs. S. A. Cohn, University of Tennessee, and M. B. Quigley, University of Alabama, report the anatomical finding.

MATERIALS RESEARCH

The amalgam filling remains the one most frequently used in restorations. Materials experts at the University of Oregon have set the stage for improved alloy fillings. They show that one of the many physical tests currently employed may suffice to predict how an alloy will perform in the mouth. The test could select materials most likely to succeed from among new materials. Measuring the way the alloy changes shape under pressure can predict more accurately than any other single test how the alloy will behave as a dental filling, according to Dr. D. B. Mahler.

TOOTH DECAY

Studies at the Massachusetts Institute of Technology indicate that an enzyme (phosphoprotein-phosphatase) from intestinal bacteria can remove phosphates from the phospho-protein framework of tooth enamel and dentin and eat away the tooth. Drs. S. N. Kreitzman, S. Irving, J. M. Navia, and R. S. Harris suggest that the enzyme could be released when certain bacteria in plaque, the microbial mat on the teeth, die. The finding provides a new approach to the study of caries (tooth decay) and of the action of dietary phosphates, which inhibit the enzyme in the test tube.

Large amounts of phosphates, continuously available in drinking water or food, have protected animal teeth against decay. An NIDR scientist, Dr. R. A. Frew, now reports that painting hamster teeth with a saturated solution of sodium trimetaphosphate for two minutes a day for 36 days, produced a 43 percent reduction in decay. The work suggests that topical fluoride applications may reduce human caries further if combined with this phosphate solution.

Since 1960, when NIDR scientists discovered that certain strains of streptococci from decayed human teeth can cause decay in hamsters, investigators have been trying to pinpoint the role of these bacteria in human tooth decay. One approach is to seeking indirect

proof of damage through surveys of their prevalence. In one study, NIDR scientists found these microbes in every decayed area examined. They further found that if plaque, an adherent film, is scraped only from healthy tooth surfaces in mouths where decay is present, it often does not contain decay-producing bacteria. Investigators are therefore urged to sample carious spots, as well as intact surfaces, to avoid gross underestimates in microbial counts.

NIDR scientists presented evidence this year showing that traditional vaccines may not be effective against tooth decay. Even though rats immunized against decay-causing Streptococcus mutans developed high levels of antibody in the blood, they suffered as much tooth decay as unimmunized rats infected with the same bacterial strain. The vaccine probably failed because bacteria clinging to teeth are not in contact with antibodies in the blood. One way to overcome this problem may be to stimulate the formation of salivary antibodies against the organisms.

DENTAL PLAQUE

In order for oral microbes to attack the teeth or the gums, they must be able to adhere to them so that they are not washed away by saliva and beverages. The film of bacteria and other substances found on teeth, and known as dental plaque, is a nesting place for infection and a sponge for holding acids. Among key findings this year are reports of three mechanisms by which bacteria can cling to smooth surfaces of teeth to form plaque. Drs. R. J. Gibbons, J. van Houte, and associates at Forsyth Dental Center, Boston, found that while some bacteria synthesize dextran (a glue-like material), other types can stick directly to enamel, and still others are bound to teeth by long-chained molecules from saliva. They report that saliva also makes many kinds of microbes clump together.

Saliva may assist bacteria in plaque to attack oral tissues in still another way. It can serve as an alternate source of energy, according to Drs. J. K. Pinter, J. K. Hayaski, and A. N. Bahn of Presbyterian-St. Luke's Hospital and Northwestern University, Chicago. Ordinarily, bacteria get their energy from carbohydrates--sugars and starches--provided by snacks and meals. This research now shows that between meals, and especially during long periods of sleep, many bacteria can switch to an alternate source of energy and extract sugar from salivary glycoproteins. Having two systems for obtaining sugar enables the bacteria to produce acid constantly and enhances decay.

NIDR scientists, J. M. Tanzer and M. I. Krichevsky, and Dr. W.I. Wood of Cornell University have demonstrated in the test tube that decay-causing microbes actually multiply more quickly when grown on simple sugars, either glucose or fructose, than they do on sucrose, common table sugar. The study shows that the important factor in decay is not just growth of particular germs, but the fact that only from sucrose can they make dextran which enables them to cling close enough to harm the tooth's slick surfaces.

In periodontal (gum) disease, the bones and gum tissues that

support the teeth are attacked so that the teeth loosen. In severe cases the teeth simply fall out. Plaque plays a key role in periodontal disease as well as in tooth decay. For example, NIDR scientists H.V. Jordan (now with the Forsyth Dental Center), P. H. Keyes, and S. Lim found that when golden hamsters are fed a corn-starch diet, and infected with a filamentous diphtheroid, a plaque forms that decays the tooth roots and destroys tissues around the tooth. But a sucrose diet stimulates certain streptococci to make decay-producing plaque on the crowns of these animals' teeth. However, albino hamsters fed the same diets and infected with the same organisms develop much less disease than golden hamsters. Both periodontal problems and tooth decay appear to depend upon the interactions of host resistance, the number and type of plaque and acid-forming organisms, and the kind of food available.

Another study by Dr. B. F. Hammond, University of Pennsylvania, shows that the same factors can cause both periodontal disease and tooth decay. He found that a variety of the Lactobacillus casei can manufacture a substance (probably dextran) that enables it to stick to teeth. This organism was found in diseased human tissue and may be involved in periodontal disease as well as tooth decay. It has long been suspected as a cause of decay in fissures on the tooth's grinding surface because it is a prolific acid producer.

Still another oral micro organism, previously thought to be harmless, may be a contributor to periodontal destruction. Dr. H. Bladen, NIDR, reports that once a microbial mat has been laid down by any of the other microbes in the mouth, Veillonella can congregate on plaque in such great numbers that its endotoxin (poison released from the bacterial cell when the organism dies) probably could accumulate in sufficient amounts to damage tooth-supporting tissues.

The importance of endotoxins held close in plaque or tissue crevices was underscored by Drs. E. Hausman and W. A. Miller of the State University of New York at Buffalo and L. G. Raisz, University of Rochester. They found that even minute quantities of endotoxin from bacteria that dwell in human gum crevices can stimulate marked bone resorption in tissue culture.

Another reason that plaque is suspected in periodontal disease is that it hardens into tarter, or calculus, which must be scraped off periodically by a dental hygienist. If allowed to accumulate, it pushes the gums away from the teeth, leaving pockets where more irritating debris can collect. P. N. Baer, C. L. White, and E. M. Tarpley, Jr., NIDR scientists, found that, in calculus formation, content is no less important than consistency of diet. Contrary to previous reports, the NIDR group found that, in rats, liquid diets (Metracal and Nutrament) failed to result in prevention of calculus.

PERIODONTAL DISEASE

Since the causes of periodontal disease are still unknown, an animal model system has been set up at the Forsyth Dental Center to study how the disease begins and progresses. Dr. S. S. Socransky and associates induced periodontal disease in germ-free rats and

hamsters by inoculating them with organisms from human periodontal pockets. Pure cultures of four of these organisms formed heavy plaque underneath the gum lines and caused gum inflammation, deep periodontal pockets, and marked bone resorption.

Drs. S. E. Mergenhagen, T. R. Tempel (U. S. Army), and R. Snyderman, working at the NIDR, found that cells and proteins in the body's defense system can react with bacteria and endotoxin to produce swelling, redness, and increased sensitivity and permeability in the gum tissues. They conclude that constant exposure to bacteria could easily cause much of the chronic inflammation of periodontal disease.

Another investigation showed that immune responses could cause some of the tissue destruction seen in periodontal disease. Drs. R. R. Ranney and H. A. Zander, Eastman Dental Center, Rochester, N. Y., have induced periodontal disease in monkeys made allergic to albumin by tucking albumin-soaked thread into the crevices between their teeth and gums. In man, at least some cases of periodontal disease may be the result of allergic responses.

Collagenase, an enzyme that breaks down collagen, the main protein in connective tissue, is believed to be a factor in periodontal and certain other diseases. NIDR scientists have found that the amount of the enzyme present in the damaged tissues of patients suffering from either periodontal disease or arthritis corresponds with the severity of their condition. More collagenase was recovered from cultures of inflamed gum tissues and of synovial tissues that line joints in rheumatoid arthritis patients than was found in cultures of corresponding normal tissues. The skin from patients with amyotrophic lateral sclerosis, a fatal disease marked by degeneration of the nervous system and wasting of muscles, also had unexplained high enzyme levels.

A new type of collagen molecule in chick cartilage that is not present in chick bone or skin has been discovered by NIDR scientists. This indicates a molecular mechanism as a factor in the specialization and differentiation of connective tissue. Drs. E. J. Miller and V. J. Matukas will now seek to determine whether the new molecule occurs in man, and if so, to explore its significance in the development and function of cartilage.

BASIC RESEARCH

Knowledge of intercellular communication should help researchers trying to stop uncontrolled growth in cancer and to initiate growth for regenerating tissues and organs. A discovery that suggests a way for embryonic cells to communicate instructions telling other cells to differentiate (become specialized cells) has been made at the University of Southern California. Dr. H. C. Slavkin found RNA in the material between two types of embryonic cells. He thinks it could be carrying messages for specialization because neither cell-type growing alone will differentiate, but either will do so when in contact with the other or with this extracellular material.

FAMILY PLANNING AND CHILD HEALTH

Scientists in the Reproduction Research Branch of NICHD have discovered the cause of the "short luteal phase," one type of female infertility, and are now studying treatment approaches in women through a new infertility clinic at the NIH Clinical Center.

The secretion of estrogens and progesterone by the ovaries is regulated primarily by hormones from the pituitary gland beneath the brain. The follicle stimulating hormone (FSH) from the pituitary induces development of the ovarian follicle, a spherical mass of cells and fluid in which the ovum develops. Adequate follicular development is essential to a functional corpus luteum, which is a mass of cells that develops within a ruptured follicle after the egg is released during ovulation.

The corpus luteum produces progesterone and prepares the uterus to receive the fertilized ovum and to retain the pregnancy. The nourishment and early development of the embryo depend on the continued action of progesterone.

Between the second and third month of pregnancy, the corpus luteum slowly regresses; its function of producing progesterone for maintenance of normal pregnancy is taken over by the placenta.

Drs. Charles Strott, Charles Cargille, Griff Ross, and Mortimer Lipsett found that in one type of infertility, accounting for 5 to 10 percent of infertility in women, the pituitary produces too little FSH, resulting in poor development of the follicle.

Consequently, the corpus luteum, since it develops from follicle cells, fails to function properly or produce enough progesterone to insure a successful pregnancy. In the normal menstrual cycle, the corpus luteum lasts about 14 days if the ovum is not fertilized; it then degenerates. The NICHD scientists found that in some women, the corpus luteum functioned for 8 days or less following ovulation--an insufficient time for it to maintain a pregnancy should the ovum be fertilized.

More women with the "short luteal phase" menstrual cycle are now being studied and treated in the infertility clinic. Since FSH is commercially available, it can be given to supplement the FSH produced in the woman's body.

Studies in the Reproduction Research Branch, NICHD, have also given insight into the mechanism whereby the corpus luteum continues to function in early pregnancy and into the reason for some early abortions (miscarriages).

Drs. T. Yoshimi, C. A. Strott, J. R. Marshall, and M. B. Lipsett devised a method for measuring a corpus luteum steroid which had never been measured before. This steroid, 17-hydroxyprogesterone, unlike similar steroids, is produced by the corpus luteum and not by the placenta, so that its excretion is an index of corpus luteum function only.

By measuring the steroid in the first 6-7 weeks of pregnancy in women in whom ovulation was induced, the scientists found that approximately 8 weeks after fertilization a critical phase is reached during which the function of producing progesterone is taken over from the corpus luteum by the placenta. If the corpus luteum does not maintain function until the placenta can take over, or if placental synthesis of progesterone is inadequate, the result is an early loss of the pregnancy.

The investigators are now studying a larger number of women to obtain further knowledge about the events of early pregnancy and the reasons for early abortion.

Similar research is being done on monkeys with the goals of regulating corpus luteum function either to save a pregnancy or to bring on the menstrual period.

HORMONES AND REPRODUCTION

Most of the reproductive processes are controlled by hormones produced by the pituitary gland. These hormones are complex molecules present in the body in very small amounts. Isolation of significant quantities for study has only come as a result of increased biochemical sophistication in techniques of protein isolation and purification.

One hormone which plays a significant role in the control of ovulation and the formation of the corpus luteum is called the luteinizing hormone (LH). Dr. Darrell Ward at the University of Texas has purified LH from pituitaries of lambs and sheep and has demonstrated that the protein molecule can be separated into two dissimilar subunits. He has studied their biological activity and their chemical structure, specifically in relation to points of attachment to carbohydrates.

Recently, Dr. Ward, working with Dr. Kris Eik-Nes, University of Southern California, discovered the first biological activity associated with an isolated subunit; the activity may have a bearing on the mechanism of action of the luteinizing hormone.

Most of the hormones involved in reproductive processes are made up of two or more subunits. Regulation of a hormone's activity now becomes possible through work on constituent units. Many individual investigators are now preparing hormone subunits in quantity sufficient for biological testing.

In order to understand the control of ovum and sperm development in the ovary and testis and the regulation of the production of the sex hormones by these glands, we must understand how pituitary hormones interact with these glands. To do this, it is necessary to label pituitary hormones with radioactive molecules and follow them into the glands to see how and where they attach.

Drs. Griff Ross and Kevin Catt of the NICHD's Reproduction Research Branch have devised two ways of labeling the pituitary

hormone HCG (human chorionic gonadotropin) and have shown that it binds itself very tightly to the corpus luteum and the hormone producing cells of the testis. HCG is responsible for keeping the corpus luteum actively functioning after fertilization.

If the nature of this binding is understood through continuation of these studies, ways to alter it might be devised and used in development of a new method of contraception.

Another investigator, Dr. Robert Canfield of Columbia University, is working on preparation of HCG to be used in biological testing both alone and in combination with other hormone subunits. One of the objectives of such studies is to find a substance which interacts with either the whole hormone or with a particular subunit to render it biologically inactive. It might then be possible to inhibit the usual HCG stimulation of the corpus luteum for contraceptive purposes.

PROSTAGLANDIN

Prostaglandins are hormone-like substances that have a remarkably wide range of effects. At the present time, there are 14 known prostaglandins which are widely distributed in mammalian tissues in very small amounts. Although rapidly metabolized, prostaglandins are among the most potent chemicals ever discovered; one-billionth of a gram produces marked effects. On the horizon now are many potential medical uses.

In the area of population research, these include induction of labor, therapeutic abortion, contraception and treatment of male sterility. If research shows that human reporductive processes could be safely and effectively interrupted by vaginal or oral administration of prostaglandins, this class of compounds would be of tremendous use in widespread fertility control. Research on prostaglandins may eventaully lead to a once-a-month pill, since these substances may be used to initiate menstruation.

The NICHD's Center for Population Research currently supports a number of studies in the area of prostaglandin research. Drs. K. T. Kirton and G. W. Duncan of the Upjohn Company are studying two prostaglandins (prostaglandin E_2 and prostaglandin F_2 alpha) and their effect on the reproductive biology of the rhesus monkey. They have demonstrated that these prostaglandins play an important role in normal and pregnant physiology of both humans and rhesus monkeys and that prostaglandin F_2 alpha can interrupt pregnancy in rhesus monkeys. It is 100 percent effective in preventing or terminating pregancy in the rat when given by injection over a three-day period but is ineffective when administered orally.

Prostaglandins are formed in most human tissues and fluids, including the female's oviduct, a funnel-shaped tube between the ovary and uterus. After the egg is released from the ovary, it goes into the oviduct, where fertilization occurs. Any interruption of the intricate balance among factors controlling the chemical environment of the oviduct or the length of time the egg spends

under support of this structure provides a potential means of contraception.

Dr. Paul Russell of the University of Cincinnati has increased our understanding of the role of prostaglandins in the oviduct, particularly the role these compounds might play in the transport of the egg from the ovary to the uterus. He has demonstrated that the type of prostaglandin in the oviduct is prostaglandin A_2. Both the A class and the E class have been shown to relax smooth muscle under certain circumstances, whereas the F class stimulates it. Dr. Russell has also shown a relationship between hormonal factors and the amount of fatty acid available for prostaglandin biosynthesis.

Since human semen is one of the richest sources of prostaglandins, attempts have been made to relate the prostaglandin concentration of seminal fluid to male fertility. Dr. Paul Risley of the University of Oregon has shown that prostaglandin E_2 potentiates contractions of certain male reproductive tissues (the seminal vesicles) more readily than others and enhances contractions stimulated by other substances. The vesicles are glandular organs whose secretions serve as a vehicle for the sperm and may possibly contribute to their nutrition.

DEVELOPMENT OF MALE CONTRACEPTIVE METHODS

Newly formed sperm are temporarily stored in a structure called the epididymis, near the testis, prior to passage to the outside. Seminal fluid, formed by secretions of various glands and ducts, carries the sperm through the epididymis and preserves them until they are ejaculated. In the course of their transit through the epididymis, sperm undergo a poorly understood process of maturation. The contribution of seminal fluid to sperm function is also inadequately known. Finally, at least in some species, sperm must reside for a time in the female reproductive tract in order to develop fertilizing capacity, and the morphological and biochemical changes associated with this process ("capacitation") are not understood, nor is its existence proved in primates.

Further study of these processes may lead to new contraceptive methods. Such methods would be based on altering the timing of sperm passage through the epididymis, the processes of sperm maturation or capacitation, sperm motility, or the chemical constituents of the seminal fluid.

It is generally agreed that new modern male methods of fertility regulation will markedly improve the effectiveness of family planning programs, and for this reason these areas of investigation are considered to be particularly important. Results of several studies were reported this year.

New chemical contraceptives for men would have to act selectively on the reproductive system. This means that unique properties of reproductive cells and processes would have to be uncovered through basic research, and drugs then tailored to interfere only with these

processes. Nonselective chemicals would not only affect reproductive cells, but might interfere with cell function elsewhere in the body.

Approximately 60 years ago it was discovered that certain dyes introduced into the bloodstream were excluded from the brain. This led to the concept of a blood-brain barrier which prevented substances in the bloodstream from reaching and therefore affecting brain cells. More recently, reproductive biologists described a blood-testis barrier. By electron micrographic studies, an NICHD supported investigator, Dr. Don Fawcett of Harvard University, conducted studies in male rats and has observed a blood-testis barrier in this species. The effect of various substances on this barrier can now be studied for the first time, opening up exciting possibilities for further research. If the barrier is shown to exist in the human and if antifertility drugs cannot be found that will pass it, new contraceptives for males will have to be either mechanical or surgical.

Working with Dr. Anita Hoffer, Dr. Fawcett has shown that a drug, alpha-chlorohydrin, interferes with a biochemical pathway which is peculiar to the epididymis and which may be essential for maturation of the sperm. The drug produced reversible infertility in male rats but caused destruction of tissue when given in large amounts. Investigations of the drug are continuing.

Dr. Fawcett has also been able to analyze the effects of various drugs on sperm motility, by taking high-speed motion pictures of sperm samples. The sperm are placed under the microscope and their tail movements recorded on high-speed film, which slows them to a perceptible speed. By simultaneously filming and comparing two sperm samples--one treated with a drug--Dr. Fawcett can instantly gauge the drug's effect on sperm motility.

Once the sperm leave the male and are introduced into the female tract, they must travel from the uterine cavity into the oviduct, where fertilization occurs. Although millions of sperm are introduced into the female, only a few are thought to reach the site of fertilization.

Dr. Luciano Zamboni at the University of California at Los Angeles, has found that in mice, sperm arrive in the oviduct as early as 12 minutes after coitus and continue to enter the oviduct for about one hour. Then the junction between the uterus and oviduct closes, preventing any further passage of the sperm. Closure of the utero-tubal junction, Dr. Zamboni found, is brought about by contraction of the several muscular layers present in the region.

The significance of this observation is that only those sperm which enter the oviduct within the first hour after mating have a chance of becoming involved in fertilization. Therefore, if sperm motility is defective, fertilization would be impossible.

Inhibition of capacitation is another approach to developing new methods of contraception, and this might be accomplished by

alteration of the hormonal environment. Some questions to be answered by research are: Does capacitation occur in the human? If so, is the capacitating activity of the uterus and oviduct innate or--since these organs are regulated by the ovary--is it dependent on stimulation by ovarian hormones?

Dr. Pierre Soupart, Vanderbilt University School of Medicine, has found that the oviduct itself is not necessary for capacitation in rabbits. Previous studies by Soupart and colleagues indicated that LH (luteinizing hormone) is able to inhibit capacitation when administered in large doses, and that capacitation is primarily controlled by LH. He controlled capacitation in the uterus by injecting pituitary hormones (either human chorionic gonadotropin (HCG) or LH), which had a double effect: stimulation of capacitation followed by progressive inhibition. This double effect was mediated by the ovary. Capacitation was stimulated by administering estrogen to the rabbits, whose ovaries had been removed.

Dr. Benjamin Brackett and colleagues at the University of Pennsylvania, like Dr. Soupart, found the oviduct to be unnecessary for capacitation. They also found that a degree of capacitation was possible apparently without hormonal activation of the uterus. However, administration of estrogen and progesterone significantly increased the fertilization rate, indicating that a uterus under hormonal control provides a more suitable environment for capacitation than one not activated by hormones.

Research on capacitation by an NICHD contractor has resulted in the invention of a new vaginal contraceptive which is 100 percent effective in rabbits. The contraceptive is a synthetic organic chemical which inhibits an enzyme, located in the head of the sperm, which is necessary for penetration of the ovum. The chemical does not affect sperm motility.

Substances found in various body tissues also inhibit the enzyme. However, these naturally occurring inhibitors were shown to be ineffective in fertility control because their effects are reversed by the capacitation process.

The investigators, Dr. William L. Williams and his colleagues at the University of Georgia, tested several chemicals for antifertility effects. They demonstrated that TLCK (tosyl-L-lysine chloromethyl ketone) prevents fertilization of capacitated sperm; NPGB (nitrophenyl p-guanidinobenzoate) and TLCK significantly decrease fertility on incubation with ejaculated sperm; and TLCK is effective as a vaginal contraceptive in the rabbit.

Although initial observations show no toxicity to the vagina, further study is indicated. The efficiency of the synthetic chemical in totally blocking fertilization in the rabbit in vivo is of special significance because present human vaginal products fail to do so.

The demonstration of other enzymes necessary for ovum penetration will lead the way toward other inhibitor chemicals being

synthesized, each with a possible antifertility effect. Their use as a systemic contraceptive in either the male or female, as well as a vaginal contraceptive, is feasible.

ORAL CONTRACEPTIVES

It is known that almost every woman taking oral contraceptives experiences an increase in certain plasma factors concerned with hypertension. However, only five to ten percent of these women develop high blood pressure.

Dr. Kevin Catt of the NICHD's Reproduction Research Branch has developed methods for measuring all five components of the renin-angiotensin system, which is one important factor that may be responsible for certain forms of hypertension.

Studies have shown that the synthesis of proteins concerned with the renin-angiotensin system can be turned on in the laboratory rat within six hours of administration of estrogens used in the oral contraceptives. This phenomenon happens generally within five days of beginning oral contraceptives in women.

Dr. Catt and his associates are now studying this process in women. Their goals are to understand the mechanisms by which estrogen activates this system and to improve current approaches to fertility control.

Women who decide to use oral contraceptives are somehow different--before starting the Pill--from women who choose other methods of fertility control. These differences--as yet unexplained--may account for some of the medical problems which have been reported in women using the oral contraceptives.

Approximately 2400 women attending a family planning program of the Los Angeles County Health Department were studied under an NICHD research contract. None of the women had ever used oral contraceptives. They were examined before beginning any contraceptive method.

The investigators found a higher rate of uterine cervical dysplasia, a precursor of cervical cancer, in women who subsequently chose oral contraceptives, than in women who chose other methods, such as the intrauterine device (IUD) or diaphragm. The suspected higher incidence of cervical cancer in oral contraceptive users may therefore be due to preexisting differences in the women themselves and not to the contraceptives.

Women choosing the oral contraceptives differed from those choosing the IUD in having a higher income and lower body weight. No further differences were found over a wide range of characteristics, including religion, ethnic group, age, age at first intercourse, age at first pregnancy, and number of children.

Principal investigator for the study was Elizabeth Stern, M.D., of the School of Public Health, University of California, Los

Angeles. The Center for Population Research of NICHD is sponsoring the study, which in future work will follow more women with dysplasia, to determine which of them progress to a more advanced disease and how quickly.

"THE DEMOGRAPHIC TRANSITION"

Economic, social and cultural forces will very largely determine the future course of world population growth, according to Dr. Dudley Kirk of Stanford University. Experts, he says, generally agree that humanity is midstream in a revolutionary change in its processes of reproduction. This is a transition from wastefully high death and birth rates to a more efficient and humane reproduction with much lower death and birth rates. This process is called "the demographic transition."

Kirk's study analyzed some of the natural forces related to trends in the birth rate in the less developed nations for which reliable statistics are available. These include countries of Africa, Asia (excluding Japan and the USSR) and Latin America (excluding Argentina and Uruguay).

His preliminary findings--subject to revision and clarification as his research proceeds--include the following:

--A growing number of countries have been entering the demographic transition since World War II, after a lapse of some 25 years in which no major country entered this transition.

--Once a sustained reduction of the birth rate has begun, it proceeds at a much more rapid pace than it did historically in Europe, and in general more rapidly than posited in United Nations projections.

--There is no direct evidence yet that current fertility reductions will terminate at levels significantly higher than those achieved in Europe and Japan.

--The relation between socioeconomic variables and fertility is clearly different within the different major cultural regions of the less developed world; quite different levels and kinds of development are associated with fertility reductions, for example, in East Asia and Latin America. In Latin America, fertility declines seem to be correlated more highly with levels of education and modern communications than with urbanization and industrialization.

These preliminary findings suggest some optimism for the future rates of world population growth, although there are still large areas of the world where declines in the birth rate have not yet occurred. In addition, no reliable assessment can be made of the progress of the demographic transition in such large countries as China, India, Pakistan, and Indonesia. What is happening in these countries will be crucial.

The demographic transition, as it has evolved to date, will not prevent an anticipated enormous increase in the world's population, which must somehow be accommodated. This increase will be greatest precisely in those countries economically least equipped to absorb large numbers of additional people.

An NICHD study indicates that the prevention of all unwanted births would substantially reduce U.S. population growth.

The urgent need for research to develop new contraceptive methods was highlighted by a study based on results of the 1965 National Fertility Study (NFS), supported by NICHD. The study estimated that one-fifth of all births in the United States between 1960 and 1965 were unwanted. Thus, 4.7 million births might have been prevented if more nearly perfect means of contraception had been available and used during that period.

A state of "perfect" contraception implies the use of completely acceptable and effective means of contraception by all who wanted to stop childbearing or postpone a birth.

The NFS was a national interview survey of 5600 married women, conducted by Drs. Charles F. Westoff and Norman B. Ryder of Princeton University. Births to women not living with their husbands and most illegitimate births are not represented in the 1965 NFS data; these estimates will be included in the 1970 NFS, which will again be supported by the NICHD.

The estimate of unwanted births was arrived at by averaging two figures: the births unwanted by both spouses, and the births unwanted by at least one spouse. NFS estimates of unwanted births may be conservative. As the authors point out, "Reliable reports on unwanted births are difficult to obtain, since the admission that a birth was unwanted reflects on the respondent's ability to control fertility and perhaps also on the status of the child."

The investigators found that couples with low education or income had more unwanted births. The incidence of unwanted births was approximately twice as high for wives with less than a high school education than for those who attended college and more than twice as high for families with annual incomes of less than $3,000 as for those earning over $10,000. Two-fifths of births among families classified as "poor" by Social Security standards were reportedly unwanted; among the "non-poor," one birth in seven was unwanted by whites and one in five by Negroes. The proportion of unwanted births increased rapidly with birth order.

Moreover, many desired births were found to be timing failures, in that they were wanted but did not result from the deliberate interruption of contraceptives. The investigators found that two-fifths of all wanted births would have occurred later if their timing had been controlled by perfect contraception. Some births, if postponed, would not have occurred at all, since couples might subsequently change their minds or become subfecund at older ages.

A classic social experiment designed to make family planning techniques available to a city population in a short time has been completed in Taiwan by NICHD grantees Drs. Ronald Freedman and John Y. Takeshita of the University of Michigan.

The Taiwan experiment demonstrates the importance of social research to the successful implementation of family planning programs. Efforts to bring contraceptive information and services to the population were concentrated in one city (Taichung) containing 36,000 married couples of reproductive age. The city was divided into 2,389 neighborhood units, each of which in 1963 was subjected to one of four promotional efforts: 1) personal visits to both husbands and wives, mailing to newlyweds and to couples with two or more children, and neighborhood meetings, 2) all of the previous approaches except the personal visit to the husband, 3) mailings only, and 4) nothing. Some neighborhood units received no promotional efforts in order to see whether couples living there would hear about and respond to the visits, meetings, and mailings received by couples in nearby neighborhood units.

The city was also divided into three major areas which varied in the proportion of neighborhood units receiving the most intense promotional efforts. This was done in order to determine whether the "diffusion effect" of the promotional campaigns was greater in the areas where a higher proportion of the neighborhood units were subjected to all promotional efforts.

The overall effect of the Taichung experiment is documented by a rise in the proportion of women using contraception from 19 percent before the campaign to 26 percent at the end of the nine-month intensive campaign and 33 percent after two and one-half years. Mailings and visits to husbands were shown to be relatively ineffective promotional devices; small group meetings were shown to be important. One of the most important results demonstrated was the major role played by the diffusion of information to couples toward whom no promotional efforts were directed.

Demographic variables--such as prior use of birth control; number of children; number of sons; whether more children were desired; whether the couple had once tried birth control and given up the effort--were found to be much more important than social and economic variables in determining who became an acceptor. The more modern couples were better able to deal with these pressures without an organized program. The organized program provided the less advanced strata with resources and support they apparently required to meet similar needs. The larger number of couples in the lower status and traditional groups gave a net result of concentrating family planning acceptances in those sectors believed hardest to reach and most important to population change.

Whether the Taichung-Taiwan experience is relevant to other countries can be answered only with research elsewhere, testing the results found by Freedman and Takeshita. For countries desiring a significant lowering of birth rates, the investigators recommend that policies be instituted to change the social and economic con-

ditions which affect fertility, in addition to providing birth control services.

CHILD HEALTH

Prenatal diagnosis offers hope for the prevention of mental retardation arising from genetic defects. Amniocentesis, a technique for diagnosis, involves drawing off a small amount of fluid surrounding the fetus and culturing the cells for chromosomal and biochemical analysis.

Drs. Henry L. Nadler and Albert B. Gerbie from the Department of Pediatrics and Obstetrics and Gynecology, Northwestern University Medical School, and the Genetic Clinic, Children's Memorial Hospital, Chicago, performed 162 transabdominal amniocenteses between the 13th and 18th weeks of fetal gestation as part of the management of 155 "high risk" pregnancies. The cultivation of amniotic fluid cells led to the intrauterine detection of 10 cases of Down's Syndrome, one case of Pompe's disease, one case of lysosomal acid phosphatase deficiency and one case of metachromatic leukodystrophy.

The experience of this study suggests that transabdominal amniocentesis early in the second trimester of pregnancy carries minimal risk to the mother and the fetus. The ability to detect genetic defects as early as the 16th week of pregnancy can give great precision to genetic counseling. If through amniocentesis, a fetus is proven defective, then parents can choose whether they want the pregnancy to go to term.

Amniocentesis is also being used to determine the maturity of the lungs of babies who must be delivered by Cesarean section or by induced labor near the end of the eighth month of gestation. At this time, amniotic fluid can signal the maturity of the fetal lungs and identify those babies who will be born "at risk" for respiratory distress syndrome (RDS). RDS therefore can be avoided by postponing delivery until the fetal lung matures sufficiently to adapt to an extrauterine environment.

Institute supported investigators, Drs. Robert C. Borer and Louis Gluck at the Department of Pediatrics, University of California, San Diego, have been able to measure the ratio of two lipids secreted by the fetal lung: lecithin and sphingomyelin. These lipids are secreted into the amniotic fluid. A sharp rise in the ratio of licithin to sphingomyelin in the amniotic fluid is an accurate indicator of the presence of adequate lung surfactant and therefore lung maturity. Surfactant is a complex lipoprotein which moistens the air sacs in the lungs and regulates the effects of surface tension on the size of the sacs, and prevents their collapse. If the sacs collapse, the baby is unable to utilize oxygen properly.

About 25 percent of infants born prematurely show signs of respiratory distress syndrome and between 20 and 40 percent of these will die. Probably between 20,000 and 25,000 newborn infants die each year with this syndrome.

Infants born to poor families often show evidence of prenatal bacterial and viral infections; a recent study showed that such infections lead to premature birth, with all its hazards to the life of the child.

Pathologists Richard L. Naeye of Pennsylvania State University and William A. Blanc of Columbia University College of Physicians and Surgeons based their study on data from 1,044 consecutive autopsies on stillborn infants, or infants who died shortly after birth.

In 36% of the autopsy cases, there was anatomic evidence of antenatal infection in the placenta, membranes, umbilical cord and/or organs of the newborn. Specific infectious agents were identified in over half the cases of infection, and the infections usually appeared to precede labor and rupture of the membrane.

Using income data and a government poverty index to classify cases by economic status, the investigators found that antenatal infection occurred in 45% of the whites and Puerto Ricans and 55% of the blacks with the lowest incomes. In the most prosperous group the rate of antenatal infection among whites was 27%, compared with 36% for Puerto Ricans and 38% for blacks.

Infants infected prenatally were, on an average, born three weeks earlier than were the noninfected infants. Since there were only small differences in the gestational age of infants from families at different socio-economic levels, the investigators concluded that the infection itself was responsible for earlier delivery.

In a long-term effort to decrease the infant mortality rate and to improve the health status of newborn infants, many aspects of the physiological events which surround delivery and birth are being explored by scientists supported by the National Institute of Child Health and Human Development.

One such team of investigators, headed by Takafumi Kudo, M.D., and J. F. Roux, M.D., of the Case Western Reserve University School of Medicine, Cleveland, Ohio, have been studying the role of the hormones noradrenalin and adrenalin before, during and after delivery, and in the newborn.

Increased noradrenalin output is related to increased physical activity and may alter the pattern of uterine contractions. By comparison, adrenalin output is more related to fear and emotional display. Both hormones have metabolic and physiologic actions, e.g., they increase cardiac output, arterial vessel tone and enhance the metabolic breakdown of carbohydrates and fats. Also, both hormones can be measured quantitatively in human urine. Labor and vaginal delivery cause marked changes in the emotional status, physical activity, cardiac output and regional blood flow of the mother.

Dr. Kudo and Dr. Roux have compared the output of noradrenalin and adrenalin by mothers who delivered vaginally and by mothers who

delivered by cesarean section. They found that while all delivering mothers show an increased output of noadrenalin above levels measured prior to delivery, the output was significantly higher in the group of mothers who delivered vaginally.

These investigators believe that increased levels of urinary noradrenalin may be related to onset of uterine activity. This belief is supported by the work of other investigators who have associated the presence of noradrenalin with uterine contractibility. It was also found that adrenalin output was only significantly increased during vaginal delivery--a fact that seems to reflect the apprehension of mothers who go through labor.

This research team found no difference in output of either hormone in infants who were delivered either vaginally or by cesarean section, and who had a good health status at birth. On the other hand, distressed newborn infants showed urinary concentrations of noradrenalin that were considerably higher than those of their non-distressed counterparts. It appears that the high levels of noradrenalin found in the distressed infant may result from an early activation of the sympathetic-adrenal system in response to metabolic acidosis. These findings may lead to the development of new indices of maternal and fetal status.

Efforts to decrease the incidence of mental deficiency by solving the problem of neonatal jaundice, which frequently causes brain damage, continue.

Gerard B. Odell, M.D., an Institute supported grantee at Johns Hopkins University School of Medicine, has continued his intensive studies of what happens to bilirubin, the principal pigment of bile, in the infant's body. Infants with too much bilirubin in their blood, a condition known as hyperbilirubinemia, are at risk of suffering neurologic impairment.

Dr. Odell has found that serum albumin (a protein in the plasma of the blood) exerts a protective action against the toxic effects of bilirubin. It is thought that serum bilirubin which is disassociated from albumin is free to diffuse into cells and exert its pernicious effect. An indirect estimate can be made to determine how much bilirubin is free to diffuse into cells by measuring the relative saturation of serum albumin with bilirubin.

Dr. Odell found that there was a significant correlation between poor psychometric performance and high saturation of the serum albumin with bilirubin during neonatal life.

Cognitive dysfunctions were studied in children four to seven years after their experience with hyperbilirubinemia in the neonatal period. Visual motor coordination, short term memory, abstract reasoning and distractibility were examined in these children.

No correlations were found between determinants of mental function at five years and the birth weights, sex, presence or absence of hemolytic disease, exchange transfusion, and the maximum

serum bilirubin. On the other hand, a significant correlation was found between the presence or absence of brain damage and the degree to which the patients' sera had been saturated with bilirubin.

Use of this new technique, measuring the saturation of serum albumin with bilirubin, will permit a more precise identification of infants likely to suffer brain damage from hyperbilirubinemia.

Another group of investigators who have been studying the problems of hyperbilirubinemia in the newborn, headed by Leo Stern, M.D., of the McGill University-Montreal Children's Hospital Research Institute, have found that the drug phenobarbital is useful in reducing the amount and the time course of normally occurring neonatal hyperbilirubinemia. It can also decrease an already elevated bilirubin level in the newborn.

Twenty full-term newborns who were given oral phenobarbital for the first four days of life had significantly lower concentrations of serum indirect bilirubin by the fourth or fifth day than a group of 20 control infants. Peak bilirubin levels in the treated infants were reached on the second day of life as opposed to the fourth day in the controls. Another 10 infants with elevated serum bilirubin levels received oral phenobarbital from the fifth to ninth day of life and by the tenth day had values lower than those in 10 controls.

Investigations by Drs. Arthur L. Rose and Cesare T. Lombroso of the Seizure Unit, Neurological Department, The Children's Hospital Medical Center and the Departments of Neurology and Pediatrics, Harvard Medical School, Boston have found that a full-term normal birth-weight neonate with convulsions who has a normal electro-encephalogram (EEG) has an 86 percent chance of being normal at age four regardless of any other clinical information or subsequent EEG data. On the other hand, a newborn infant with convulsions and grossly abnormal EEG's has only a 7 percent chance of normal development.

Further, in the experience of the investigators, neurological signs in a convulsing neonate have little value in predicting the outcome for the child several years later.

These findings emerged during a study of 137 full-term infants who developed seizures during the first three weeks of life and were followed for a mean period of almost four years. At the end of the study, about 50 percent of the subjects were found to be normal, 30 percent had survived with some serious neurological defect, and 20 percent had died.

In 75 percent of the cases, it was possible to assign a clinical or a pathological diagnosis. The etiology of about 25 percent of the cases was unknown.

They point out that since seizures in newborns are rarely as violent as in older infants or children and are almost never generalized, the emergency they present seems more related to detection of underlying causes.

Children who suffer from undernutrition in the first year of life are shorter, weigh less, have a smaller head circumference and a lower developmental quotient three to four years later than children the same age who were not undernourished.

Drs. H. Peter Chase and Harold P. Martin, at the University of Colorado Medical Center, studied children who were hospitalized for malnutrition during the first year of life. On the basis of social and medical histories, undernutrition was assumed to have been present from the time of birth to the time of admission in all cases.

The study suggests that undernutrition in the first year of life is detrimental to later development. This is the period of most rapid postnatal brain growth, cellular division and development of nerve cell covering in the human organism (myelination). Children undernourished for more than the first four months of life showed signs of cerebellar damage.

Language was the poorest area of development in both the control and test children although it was most severely impaired in the test children. One of the cases suggests that some undernourished children may catch up with their peers in physical growth, given the proper environment, but that head growth and brain function remain impaired.

To prevent the ill-effects of undernutrition, early diagnosis is essential. The investigators suggest that this might be accomplished by more emphasis on visiting-nurse services to high-risk families, and regular physical examinations in early infancy. If financial aid, social assistance and nutritional education are ineffective, day-care centers may be necessary to assure adequate nutrition of these infants.

ADULT DEVELOPMENT AND AGING

Investigators at the NICHD Gerontology Research Center, Baltimore, Maryland, are continuing to gather information on active, healthy, community-dwelling men participating in longitudinal studies on aging. The 600 volunteer participants, aged 20-96 years, visit the Center every 18 months (every year after age 70) to undergo a wide variety of tests. These physiological, psychological and medical tests are designed to discover how each individual ages by observing him at different points in his life span.

As part of the longitudinal study, results from "tapping tests" given to 325 study volunteers, aged 20-79 years, were analyzed by Dr. Nathan W. Shock and Arthur H. Norris during the year. The test involves tapping alternately between two targets drawn on paper. Target widths and the distance between targets are varied by design. This deceptively simple test is used to measure two control processes--a faster (motor) one concerned with arm and hand movements and coordination; a "homing" in (visual) one representing finer control.

Data analysis suggests that factors of position sense and

motor control decline more with age than do the decision making processes responsible for accurate homing in on the target. Investigations of this type are helping Center scientists clarify the decline in older people's ability to perform daily activities.

The longitudinal study group is also a unique resource for guest scientists wanting to test various ideas on a stable population group that may not be readily available near their own research institutions.

Recently, Rachelle Dattner, City University of New York, used longitudinal participants to test the hypothesis that older normal adults cannot alter their responses to various stimuli as easily as young adults. In other words, their behavior becomes more rigid.

Investigator Dattner had men generate different hypotheses about the content of blurred slides depicting common objects or scenes. Each object or scene was represented by a series of 15 slides. Each slide was blurred to a different degree--the first blurred beyond recognition and the last in sharp focus. She expected the older subjects to be more persistent in erroneously identifying blurred slides, and that they would generate fewer hypotheses of their content than would the young.

The first part of her hypothesis was proven wrong. The old subjects did not show an increased tendency to make erroneous responses to the earlier slides where the pictures were very blurred. On the other hand, the older subjects did not produce as many hypotheses relating to slide content as did the young.

This indicated a decrease in the older men's constructive processes involved in perception. However, the age differences noted in this study were considerably less than those observed in studies on less active populations. The results of this study suggest that continued activity by older individuals may reduce the incidence of age deficits in their constructive processes related to perception.

Operant conditioning techniques have been used for many years to change and control actions involving voluntary skeletal muscles. During the last decade, further research has shown that involuntary body responses can be operantly controlled. Such responses include heart rate, blood pressure, regional blood flow, etc. Several studies have also shown that patients with pathological involuntary body responses show improvement after operant training.

Investigators at the NICHD Gerontology Research Center, Baltimore, Maryland, have found that some patients with cardiac arrhythmias (abnormal heart rhythms) can learn to control these abnormalities and even maintain such control after leaving the hospital. Their research also showed that older as well as middle-aged patients can learn to effectively control heart rhythm through operant conditioning.

62-645 O - 71 - pt. 3 - 10

Drs. Theodore Weiss and Bernard T. Engel studied eight patients in the Center's Laboratory of Behavioral Sciences. They used operant conditioning techniques to train patients to control premature ventricular contractions.

All eight patients exhibited some ability to control heart rate during training; five of these also showed a decrease in premature ventricular contractions associated with learning to control heart rate. Even more significant from a clinical point of view, four patients showed continuing ability to voluntarily control their heart rhythm after completion of training sessions when they returned to their homes. One woman has exercised such control now for over two years. Two other patients, aged 62 and 68, respectively, learned to effectively control their heart rhythms indicating that training can still be accomplished in the later years of life.

These findings suggest that at least some aspects of cardiac ventricular function can be brought under voluntary control. Once such control is accomplished it can help bring about beneficial changes in cardiac function.

Dr. Engel and Mr. Sheldon Gottlieb have also developed a highly reliable animal model to use in studies of learned cardiac control. Three rhesus monkeys were taught to control their heart rates in response to light cues. This animal model preparation is proving extremely valuable in attempts to explain the physiological mechanisms underlying cardiac changes occurring as a result of voluntary cardiac control. In addition, the monkey is an excellent laboratory subject that may be useful in helping to design new procedures to benefit human patients.

Many of the current ideas concerning biological aging are based on changes with age in the expression of genetic information and activity. These changes may occur either in the structure or in the concentration of genetic material, such as deoxyribonucleic acid (DNA), or in the proteins synthesized as a result of transfer of genetic information by ribonucleic acid (RNA).

This year, Dr. Philip Gold in the NICHD Gerontology Research Center Laboratory of Cellular and Comparative Physiology found that major portions of soluble (dissolvable) RNA in rat kidneys show a two-fold decrease in replacement rate with age.

The investigator observed that the length of time required for 50 percent of the RNA to be replaced was 9.5 days for the old rat kidney but only 5.0 days for the young kidney. Soluble RNA in rat spleen also manifested a considerable reduction in replacement rate with aging but no age-associated differences were found in liver.

Age changes such as those seen in this study may very well alter the rate at which necessary cell constituents are produced. However, further studies will be needed before the exact physiological significance of such changes is known.

ENVIRONMENTAL HEALTH SCIENCES RESEARCH

NITRILOTRIACETIC ACID (NTA)

The search for substitutes for phosphates as "building agents" in detergents has resulted from the recognition that phosphates contribute to the eutrophication in water supplies. One compound developed as a substitute is nitrilotriacetic acid (NTA), a chelating agent which because of its ability to complex with calcium and magnesium can be substituted for phosphate.

Though the current use of this compound is limited, it has been projected that by 1975 over one billion pounds would be used in household detergents. The chemical properties of this strong chelating agent were recognized as a basis for potential hazards from excessive concentration in water supplies, and a series of studies was performed on the compound prior to its introduction into common use. Health concerns resulting from the environmental distribution of this compound reside in several areas: (1) its potential persistence in water supplies, (2) its solubilizing metals in water and sewage systems with potential toxic concentrations being made available, and (3) alteration in metal metabolism in man. Under industry sponsorship, environmental and toxicological studies were performed on NTA; and it was shown that the material under aerobic conditions is biodegradable and that, as a result, both environmental and health hazards would appear to be minimal. Studies on NTA metal chelates were not performed, however. At the request of the Federal Water Quality Administration (FWQA), studies on the toxicity of the chelates were undertaken by the National Institute of Environmental Health Sciences to assure maximum degree of safety in the use of this material. The toxicological studies undertaken by NIEHS included general systemic effects as well as specifically the potential teratogenicity of both the unchelated and chelated NTA. In this way, the theoretical hazards posed by the universal distribution of a potent chelating agent could be studied in animal model systems.

In a series of experiments undertaken by Dr. Diane Courtney and Dr. Neil Chernoff of the Pharmacology and Toxicology Branch, two metals, cadmium chloride and methyl mercury chloride, were studied in combination with NTA.

Administration of NTA to mice or rats produced no significant toxic effects on mothers or fetuses.

The effects of cadmium chloride or cadmium chloride/NTA chelate showed that the chelate produced maternal mortality and fetal abnormalities at significantly lower dose levels and in much higher percentages than cadmium chloride alone produced.

Methyl mercury was also studied in protocols similar to those used with cadmium chloride. Methyl mercury/NTA was fetocidal with 53 percent mortality) while the equivalent amount of methyl mercury alone was similar to the controls (5 percent). Abnormal fetuses were produced by a lower dose of methyl mercury/NTA compared to the methyl mercury chloride. The combination of methyl mercury and NTA

appears to enhance both the fetal toxicity and the teratogenicity of methyl mercury.

In summary, at the doses employed, all considerably higher than would ordinarily be encountered by the human population, cadmium and methyl mercury administered alone to two species of animals yielded a small number of significant abnormalities. In contrast, each of these two heavy metals when administered at similar doses simultaneously with NTA yielded a significant increase in embryotoxicity and congenital abnormalities.

The teratogenic effects produced by the cadmium/NTA and methyl mercury/NTA combinations are similar to those caused by the metal alone. These experiments have indicated that the toxic and/or fetotoxic effects caused by these metals may be potentiated by the presence of NTA.

Another study, supported by and performed in collaboration with NIEHS, was conducted by Dr. Robert A. Goyer at the University of North Carolina at Chapel Hill. His findings on the toxicity of lead/NTA chelates in the rat similarly produced evidence of synergistic action with respect to lead toxicity.

MERCURY

Organic mercurial levels in water, fish, and other foodstuffs have become a matter of serious concern in the U.S.A. Japanese and Swedish experiences of the past two decades provide a firm foundation for realistic apprehension over the toxicity of these compounds. Building on previous animal models, Dr. Ronald Klein and Dr. Sheldon Herman of the Pathologic Physiology Branch have reproduced in rats acute and subacute Minamata disease, a severe neurological disorder resulting from poisoning by organic mercury and leading to severe permanent neurological and mental disabilities or death.

Murine Minamata disease has been produced via subcutaneous injection of methyl mercury hydroxide, clinically manifest initially by weight loss and decreased food ingestion followed by lethargy, ataxia, priapism, crossing of the hind limbs, and death in two to four weeks.

Pathologic changes have been found in the central and the peripheral nervous system and certain visceral organs. Demyelinization of peripheral nerve fibers occurred three days after initial exposure. Glomerular changes have been found in rats treated with sublethal levels of methyl mercury. Inhibition of several detoxifying enzymes in liver has occurred 24 hours after initial exposure as have marked alterations in the ribosomes of the brain, kidney, and liver.

A major goal of research in this area is to identify early diagnostic and therapeutic approaches to organic mercurial intoxication.

CADMIUM

Cadmium enters the environment as a major by-product of numerous industrial processes and in consumer products. Kidney damage has occurred in alkaline battery workers exposed to cadmium. Cadmium is present in cigarette smoke, and its role in the toxicity of smoking is under study. Its use in food containers with acidic foods has led to cases of cadmium poisoning following ingestion.

Several reports have indicated that cadmium may cause abortion in the mouse and teratogenic effects in the hamster. A study is in progress in the Pharmacology and Toxicology Branch to determine the extent of fetal involvement as a result of maternal cadmium intake in experimental animals. Preliminary studies have shown a variety of effects from teratogenicity to death in the fetuses of rats. Of special interest is the demonstration of a dose response relationship during the second half of organogenesis.

BERYLLIUM

Beryllium is a metal widely used in alloys, rocket fuels, and in the electronics industry. Its compounds as dusts or fumes are known to cause granuloma formation in humans; and beryllium salts are known to be carcinogenic in experimental animals including primates. To increase our knowledge in this area, research is in progress at two university-based centers supported by grants from NIEHS; one at the University of Cincinnati School of Medicine and the other at the Vanderbilt University School of Medicine. In addition, Dr. Andrew L. Reeves, a grant recipient at Wayne State University, is also engaged in studies on beryllium toxicity.

Cell organelles are being studied to determine the mechanism whereby inhaled beryllium and other metals become localized in the cell and to determine whether these contaminants interact with or replace metals normally present in tissues. Little is known at this time about the fundamental mechanism by which beryllium causes its biological effects. Results of ongoing studies using tissue culture methods suggest that beryllium concentrates in the nucleus of the cell and inhibits mitosis, synthesis of DNA, and synthesis of nucleolar but not nuclear protein. The importance of protein denaturation, enzyme inhibition, and autoimmune hypersensitivity in the pathogenesis of pulmonary berylliosis is also being investigated. Beryllium interference with DNA synthesis may provide the key to the carcinogenic properties of this metal in experimental animals.

ALKYLATING AGENTS

Alkylating agents are highly reactive compounds which react with electron rich groups; e.g., amino, sulfhydryl, and hydroxy. These agents frequently show some preferential localizations, probably as a result of differential distribution and binding with tissue components. They are widely distributed in our environment and found in all categories of pesticides, as chemical intermediates in many industrial processes and as waste products of industry. Thus, environmental exposure to alkylating agents follows from many sources.

Dr. Robert G. Owens, Chief of the Cell Biology Branch, is investigating the basis for preferential localization and binding in cells and tissues which are primary targets for various alkylating agents. He is investigating the effect of chronic exposure on threshold toxic doses, the molecular basis for preferential accumulation, the enzymes and metabolic processes most sensitive to a variety of toxicants, and the molecular mechanisms for toxicant interaction with target receptor site. Intermediary metabolism, genome and feedback regulation, protein synthesis, and energy releasing and conserving processes are the endpoints being quantified.

Dr. Owens' studies in rats on the metabolic targets of alkylating agents indicate that phenylmercuric acetate (PMA), 2-chloroethylmethane-sulfonate (CEMS), and triethylphosphoramide (TEPA) accumulate differentially in the various organs of the rat. Follow-up studies indicate the effects by PMA and TEPA on organic acid metabolism in the liver and possibly in other organs. Parallel histopathological changes in various tissues after treatment with these agents have also been shown. Although no crucial and highly specific changes are traceable to the toxicants, degenerative changes typical of aging at an accelerated rate are noted. Experiments designed to determine the molecular basis for the degenerative manifestations of senescence following administration of the chemical are in progress.

PESTICIDES AND SYNERGISTS

Members of the NIEHS staff continued work on the teratogenicity of 2,4,5-T and its esters. They concluded that not only are 2,4,5-T and its esters teratogenic in mice but also that the contaminant dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) is exceptionally toxic and teratogenic.

Accidental or suicidal ingestion of Paraquat by humans has been reported to produce a proliferative and a delayed effect on the lung which can result in death. The herbicide is used extensively as a substitute cultivator or week killer and is thereby made accessible to the lungs during spraying. The unusual proliferative development following a single dose of Paraquat is now being studied in rats by Dr. Charles Sharp of the Pharmacology and Toxicology Branch. In investigating the toxicological aspects of Paraquat poisoning, he found that the agent persists in the lung up to 11 days after exposure. This finding questions the "hit-and-run" concept of action although it is still possible that a process initiated by the Paraquat might proceed with a lack or minimal need for persistence of the Paraquat.

Use of the carbamate group of pesticides will undoubtedly increase as they are being substituted for the chlorinated hydrocarbons. The carbamates are all acetylcholinesterase inhibitors. Their widespread use could conceivably result in sufficient maternal uptake to affect the fetus. There are indications that at least carbaryl is teratogenic in laboratory animals. In a study underway in the Pharmacology and Toxicology Branch, the effects of the carbamates on fetal levels of acetylcholinesterase

are being measured. The technique may provide a useful and simple screen for acetylcholinesterase-inhibiting effects of environmental agents in general. Thus far acetylcholinesterase levels have been determined in fetuses of 13-22 days of gestation. There is a gradual increase in enzyme activity as gestation proceeds. Higher levels of activity are found in the limbs than in the head or in various regions of the brain. Measurable amounts of the enzyme have been found in fetuses of all ages tested.

The present widespread use of piperonyl butoxide as a synergist for insecticides in home and garden raises the question of its toxicity to mammalian organisms. Dr. Anna Ottolenghi of the Pathologic Physiology Branch has evaluated the toxic effects of chlorinated hydrocarbon pesticides and piperonyl butoxide on pregnant hamsters. Animals treated with aldrin, dieldrin, and endrin show a two-fold increase in the frequency of resorption and intrauterine death of the fetuses when compared to controls. Administration of piperonyl butoxide alone has a similar enhancing though more variable response. Combination of the synergist with dieldrin and endrin gives consistently high proportion of resorptions, the average number exceeds 50 percent and all treated animals are affected. In contrast, aldrin and the synergist do not appear to cause a signigicant increase. This investigation strongly suggests that the development of the fetus is impaired by doses of these compounds which are not lethal to the mother and well below the accepted LD_{50} value for the same species.

NATURAL PRODUCTS

Toxigenic species of the fungus Alternaria are apparently ubiquitous. A number of species has long been recognized as important plant pathogens, and recent studies indicate that many species associated with agricultural commodities produce metabolites toxic to mammals. Thus, there is growing evidence that Alternaria may rank in importance as potential hazards in foodstuffs with the better known toxigenic Penicillia, Aspergilli, and Fusaria.

Several toxic metabolites of Alternaria spp. have been isolated and identified, and a number of others have been isolated but only partially characterized. Some of them are toxic to a wide spectrum of organisms, including bacteria, fungi, viruses, and higher plants. NIEHS scientists, Dr. Ronald W. Pero, Dr. Robert G. Owens (both of the Cell Biology Branch) and Dr. Stephen W. Dale (Analytical and Synethic Chemistry Branch) in combination with Dr. Donald Harvan of North Carolina State University, have isolated a previously unknown metabolite from four-week old cultures of the fungus Alternaria tenuis. The compound was given the trivial name altenuene. Altenuene is structurally related to two previously characterized A. tenuis metabolites, alternariol and alternariol monoethyl ether.

An increasing awareness has developed regarding the widespread occurrence of toxin-producing microorganisms in foodstuffs; and it has been shown that metabolic products from these organisms may cause serious pathologic lesions. A number of grants are being supported by NIEHS for the detection, identification, and

biological evaluation of these toxic products in foods; these include grants to Dr. T. Calvin Campbell of Virginia Polytechnic Institute, Dr. Eugene B. Smalley of the University of Wisconsin, Dr. Roslyn B. Alfin-Slater of the University of California at Los Angeles, and Russel O. Sinnhuber of Oregon State University.

These NIEHS grantees are investigating aflatoxins, metabolic products of the mold Aspergillus flavus, to improve methods for their detection and identification in food samples, to assess their toxicities, and to determine how these toxins are metabolized by the animal ingesting them and the pathways whereby they are transmitted through milk to the offspring. Some grantees have shown that zearalenone, a toxic metabolite of the fungus Fusarium, induces abortion and fetal resorption when fed to rats. Support will be continued to assess the hazard of this and related metabolites added to cattle feeds.

FOOD ADDITIVES

The widespread use of sodium nitrite as a preservative in meat and fish as well as the growing use of high nitrogen fertilizers raises the question of the possible conversion of nitrate to nitrite in foods and water. The role of nitrite as an environmental reagent in the possible production of nitrosamines, a group of potent chemical carcinogens, points to yet another potential environmental hazard. The role of nitrite in methemoglobin formation in contrast is well documented. Because nitrite in baby foods may contribute to the onset of methemoglobinemia, it is important to determine conditions enhancing formation of nitrite as well as other reduction products. The levels of nitrate in a variety of baby foods have been studied by Dr. Lawrence Fishbein, Chief of the Analytical and Synthetic Chemistry Branch, and under parameters of ambient and elevated temperatures as well as exposure to microorganisms the possibility of nitrite formation was investigated.

The average nitrate content of carrots, spinach, green beans and squash lies between 30 and 100 ppm except for beets where it reached 250± 100 ppm. There were no detectable differences among brands but considerable variations in nitrate content from lot to lot within brands of all foods tested (nitrite concentrations were zero or near zero). When foods were heated to 80 degrees centigrade for 30 minutes and cooled to room temperature (1.5 hours), no significant changes in nitrate content were found. No significant changes were observed following exposures of the various baby foods to air at room temperature for one week. However, in all vegetables tested, the addition of microorganisms resulted in highly significant decreases in the nitrate levels. Carrots, spinach, and green beans showed no increased nitrite levels because reduction progressed all the way to ammonia formation, but the nitrite level increased in beets exposed to microorganisms, particularly at 35 degrees centigrade.

An NIEHS grantee, Dr. Frederick Coulston of Albany Medical College in New York, is testing the artificial sweetener, saccharin, to characterize the metabolic products of that compound. Oral

administration to rats has shown no significant tissue residue; however, four metabolic products were detected in the urine. These are being identified for further testing to assure the absence of toxicity of the metabolites.

MICROWAVES

Much of the research of the biologic effects of microwaves has been carried out in microwave fields of unknown characteristics. Over 100 percent variation in experimental results have been reported for supposedly identical exposure levels. Many investigators have stated in their publications that they are not certain what the field intensity was at the specimen. In order to obtain meaningful results, it is necessary to have a well defined, calibrated, uniform microwave field. With the assistance of consultants from the Georgia Institute of Technology, Dr. Donald I. McRee and Dr. Phillip J. Walsh of the Biophysics and Biomedical Instrumentation Unit have designed a biological exposure system to meet the desired set of specifications. This system incorporates the latest developments in microwave generation and measurement equipment. There is very little information concerning the effects of low-level, long-term exposure of biological material to microwave radiation. Now with the microwave exposure system and dosimetric studies proposed in this project, accurate quantitative investigations can be accomplished.

MEMBRANES

There is abundant evidence that the critical site of interaction between environmental agents and cell components is at the membrane level. This is as much so for the desired activity of drugs as it is for the adverse effect of toxicants. Toxicant membrane interactions are therefore important in nerve and muscle cells where electrical impulses associated with the membranes serve to control movement, both voluntary and involuntary, as well as sensory phenomena. Investigations of membrane properties and associated phenomena and the effects of various environmental toxicants on these properties are fundamental to understanding and providing a basis for control of potentially hazardous compounds whose primary targets are membranes and/or specific membrane components.

In research supported by NIEHS, Dr. D.C. Tosteson and associates of Duke University Medical Center are characterizing the interactions of various environmental toxicants with nerve cell membranes to determine those most relevant to maintenance of physiological activity. Work includes the determination of the effects of certain heavy metal ions on nerve action on neurons in the cerebral cortex or in the brain stem of cats. He has found that nickel, manganese, and zinc ions depressed the firing of spontaneously discharging or excited neurons. Studies on iron, lead, and cobalt ions are as yet unfinished.

Mitochondria also provide a sensitive tool with which to study environmental agent-membrane interactions inasmuch as phosphoryla-

tion and electron transport require intact membranes for optimal function. Dr. B. Dean Nelson of the Cell Biology Branch has been investigating the effects of environmental agents on the biochemistry and biogenesis of mitochondria. In in vitro studies on yeast cells, various types of pesticides have been tested, including representatives of chlorinated hydrocarbons, cyclodienes, methylenedioxyphenyl compounds, triazines, carbamates, 2,4-D and its derivatives, organophosphates, and miscellaneous pesticides. Only certain cyclodienes (chlordane, heptachlor, aldrin, and lindane) appear to induce respiratory deficient nutants. These preliminary results provide the first indication that the toxicity of certain pesticides may be due to direct action on energy metabolism and emphasize the need for further studies on mitochondria in peripheral nerve or other cells where the high lipid content would be expected to favor accumulation of lipophilic toxicants.

ENDOCRINE TRACE ELEMENT INTERACTIONS

Studies by Dr. William Jurgelsky of the Pathologic Physiology Branch are in progress to define the structural and chemical changes that occur within the hypothalamic-pituitary-thyroid axis of the opossum in response to iodine excess and iodine deficiency. The opossum provides a unique model because of the availability of embryos for experimental manipulation in the earliest stages of organogenesis. Relevance to the situation in man is suggested by the development of intrafollicular thyroiditis in response to the administration of potassium iodide at levels within the therapeutic range for humans. Combined structure-function studies in progress have shown alterations in hypothalamic-pituitary-thyroid axis in response to iodine excess or deficiency.

MUTAGENESIS

The mutagenic potential of a chemical or physical agent depends significantly upon the ratio of mutagenic to lethal lesions and upon the ability of repair processes to preferentially repair potential lethal defects. Thus, substances which interfere with or inhibit preferential repair of lethal defects are likely to preclude mutagenesis via a killing affect whereas substances augmenting preferential repair on inhibiting repair of mutagenic alterations are certain to increase the frequency of induced, and possibly of spontaneous, mutations.

Studies by Dr. W. G. Flamm of the NIEHS Cell Biology Branch indicate that two types of DNA lesions may result from interaction between DNA and alkylating agents; e.g., covalent crosslinks and monoalkylated moieties. These studies indicate that the covalent crosslink, which prevents DNA synthesis and is therefore lethal, is rapidly and preferentially repaired. The monoalkylated strand is less rapidly dealkylated but can act as a template for semiconservative DNA replication. Monoalkylation, therefore, may register as a mutation whereas potentially lethal alkylation may be repaired. Studies are in progress now on the effects of caffeine on the rate of removal of both mutagenic and lethal lesions.

COKE-OVEN WORKERS

Studies are in progress by Dr. J. William Lloyd of the NIEHS Epidemiology Branch and Dr. Antonio Ciocco of the University of Pittsburgh to determine which excesses and deficits in cause-specific mortality are associated with particular occupational subgroups in the steel industry and the possible relation of variations in mortality to length of industrial exposure.

Analysis of Allegheny County data through December 1961, showed that non-white coke-oven workers employed at the "topside" of the ovens had experienced lung cancer mortality markedly in excess of that predicted by the mortality rates for other non-white steelworkers (14 observed vs. 2.2 expected). The level of risk for white "topside" workers could not be determined because of the small number of white men employed in that area. The mortality experience of men employed at other areas of the coke-ovens was also suggestive of a possible lung cancer excess for white (8 observed vs. 5.3 expected) and non-white (9 observed vs. 5.9 expected) employees.

The finding of such a striking mortality differential in the non-white "topside" workers could not be explained by any bias in selection or differences in demographic characteristics of coke-oven workers and other steel workers in Allegheny County. On the other hand, an earlier unpublished study of U. S. coke-oven workers showed a lung cancer excess limited to non-white workers in Allegheny County. A number of other occupational groups within the steel industry may have experienced higher than expected mortality but because the number of years at risk through 1961 for men employed in these occupations was too small to allow for a firm conclusion of excess risk, the study period was extended through 1966. These studies will provide information regarding the pathogenesis and epidemiology of cancer and other chronic diseases as related to certain occupational exposures. They are also of great value in developing methodologies for field studies of chronic illness consequent to exposure in the occupational environment.

UNDERGROUND URANIUM MINERS

Objectives of a project by Dr. Frank E. Lundin, Jr., of the Epidemiology Branch in cooperation with the Bureau of Occupational Safety and Health (BOSH), are to study the cause-specific mortality experience of underground uranium miners in relation to routine medical examination findings, cigarette smoking, and airborne radiation exposure data; to determine the quantitative relationship between airborne radiation exposure and the incidence of respiratory cancer; to delineate the role of a number of factors which might influence carcinogenic response to airborne radiation; and to develop realistic models for relating environmental exposure to cancer and other chronic diseases.

A study of mortality experience among 3,415 white underground uranium miners during the period 1950 through September 1967, has shown an excessive occurrence of respiratory tract cancer (62 deaths observed vs. 10 expected). Study of quantitative

relationship between airborne radiation and respiratory cancer shows that age-standardized incidence tends to increase progressively from the lowest cumulative exposure category to the highest. The dose-response relationship persists when confounding variables are taken into account, among them being time since onset of exposure as well as cigarette consumption. The carcinogenic effect of airborne radiation is specific for the respiratory tract.

The pathology of respiratory cancer in uranium miners is unlike that observed among an age-smoking-residence matched control group while being similar to that observed among factory workers exposed to a radiomimetic agent, mustard gas. Mortality from respiratory tract malignancy increased from a four-fold excess in an earlier analysis to a nine-fold excess for the succeeding 3 year, 9 month period. A relatively greater excess occurred after the age of 45 years. The age effect could not be explained by amount of radiation exposure and number of years after onset of underground uranium mining. The great excess of lung cancer among U. S. uranium miners is largely limited to cigarette smokers. However, data are insufficient to determine whether non-cigarette smokers have a significantly increased risk.

EYE INSTITUTE

In 1970, significant progress against vision disorders was made by National Eye Institute and Institute-supported scientists in four major categories: disorders of the retina and choroid, inflammatory disease, glaucoma, and strabismus.

DISORDERS OF THE RETINA AND CHOROID

The retina is the photoreceptive tissue lining the eye that converts light into nervous impulses which are transmitted to the brain. This immensely complicated structure reflects not only disorders occurring immediately within it but problems in the brain as well. The retina can be seen and studied directly by means of special instrumentation.

A variety of systemic disorders are diagnosed by observing changes in retinal nervous elements and blood vessels. Changes in the choroid, a tissue rich in blood vessels which provides nutrition for the overlying retina, may also indicate disease in the retina and elsewhere.

Significant advances in diagnosis of retinal and choroidal disorders have been made possible through the development and increasing use of fluorescein angiography by Institute grantees. This technique permits the direct observation of blood flow through ocular vessels and can assist in pinpointing the site of disease.

Lasers. During 1970, evaluation of the clinical efficiency of various types of lasers to treat retinal and choroidal disease continued with grant support from the National Eye Institute. Those which have remained the preferred instruments for human therapy are the argon laser which emits a continuous beam of green

light, and the photocoagulator which emits a bright white light. Institute grantees, Christian Zweng of the Stanford University School of Medicine and Arnall Patz of John Hopkins University School of Medicine, demonstrated that the continuous beam of the argon laser, used in conjunction with fluorescein angiography and a delivery system which enables fine focusing and precise aiming, permits its use at power levels which will not damage the underlying choroid.

Retinal detachment. Research to refine the treatment of retinal detachment (separation of the retina from the choroid leading to blindness if not treated) was conducted by a number of investigators supported by NEI. Harvey A. Lincoff of Cornell University Medical College demonstrated that cryosurgery (freezing) may be an alternate to diathermy (heating) in reattaching the retina. It is possible that for certain cases, cryosurgery may permit treatment of retinal detachment on an outpatient basis. This change in clinical procedure could have profound economic effects in reducing the costs of medical and hospital care currently associated with this condition.

More effective instruments for the treatment of retinal breaks and detachments were developed. A retinal cryopencil has been designed by Charles L. Schepens at the Retina Foundation in Boston. With this device, extremely low temperatures are produced from the expansion of carbon dioxide. The cryopencil has been used successfully in the more efficient treatment of retinal breaks, lattice degeneration, and tumors.

Experimental retinal detachment in the monkey has been successfully treated by Robert Machemer of the University of Miami by replacing the vitreous humor with air. Clinical applications are contemplated.

Ultrasound. Ultrasound as a useful tool in ophthalmology was further developed during the year. The technique was used by Adnan Sokollu of Case Western Reserve University to produce focal chorioretinal lesions (a form of "spot-welding"), diagnose diseases in the eye and orbit, localize and describe orbital tumors, and locate foreign bodies in the eye.

Narcolepsy diagnosis. Narcolepsy, a condition characterized by sudden and uncontrollable attacks of deep sleep, has been diagnosed by R. W. Hollenhorst of the Mayo Foundation in Rochester, Minnesota, observing the reaction of the pupil in darkness. The pupillary size in darkness and the reaction time to a controlled light stimulus were measured. In narcolepsy, the pupil is found to be smaller than normal in total darkness and to react more sluggishly to light. This finding could have significant application in pretesting and screening for this disorder in drivers and others involved in high-risk jobs.

RLF. Retrolental fibroplasia (RLF) was believed to have been eliminated as a result of NIH-supported investigations which revealed its cause. But this disease continues to be a problem

because of the administration of oxygen to infants suffering respiratory distress. Present efforts in this field are directed toward determining oxygen concentration in the tiny retinal arteries and to detect pre-RLF vessel changes in newborns as a means of early diagnosis and prevention of pathological changes in the retina.

Arnall Patz of Johns Hopkins University developed an RLF animal model using fluorescein angiography which permits the action of oxygen on the immature vessels to be accurately correlated with the metabolic needs of the retina.

Color Vision. A significant advance in describing the mechanism of color vision at the cellular level, thereby aiding the understanding of the visual process and retinal pathology was made by Peter Gouras of the National Eye Institute. He observed that three mechanisms in the cone cells of the retina, for red, green, and blue, converge on single neurons in the visual cortex which subserve foveal, or fine vision. This finding provides the first description of color vision at the level of a single nerve cell.

Retinitis pigmentosa. The reversal with vitamin A therapy of a form of retinitis pigmentosa, an inherited disorder which causes night blindness and a gradual loss of visual field, in patients with a rare metabolic disorder, the Bassen-Kornzweig syndrome, was also reported by Dr. Gouras. This is the first time a degenerative disease of the retina has been reversed, indicating the possibility of long-term or even permanent management of this and other forms of retinal degeneration.

INFLAMMATORY DISEASE

Corneal disease. An epikeratoprosthesis, a contact lens which is fixed by an adhesive to the cornea was used by Claes H. Dohlman at the Retina Foundation to act as an artifical covering for the cornea in the treatment of bullous keratopathy, blistering of the cornea which may result from severe disease or trauma. In addition to improving vision, this therapy was valuable in relieving pain. In monocular aphakia (absence of the lens in one eye) it was useful in those cases where regular contact lenses were not tolerated. However, it may become detached from the cornea, requiring reapplication. This technique offers a stop-gap therapy which may postpone the necessity for corneal transplantation. Where the cornea is relatively unscarred, good vision is obtained with this therapeutic procedure and prosthesis.

The use of heparin to relieve clotting and promote healing in blood vessels adjacent to the cornea, a common complication of several diseases of the cornea, was demonstrated by Samuel B. Aronson of the University of California, San Francisco. This therapy has been encouraging in comparison to the clinical results obtained with other recommended modes of management.

Herpes virus infections. Theories which would explain both the recurrence of herpes virus infections in some individuals as well as the frequency of infections, were advanced in NEI-supported studies

by Peter R. Laibson at the Wills Eye Hospital in Philadelphia. Herpes virus causes harmless fever sores in the mouth but can cause serious damage when it infects the cornea. A herpes-specific antibody which should neutralize the virus is known to be present in tears. Dr. Laibson believes that recurrences of herpes simplex are likely to be due to a chronic infection of the lacrimal glands which make tears rather than to any latent infection within the cornea itself. The level of herpes antibody in tears is independent of the level of circulating antibody in the bloodstream. Antibody can be present in one eye and not the other and vary from time to time.

An explanation for why herpes virus isolated from conjunctiva continues to be infectious despite the presence of sufficient antibody was offered by Herbert E. Kaufman of the University of Florida who demonstrated that circulating gamma-G antibodies envelop the herpes virus and protect it from the specific neutralizing antibody secreted in the eye. The concept of a "protective" gamma-G antibody is novel and may bear fruit in the field of oncology as well, since herpes virus has been implicated in cancer of the cervix and Burkitt's lymphoma.

For those patients requiring corneal transplantation in the management of chronic corneal herpes simplex infection, an optimal course of treatment has been derived. Management combines steroid and antibiotic drugs with corneal transplantation immediately following the recovery from inflammation. Corneal grafts performed at the University of California, San Francisco, remained 80 percent clear with this regimen. These results compare favorably with patients referred for transplantation years after inflammation had subsided. The therapy frequently resulted in 20/30 vision in less than six months. The final step in rehabilitation of these patients is the use of corneal contact lenses principally for correction of irregular corneal stigmatism.

Cataract. Progress toward the medical management of cataract was made during the year by NEI grantee Jin Kinoshita of Harvard University who was able to prevent the formation of galactose cataracts in rabbit lenses cultured in a galactose medium. Rabbit lenses cultured in the sugar medium will develop opacities and swell during the first four days of culture. But, when tetramethylene glutaric reductase (TMG) which inhibits aldose reductase, the enzyme implicated in cataract formation, is added to the medium, cataracts do not form during an eight-day incubation period. This is the first time an experimental cataract has been successfully prevented.

Treating damaged corneas. In analysis of normal and damaged corneas, Stuart I. Brown of Cornell University Medical College, demonstrated that the normal cornea does not produce detectable quantities of the enzyme collagenase, which causes rapid breakdown of the cornea following injury. The enzyme is found in deep abrasions, alkali burns, and in corneal ulcers. Use of corticosteroids increased 15-fold the destructive action of the enzyme. The amino acid cysteine, a known collagenase inhibitor, was the most effective agent for preventing ulcers in alkali-burned rabbit corneas and is now being used on patients with alkali burns and those suffering from

corneal transplant rejection.

GLAUCOMA

The term glaucoma refers to a group of ocular disorders all characterized by an elevation in the intraocular pressure which will cause a loss of retinal function and eventual blindness if the condition is untreated. Despite the fact that if detected early, most glaucoma can be controlled by medication, it remains one of the leading causes of blindness in the Nation. An estimated 1.7 million persons suffer with this disorder.

Therapy. Better control of the intraocular pressure by medical therapy is under continuing study in several major laboratories. One of the most promising areas of study involves the effort to enhance the effect of the adrenal hormone norepinephrine on the sympathetic nerves of the eye, which subsequently lowers the intraocular pressure. Investigators at Johns Hopkins University have been particularly interested in this approach and have stimulated such research at Yale University, Mt. Sinai, and Washington University with NEI support.

Bernard Becker of Washington University School of Medicine in St. Louis is following 1,000 patients with open-angle glaucoma to demonstrate the possible association of other systemic and ocular diseases with this disorder. Diabetes has been found more common among glaucoma patients and in those who respond to topical corticosteroids with a high increase in intraocular pressure. Glaucoma has been found more frequently in diabetic populations. The high response to steroids appears to be associated with a less proliferative retinopathy in diabetics, but glaucoma patients with diabetes appear to develop visual field loss more readily. In another part of this study a test was developed employing the anticonvulsant drug sodium diphenyhydantoin (Dilantin) which may be useful in determining which of the subjects who respond to steroids may develop chronic simple glaucoma.

Primary open-angle glaucoma, the leading cause of blindness in adults, is unusual in adolescents and young adults. The glaucoma which occurs in young patients is usually due to a recognizable abnormality of the eye's anterior chamber angle or results from other ocular disease. However, several young patients with visual loss from primary open-angle glaucoma were referred to a research team headed by Dr. Robert Goldwyn at the Washington University School of Medicine in St. Louis prompting a review of the glaucoma records of one referral practice. An analysis of 111 glaucoma patients, aged 10-35, revealed that 25 percent had primary open-angle glaucoma. This finding led the Institute-supported investigators to advise that tonometry (a test to measure the intraocular pressure) be performed on all patients old enough to cooperate, especially those with a family history of glaucoma.

In another Institute-supported study, Mansour F. Armaly at the University of Iowa subjected the standard water-drinking test, a provocative test for primary open-angle glaucoma, to critical eval-

uation. He found that the induced rise in intraocular pressure normally becomes greater with age and is independent of the initial pressure level. There is also in aging a normal reduction in the flow of the intraocular fluid from the eye. These findings revealed that failure to account for age constitutes a major error in the test as usually performed. The investigator has developed various norms based on age and initial pressure in order that interpretation of data may provide more valid prognostic information.

STRABISMUS

The study of eye movement (ocular motility) concerns the ability of man to direct and maintain the visual axes of the eyes upon both moving and stationary objects. This permits integrated binocular visual perception and the unique quality of depth perception. Elaborate anatomical and physiologic mechanisms underlie the rotation of the eyes. "Strabismus" is a deviation of the eyes which a patient cannot overcome. Continuing deviation may lead to the disorder known as amblyopia, the loss of functional visual acuity in the eye without a precipitating organic cause.

Research in strabismus is directed toward understanding the sensory and motor features necessary for binocular single vision. E. W. Baugh at Harvard University identified for the first time a group of cells in the visual cortex of macaque monkeys which play an important part in stereoscopic depth perception. The cells are believed to link the visual fields from each eye thereby creating the ability for three-dimensional vision. These observations will contribute to greater understanding of the mechanisms involved in human disorders of binocular vision.

NEI-supported studies by Leo Ganz of Stanford University Medical School of visually-deprived young kittens indicated that blocking the sight in one eye induces changes in the connection of optic nerve fibers to the visual cortex in the brain. Certain visual cortex neurons have very selective receptive fields and are particularly important in the perception of visual form and for making fine spatial adjustments. However, the kittens' deprived eye could activate only those cells having larger receptive fields and which are less selective with regard to shape, orientation, and direction of motion. When using only the deprived eye, these animals had great initial deficiencies in perceptual-motor coordination, in depth estimation, and in the ability to discriminate among visual forms in a controlled visual environment. When the deprived eye was exposed to a normal visual environment, some of these deficits were corrected. This effect simulates in some respects the clinical response to treatment of amblyopia in young children.

Models. A model for the study of amblyopia ex anopsia (visual loss from disuse resulting from some type of occlusion) was developed by Gunter K. von Noorden of Johns Hopkins University using rhesus monkeys whose one eye was surgically closed for four weeks after birth. Severe permanent visual impairment was observed in the deprived eye. But when the eye was closed at age 3 months or after, rapid functional recovery of vision resulted.

Dr. von Noorden also developed a strabismic amblyopia model by operating on rhesus monkeys to produce an inward-deviated eye. Visual acuity was good in animals operated on in the first week of life. But recovery of visual acuity was very slow after closure of the experienced eye. In addition, amblyopia was absent in monkeys in which the eye was deviated later in life and in a group in which the eye was turned outward. The visual behavior pattern of strabismic monkeys is strikingly similar to that of human patients and may serve as an experimental model.

OTHER RESEARCH

Embryology. Studies of the development of the visual tissues in embryos advanced understanding of congenital diseases of the eye and of refractive errors, the most common form of visual impairment. Alfred J. Coulombre of the National Eye Institute furthered his studies on the interdependence of the developing visual structures by demonstrating the cellular events leading to the destruction of the developing cornea that occur when the lens is extracted early in life of a chick embryo. Dr. Coulombre also described the influences on the shape and volume of the developing lens and that the neural layer of the retina from the mouse can induce the pigment epithelium of the chick retina to regenerate chick neural retina.

Cystinosis. Vernon G. Wong of the Institute developed a simple technique for the biochemical diagnosis of cystinosis in collaboration with investigators from the National Institute of Arthritis and Metabolic Diseases. Cystinosis, a hereditary disorder which usually leads to death from kidney failure within the first decade of life, is characterized by large increases in the concentration of the free amino acid cystine within cells of a variety of tissues. Crystalline deposits of cystine form in the eyes. By developing a specific, simple, and rapid method for determining the presence of cystine in samples of conjunctiva, Dr. Wong and his associates significantly improved upon previous methods of cystinosis diagnosis which were both cumbersome and time-consuming.

BIOLOGICS STANDARDS

HEPATITIS RESEARCH

The control of hepatitis remains a major challenge in medical virology. In the field of biologics, the disease constitutes a serious risk in the administration of blood and blood products. Transfused blood is known to cause more than 30,000 cases of overt hepatitis and 1,500 to 3,000 deaths every year in the U. S. Since there are many subclinical cases of viral hepatitis, the actual incidence has been estimated as high as 150,000 cases a year. Because of this risk, and the hope for possible development of a vaccine against the serum hepatitis agent, the Division of Biologics Standards has for many years maintained an exploratory hepatitis research program.

In 1968, the DBS expanded this program under the direction of

Dr. Lewellys F. Barker. Recent findings had linked hepatitis to a hitherto unknown factor found in the blood of an Australian aborigine. This factor, discovered in 1965 by Dr. Blumberg of Philadelphia, behaves like an antigen when the serum of a multiple-transfused patient is used as an antiserum. It was later shown that this antigen was intimately related to serum hepatitis. The detection of Australia or hepatitis-associated antigen (HAA) has made it possible for the first time to identify specifically by an in vitro test a proportion of blood which carries a high risk of transmitting post-transfusion hepatitis.

During the past year, Dr. Barker and his staff have evaluated the efficacy of test procedures for HAA detection and their practicality for blood donor screening. Plasma from patients with icteric viral hepatitis, which the DBS had stored since 1952 at -20°C, proved invaluable. Using these studies, it has been shown that serum hepatitis can be transmitted by blood and blood products that contain HAA in amounts too low to be detected by current testing techniques. However, it has been shown that some infectious blood donors are chronic carriers of this antigen and it is postulated that by detecting these individuals and removing them from the blood donor pool, there will be a significant decreased incidence of post-transfusion hepatitis. Recent studies have shown that by identifying and eliminating bloods which are positive for Australia antigen it may be possible to reduce the number of cases by approximately 25 percent.

To broaden and extend the scope of its HAA and transfusion-associated hepatitis studies, the DBS initiated a contract with the New Jersey Department of Health. All donor blood collected in New Jersey was tested for HAA. The study developed solid information on HAA-positive blood donors and also established a bank of blood donor serum specimens for use in evaluating sensitivity and specificity of other test techniques for the detection of HAA as they are developed.

In addition to the assessment of all practical methods for HAA antigen testing, the DBS has been involved with standardization of the antisera which are subject to licensure through the Division.

Federal regulations for specific standards of safety, purity and potency for hepatitis-associated antibody (anti-Australia antigen) were developed by DBS this past year and a number of manufacturers will be licensed early in 1971 for commercial distribution of the reagent.

To aid blood centers and hospital blood banks in hepatitis screening, the National Heart and Lung Institute National Blood Resource Program has supported the acquisition and processing of a supply of the antibody-rich plasma required in serological tests developed thus far. The supply is being distributed via State and territorial Health Departments to tide over the Nation's blood banks until commercial preparations become available.

With the aid of the National Hemophilia Foundation, blood samples were collected from a large number of hemophiliacs for

screening by the Division of Biologics Standards to identify potential donors whose blood was exceptionally rich in antibodies to hepatitis by virtue of frequent exposure to the virus in the course of transfusion therapy. Antibody-rich plasma from this select group of donors was subsequently sent to the Massachusetts State Laboratory, where it was pooled, processed, packaged in 2 milliliter units, and stored for subsequent distribution by the National Blood Resource Program.

RUBELLA

Rubella virus vaccine became generally available in the United States in June 1969, and by October 1970, approximately 28 million doses had been distributed in this country. Practical experience with the vaccine since licensure supports investigative data pertaining to vaccine safety and effectiveness.

The DBS rubella virus research program has continued, under the direction of Dr. Harry M. Meyer, Jr., and Dr. Paul D. Parkman, whose studies resulted in 1965 in a vaccine virus strain from which two of the presently commercially available vaccines are produced. Their recent studies, as well as those of other investigators, have furnished additional information concerning the quality and durability of rubella vaccine-induced immunity.

It is known that clinically inapparent reinfections often develop in immune persons if re-exposed to infections such as poliomyelitis and rubeola (measles). Rubella appears to follow this pattern. Results of experiments in rhesus monkeys, conducted by Drs. Meyer and Parkman in 1965, showed that animals immunized with either natural or attenuated rubella virus could undergo modified reinfection if challenged later with natural virus. In 1966, they showed that persons with antibodies as a result of natural rubella, or vaccination, could also experience increases in antibody after re-exposure to the virus. These reinfections were subclinical, abbreviated, and most common in persons with relatively low antibody levels. In the past two years, several groups have confirmed and extended these findings.

Recently there has been some discussion among scientists in the interpretation and significance of the data on reinfection as it relates to the national immunization program. During the past year the problem of reinfection has been re-examined in considerable detail. One study, carried out by DBS investigators during the course of a rubella outbreak at the Arkansas Children's Colony made it possible to determine the effect of exposure in rubella-susceptible persons, vaccinated individuals, and others with natural immunity as a result of earlier rubella. Infection occurred in 22 of the 33 susceptibles and all had signs and symptoms of rubella. None of the 22 previously vaccinated or 66 naturally immune persons in the study developed rubella. A rise in antibody, indicative of subclinical reinfection, occurred in five vaccinees and in one person with natural immunity. None of these reinfected individuals showed evidence of virus in the blood, i.e., were viremic, and only two of the five vaccinees showed demonstrable

amounts of virus in throat swabs collected during the period of antibody rise. All susceptibles contracting rubella were viremic and excreted virus.

The DBS team observed that the level of antibody at the time of exposure appeared important in influencing resistance to reinfection, although any detectable level of antibody afforded protection against disease, prevented viremia, and modified the pattern of virus shedding in the throat.

The recent study continues to support conclusions reached over a year ago that 1) challenged vaccinees are protected, rarely shed virus, and are not demonstrably viremic; 2) vaccinated persons with antibody, even if reinfected, are not likely to participate in the spread of rubella virus in communities; and 3) rubella vaccine will provide significant fetal protection if an immunized person is at some later date exposed to rubella during pregnancy, since vaccine-induced antibodies have been demonstrated to serve as a barrier to viremia.

EPSTEIN-BARR VIRUS (EBV)

The central question concerning Epstein-Barr virus (EBV) is its possible relationship to at least two malignant diseases: Burkitt lymphoma and nasopharyngeal carcinoma. Because all efforts so far have failed to establish a suitable animal model to transmit EBV infection and observe the effect, most of the DBS studies were concentrated on the effect of EBV on human leukocytes *in vitro*. It was found that EBV caused human leukocytes to proliferate in culture resulting in a cell transformation with infinite growth potential. On the other hand, the uninfected control leukocyte cultures from the same donor failed to proliferate and disappeared in culture within 3 to 5 weeks.

Results of recent studies by Dr. Paul Gerber, DBS, demonstrate that EBV infection results in a striking increase of cellular deoxyribonucleic acid (DNA) synthesis within 5 to 7 days following *in vitro* infection of human leukocytes. Since only tumor-producing DNA viruses e.g., polyoma, SV40, and certain adenoviruses are known to stimulate cellular DNA synthesis, these results suggest that EBV may have tumor-producing properties. This would indicate that this virus alone, or in conjunction with other factors, may indeed be the causative agent of certain disorders of the lymph cell system.

CHOLERA

Cholera is presently of great concern not only to the nations of Asia, including Viet Nam, but also in the Middle East, Africa, and parts of Europe. The latter areas have been free of cholera for many years.

Although the threat of cholera can be controlled by improved sanitation, this approach is, for practical purposes, unattainable in many of the countries at greatest risk. Cholera vaccine

continues to be the major weapon for combatting this disease. Some 80 years have passed since the first attempts were made at active immunization against cholera but use of the vaccine has been, until recently, based largely on circumstantial evidence of efficacy.

The DBS has cooperated for a number of years with the Pakistan-SEATO Cholera Research Laboratory in Dacca in conducting properly controlled field trials of available vaccines. Results of the trials have varied widely. In general, vaccines have given 30 to 90 percent protection but in most cases protection is of short duration lasting only three to six months.

Extensive research is now in progress throughout the world directed towards more effective immunization against cholera. The most promising development stems from studies which show that the cholera vibrio, while multiplying in the intestinal tract, produces and excretes a potent toxin which causes the classic symptoms of cholera. This toxin is antigenic and stimulates antibodies (anti-toxin) which neutralize it. DBS studies, under the direction of Dr. John C. Feeley, have shown that the toxin antigen is not present in significant amounts in presently available vaccines. Cholera patients develop antitoxin in convalescence. This raises the possibility of immunizing against the toxin by use of a toxoid, such as has been successfully used for many years with tetanus and diphtheria. DBS scientists have cooperated with a number of laboratories in preparing a purified and detoxified cholera toxin, which has been shown to be effective in preventing the disease in animals. A quantity of this material has been subjected to extensive safety and potency tests in animals.

Studies in volunteer subjects to assess the safety and antigenicity of the product are now being carried out in this country. If favorable results are obtained with regard to safety, similar studies will be carried out by the Pakistan-SEATO Cholera Research Laboratory. If, in turn, these results are favorable, a large-scale clinical field trial can be initiated to assess the value of the toxoid. This will take several years.

POISON IVY AND POISON OAK

Poison ivy and poison oak are indigenous to the United States. Although 85 to 95 percent of the population react to the toxic extract of the plants, only about 50 percent suffer a poison ivy-poison oak dermatitis. Presumably the other 50 percent have a very low level of sensitivity to the plants.

The sap of the poison ivy and poison oak plants contains an active ingredient known as urushiol. The urushiol from each of these plants is chemically similar and both can be extracted readily by alcohol or ether. Extracts can be administered either orally or parenterally in an attempt to prevent the disease from recurring. Commercially prepared crude extracts have been available for many years, but they vary in potency.

For the past six years, the DBS has carried out an extensive

research program on the isolation, chemistry and nature of urushiol. Under the direction of Dr. Harold Baer, standards of potency are being developed for the production of poison ivy and poison oak extracts to achieve a rational basis for the prevention and treatment of poison ivy and poison oak dermatitis. In support of these studies, quantities of the active ingredients of poison ivy and poison oak for laboratory and clinical studies are being prepared under contract at Columbia University. As a result, standardized preparations of urushiol, prepared from fresh leaves of the plants, have been made available for experimental use.

During the past year, the results of another DBS contract study on desensitization, conducted at the University of California with prison volunteers, were reported. The subjects were quantitatively patch-tested with serial dilutions of urushiol to determine the extent of their sensitivity to the plant. They were then given daily oral doses of urushiol in increasing amounts for about three months. During this time, the subjects were patch-tested every month for evidence of sensitivity. In nine of 13 subjects the procedure produced a decrease in sensitivity to poison oak. Although patch-test reactions and rashes occurred in some, these side effects disappeared as the subjects became less sensitive. However, sensitivity returned when ingestion of urushiol was discontinued. The investigators believe this indicates that a maintenance dosage is necessary for desensitization. Additional studies are now in progress to determine the validity of these observations.

MYCOPLASMA

The DBS has for the past several years conducted research on the detection, isolation, and identification of mycoplasma in cell cultures. These studies, under the direction of Dr. Michael F. Barile, have resulted in the establishment of cell cultures free from these agents and in the introduction of test procedures to ensure the exclusion of mycoplasma from vaccines.

Mycoplasma, once called PPLO (pleuropneumonia-like organisms), were first identified more than 60 years ago as the cause of pleuropneumonia in cattle. In 1962 they were found to be the causative agents of a human disease--primary atypical pneumonia. Evidence of the implication of mycoplasma in other human diseases has occurred with increasing frequency since these organisms have been subjected to study by laboratory techniques including electron microscopy. For at least 13 years it has been known that tissue cultures harbor mycoplasma as contaminants.

Dr. Barile has recently initiated an expanded program of research to establish the presence of mycoplasmas in animals and their possible role in animal diseases. Tissues of monkeys, dogs, and ducks, commonly used to prepare cell cultures for production of viral vaccines, were obtained for these studies under a DBS contract. Results thus far reported include:

. The first isolation and identification of simian mycoplasma strains. Most of the 70 mycoplasmas isolated were shown to be

related to known mycoplasma species of man. A new species of mycoplasma, designated M. primatum was also isolated from monkeys.

. In the first comprehensive study on isolation and identification of canine mycoplasma, 249 strains were recovered. These findings confirmed the presence in dogs of three previously isolated canine species and established the presence of a new species, M. edwardii.

These studies are expected to continue to provide useful information, relevant to development of test procedures required for the control of viral vaccines.

The influence of mycoplasma on virus replication is also under study by Dr. Barile in collaboration with Dr. Stanley Singer, DBS. An attempt is being made to observe mycoplasma virus interaction in vitro and to utilize these findings in studies on animals infected with mycoplasmas to determine how they handle virus infection. This may be significant in determining why one person exposed to a virus infection reacts differently from another exposed to the same infection.

BCG VACCINE

Vaccination plays a major role in the world battle against tuberculosis. All countries which have such programs employ a vaccine strain of Bacillus Calmette-Guerin (BCG), which originated in the Pasteur Institute, Paris. These strains have been handled under various conditions in laboratories throughout the world and have developed differences in characteristics. The effect of the differences in strain characteristics on the relative efficacy of vaccines prepared from them is of prime concern to the World Health Organization and to national vaccine control laboratories.

In the Division of Biologics Standards, Dr. Sotiros Chaparas is conducting a study on antigenic differences and similarities of 12 strains of BCG from nine countries, using techniques designed to separate and identify antigens. The ability of these strains to induce antibodies and to induce skin sensitivity to tuberculin is also being studied. Results of these studies will be useful in the selection by DBS of a suitable strain for a reference standard in the control of BCG vaccine production.

ARTHRITIS

Over 17 million Americans suffer from arthritis, a group of diseases characterized by inflammation and impairment of the joints. Of the many forms of rheumatic disease, rheumatoid arthritis is the most serious and crippling. It is a major subject of study supported and conducted by the National Institute of Arthritis and Metabolic Diseases. Although the primary cause of this disorder is as yet unknown despite an intensive research effort, early diagnosis and proper treatment benefit 9 of 10 such patients, and 7 of 10 are enabled to avoid severe disablement.

An investigator at Massachusetts General Hospital, Dr. Stephen M. Krane, has recently proposed a mechanism for the joint destruction characteristic of rheumatoid arthritis. In an earlier study he had isolated a collagen-degrading enzyme from the joint linings of rheumatoid arthritis patients. He has now examined more closely the activity of this enzyme, which he has detected in synovial joint fluid of patients which rheumatoid arthritis. His studies have revealed that this patticular enzyme, a synovial collagenase, has the specific ability to degrade chemically and destroy joint cartilage. Thus, it may play an important role in the joint destruction characteristic of rheumatoid arthritis.

Another scientist at New York Medical College, Dr. Israeli A. Jaffa, has shown that penicillamine may be of value in the treatment of rheumatoid arthritis patients with sustained disease activity. In an eight-year clinical study, most patients responded with a 50 percent or greater degree of improvement as evidenced by a reduction in subjective and objective signs of active disease.

In a rather novel approach to the management of rheumatoid arthritis, an investigator at the State University of New York, Brooklyn, has shown that large oral doses of an amino acid, histidine, may alleviate several symptoms of the disease.

It has been known for ten years that patients with rheumatoid arthritis have subnormal serum levels of histidine. This knowledge prompted Dr. Donald A. Gerber to study the effects of histidine replacement therapy in such patients.

Daily treatment of 70 patients with L-histidine for periods averaging nine months resulted in significant improvement in grip strength, walking speed, and in a laboratory measurement of abnormal concentrations of certain blood components that characterize rheumatoid arthritis.

Thus far, there has been no evidence of adverse side effects, and it would appear that L-histidine may be an effective and harmless way of producing clinical improvement in some patients with rheumatoid arthritis. Further clinical studies in a large number of patients are planned in order to determine the efficacy of such therapy.

Institute scientists in Bethesda, Drs. A. Steinberg, G. Daley and N. Talal have shown that successive administration of a synthetic RNA (ribonucleic acid) and an immunosuppressive drug induces specific tolerance to nucleic acid antigens in a strain of mice that spontaneously develops systemic lupus erythematosus. The finding may ultimately have important clinical implications.

The spontaneous disease developed by the mice is a useful model for human systemic lupus erythematosus (SLE), a grave multisystemic disease which primarily affects women. Both mice and humans develop antibodies to their own DNA (deoxyribonucleic acid) and deposit DNA- containing immune complexes in their kidneys, a development which almost invariably is fatal.

Successive administration of the synthetic RNA analog, polyinosinic-polycytidylic acid (PI:C), and of the potent immunosuppressive drug, cyclophosphamide, now has been found to induce specific tolerance to the nucleic acid antigen, PI:C, in the mice. This is the first demonstration of experimentally induced tolerance to a nucleic acid antigen. The therapeutic approach of inducing specific tolerance may be useful in human patients with "autoimmune diseases" such as SLE, or in the field of transplantation. It might avoid many problems of toxicity and infection currently associated with such standard therapy as long-term corticosteroid drugs and other immunosuppressive agents.

DIABETES

Of all the metabolic diseases, diabetes, which affects millions of Americans, is probably the best known. It is not the best understood, however. In fact, the more the disease is studied, the more complexities and enigmas are found, and therefore reviews and revisions of theories concerning its origin and nature are required.

The most significant and far-reaching diabetes-related study in many years was reported in 1970. It concerned the effects of tolbutamide (brand name Orinase), an orally administered anti-diabetes drug which has been used by an estimated 800,000 American diabetic patients.

The 10-year study, supported by the Institute was conducted by the University Group Diabetes Program (UGDP). It has revealed that tolbutamide is no more effective than diet alone in the treatment of mild, adult-onset diabetes, except insofar as it lowers blood glucose levels. Moreover, the drug was found to be less effective than diet, or diet and insulin, in reducing mortality from heart disease and related conditions in such patients.

The UGDP study was carried out in 12 different university medical centers with well-established diabetes clinics. The 823 study patients were placed on a diabetic diet and were divided at random into four equal groups. In addition to the diet common to all, one group received 1.5 grams of tolbutamide daily, a second group 10-16 units of insulin daily, a third group individualized insulin dosages sufficient to control blood glucose levels, and the fourth group a placebo (inactive starch tablet).

The objective of the study was to ascertain the effectiveness of these four methods of treatment in prevention, or long-term postponement, of the onset of the blood-vessel related complications of diabetes (heart disease, kidney degeneration, blindness, and others) which make this disease a particularly serious disorder once they make their appearance.

During the ten-year study period, ten cardiovascular deaths occurred in the placebo-treated group, twelve in the group that received individualized insulin dosages, and 13 in the group treated with a fixed insulin dosage. In the tolbutamide-treated group, 26 patients died of cardiovascular disease, and this increased

death rate was noted in a majority of the twelve clinics.

The duration of the study, well beyond the standard periods for drug testing, was of critical importance. During the first three years there were no significant differences in death rates between the groups, but in the fourth year, for reasons as yet unknown, the cardiovascular death rate in the tolbutamide-treated group began to rise and continued to increase thereafter.

Pending the results of further studies, the investigators recommend that tolbutamide be considered for use only in patients with symptomatic adult-onset diabetes who cannot be adequately controlled by diet alone or by diet and insulin. The Food and Drug Administration, after reviewing the results of this study with the aid of outside expert consultants, has announced a similar conclusion - that tolbutamide and related antidiabetic compounds should be used only as a third line of defense against diabetes, that is when diet alone or diet with insulin are ineffective.

GASTROENTEROLOGY

Several research findings are providing promising leads and approaches in the search for improved diagnosis and treatment of gastrointestinal disorders, such as peptic ulcer and regional ileitis. Such disorders afflict persons of all ages, but mostly young and middle-aged groups at the peak of their most productive years.

It is well-established that normal nutrition can be restored and maintained for many months by intravenous administration of essential nutrients. To date, however, problems of effective long-term access to appropriate blood vessels have prevented efforts to provide prolonged total intravenous feeding.

Dr. Belding Scribner of the University of Washington (Seattle), who devised the permanently implanted arteriovenous shunt for artificial kidney patients, has now converted the shunt to an "artificial gut" system which can provide prolonged total nutrition to patients devoid of effective bowel function. The system can be self-operated around the clock and has potential for maintenance of health of patients with chronic bowel disease. Use of the artificial gut system is foreseen in patients with too little remaining bowel, following massive bowel resection, to maintain nutrition, and in the temporary treatment of ileocolitis, mesenteric thromboembolism, and various bowel diseases in infants.

Massive resection of the small bowel for inflammatory bowel disease, or for other reasons, can create serious physiologic and metabolic problems. Typically, patients with a resultant "short-bowel syndrome" develop severe diarrhea and lose excessive and, in some cases, life-threatening amounts of water and essential electrolytes in their stools. Concomitantly, because of impaired absorption of different nutrients, patients may develop malnutrition of varied severity. To date no form of therapy has been completely satisfactory.

Use of a dietary regimen in which 50-75 percent of the long-chain fats are replaced with medium-chain fats now has led to a gradual decline in fecal loss of water and electrolytes and to significant improvement in nutritional status in such patients. There was a remarkable improvement in nutritional status on long-term follow-up (6-12 weeks), one patient having gained 20 pounds and another 10 pounds during that time.

The investigator, Dr. J. A. Balint of Albany Medical College, New York, recommends conservative treatment of patients with short-bowel syndrome and, particularly, a prolonged trial of substitution of medium-chain fats for long-chain dietary fat.

Gastrin, a hormone which stimulates secretion of gastric juices, was synthesized by Institute grantees in England several years ago. Other grantees subsequently produced antibodies in rabbits that were directed against the functional portion of the gastrin molecule, and showed that these antibodies are able to inhibit the ability of exogenous gastrin to stimulate gastric acid secretion in rats.

Dr. J. E. McGuigan of Washington University (St. Louis) now has shown that the same antibody preparation also inhibits the potent gastric acid stimulatory action of native gastrin. This finding may have important clinical application. It is possible that gastric acid secretion rates, as well as disease processes associated with excessive gastric acid secretion, such as peptic ulcer, may be modified by antibodies directed specifically against endogenous gastrin molecules.

An Institute-supported investigator at the University of Minnesota, Dr. O. H. Wangensteen, has successfully employed a laser beam in the treatment of bleeding gastric ulcers in animals. The effectiveness of this internally applied laser cautery in controlling such bleeding suggests the possibility of its trial in certain poor risk stress ulcer patients with massive bleeding. Such treatment would be an alternative to surgery, which in certain groups of patients is connected with a significant mortality and incidence of rebleeding.

CYSTIC FIBROSIS

The National Institute of Arthritis and Metabolic Diseases is deeply committed to a broad multi-disciplinary research program in cystic fibrosis, an inherited metabolic disease which affects one in every 1500-2000 newborn infants. Cystic fibrosis is characterized by malfunctioning exocrine glands, resulting in production of sweat with a high salt content, secretion of abnormally thick, viscous mucus, and progressive chronic lung disease.

A new finding that may help explain these facets of the disease has been provided by Dr. G. E. Gibbs of the University of Nebraska. He has described decreased activity of beta-glucuronidase, an enzyme involved in the metabolism of mucopolysaccharides (a group of complex carbohydrates) and salt transport, in certain skin components in children with cystic fibrosis. The finding may

increase our understanding of the excretion of abnormally viscous mucus from various exocrine glands, and the abnormally high concentrations of salt in the sweat that characterize this inherited metabolic disorder.

Several other studies have suggested that beta-glucuronidase may be a necessary component of the salt-secretion mechanism and may play a role in mucopolysaccharide metabolism. Other Institute grantees recently have shown that a specific type of material, presumably of mucopolysaccharide nature, accumulates abnormally in cultured connective tissue cells from patients with cystic fibrosis. In view of the known connection between beta-glucuronidase and mucopolysaccharide metabolism, the finding of decreased beta-glucuronidase activity in cystic fibrosis may provide insight into the basic cause of this disorder. Further study will be required to learn if such decreased enzyme activity represents decreased synthesis, abnormal enzyme structure, or enzyme inhibition by some other substance.

Another Institute-supported scientist at the University of Texas, Dr. Barbara H. Bowman, has isolated and characterized a protein fraction that may be responsible for several metabolic defects observed in cystic fibrosis patients.

Several other studies had indicated the presence of an abnormal factor in the serum of cystic fibrosis patients that may cause interruption of normal ciliary action in the bronchial mucosa of several experimental animals. Dr. Bowman recently showed that this abnormal serum factor also caused cessation of ciliary movement in oyster gills within 30 minutes. (Cilia in prepared oyster gill tissues normally remain active for approximately one hour). The researcher feels that this serum factor may be useful in identifying cystic fibrosis patients and carriers.

Dr. Bowman has now isolated the ciliary inhibiting factor from the sera of cystic fibrosis patients and carriers. This protein fraction, which is undetectable in normal serum, may be responsible for the defects in membrane transport and respiratory ciliary function observed in patients with cystic fibrosis.

KIDNEY DISEASE

From improved methods of diagnosis of kidney disease to improved techniques of kidney transplantation, the Institute, through a sizeable program of extramural grants and its Artificial Kidney-Chronic Uremia Program is supporting a wide variety of approaches to ensure a comprehensive attack on the whole problem of kidney disease and urologic disorders.

At the University of California, San Francisco, Drs. Samuel L. Kountz and Folkert O. Belzer have shown that tissue matching of both white blood cells and kidney cells markedly improves the survival rate of transplanted human cadaver kidneys. Conventionally, only the white cells of the donor and potential recipients are tissue-typed and, subsequently, the best matching combination is selected.

Under the new system, the recipient's white cells are typed and cross-matched to the cadaver donor's kidney cells as well as white cells.

Apparently there is antigen on the kidney cells not detected on white cells during phenotyping. Thus, many apparent "good" matches based on white cell-white cell typing alone can now be revealed as merely "fair" on the basis of the more complete double matching system, and poor outcome of cadaver transplants due to rejection can be more easily predicted and avoided.

It was concluded that use of both white cells and kidney cells for tissue typing is a practical and preferred method of donor-recipient matching in cadaver kidney transplantation, likely to improve the long-term outcome of such transplants significantly.

A presterilized, disposable "envelope kidney" that saves many hours of preparation time in home dialysis has been developed for use with the conventional Kiil artificial kidney machine. The envelope kidney, developed by Dr. Yukihiko Nosé and associates of the Cleveland Clinic Foundation, is essentially a sealed sandwich of Cuprophan PT-150 membranes supported externally by a fiber screen. Blood ports for attachment to the patient's circulation are included within the sterilized, sealed package.

Preliminary clinical results from trials of the envelope kidney have been excellent, with no adverse reactions, and with blood purification performance as good as or better than with standard membranes in the Kiil apparatus. At this point, no road blocks are foreseen to commercial production and routine use of the envelope kidney.

Dr. Morton B. Weinstein, University of Miami (Fla.), has shown that relatively large doses of the male hormone testosterone can stimulate red blood cell production (erythropoiesis), and lessen transfusion requirements, in adequately dialyzed patients with advanced kidney (renal) failure and associated anemia.

The anemia which often accompanies advanced renal failure, and which may require regular periodic blood transfusions, has been attributed to diminished renal secretion of erythropoietin, a factor which increases the production of red blood cells. Although androgenic hormones stimulate renal or possibly extrarenal production of erythropoietin and, thus, are therapeutic in a variety of anemias, their use in uremic patients with anemia who are on regular dialysis therapy had not been explored.

Hyperparathyroid bone disease, manifested by hypercalcemia, calcification of soft tissue, and decalcification of bone, is a well-recognized accompaniment of renal failure and chronic hemodialysis. Although the condition usually responds to surgical removal of the parathyroid glands, it has been difficult to manage medically because uremic patients characteristically develop vitamin D resistance with attendant impaired intestinal calcium absorption.

Dr. Neal S. Bricker of Washington University, St. Louis, has studied the natural development of hyperparathyroidism in advancing renal disease and has demonstrated that early secondary hyperparathyroidism can be prevented in animals by maintaining a low dietary phosphate intake, a finding which may have clinical significance for renal patients.

Almost simultaneously, dihydrotachysterol (DHT), a compound structurally similar to vitamin D, has been found capable of arresting the hyperparathyroid bone disease seen in patients on long-term dialysis. Marked improvement was observed in all six patients treated in preliminary studies, suggesting that remission of such bone disease is possible by medical means without resort to parathyroid gland surgery.

According to Dr. Michael Kaye of Montreal General Hospital, in patients receiving DHT calcium absorption increased in every case, plasma ionized calcium rose, elevated serum alkaline phosphatase values fell, and impressive radiological healing was seen. Bone biopsy confirmed these findings. Bone pain promptly disappeared and, in some instances, progressive "eating out" (pathologic, increased porosity) of bone was reversed and new bone structure was observed.

NUTRITION

Nutrition is another important field in which the Institute has a vital interest. Several research findings in this particular area during the past year merit special recognition. One of these concerns vitamin D, which, by regulating the absorption of calcium and phosphorus from the intestinal tract, acts to maintain normal bone metabolism.

In earlier studies Dr. H. F. DeLuca of the University of Wisconsin had isolated the major biologically active form of vitamin D, 25-hydroxy-cholecalciferol (25-HCC), had identified the liver as the site of vitamin D conversion to 25-HCC, and had shown that 25-HCC is markedly more effective than the conventional form of the vitamin in preventing or treating rickets in animals.

He has now shown that patients with vitamin D-resistant rickets respond positively, both symptomatically and radiographically, to high doses of 25-HCC with no evidence of toxicity. His findings suggest that 25-HCC will prove to be a safe, effective treatment for vitamin D-resistant rickets.

Two other closely related findings concern the evaluation of protein malnutrition and methods for reversing the condition. Several years ago an Institute grantee showed that a protein-deficient diet causes a decrease in diameter of the human hair root. Subsequently, he demonstrated decreased hair root diameter in children with kwashiorkor, maramus, and milder degrees of malnutrition. Dr. Robert G. Crounse of the Medical College of Georgia now has shown that analysis of hair roots for their protein content provides an even more sensitive means of evaluating nutritional

protein deprivation. The new procedure is more objective than estimation of hair root diameter, which may vary for several reasons. It is also very sensitive to relatively low levels of protein deprivation as shown by the fact that low hair root protein values were often found in malnourished patients even when serum protein levels were, as yet, normal.

Refeeding of several malnourished patients resulted in increased hair root protein content as these patients gained weight. Comparison of individual hair root volume with protein and DNA content indicated that the hair root responds to protein deficiency by a decrease in both cell number and root size, as well as in protein content. In view of the ease of biopsy of this tissue and sensitivity of the hair root to nutritional influences, hair root analysis may be a clinically useful means of evaluating the adequacy of the protein nutritional state.

Meanwhile, Dr. G. G. Graham of Johns Hopkins University and Dr. J. M. Baertl of the British American Hospital, Lima, Peru have shown that cottonseed flour can be a nutritionally acceptable sole source of protein under conditions where the classical sources of quality proteins (milk, eggs, meat, etc.) are not available. Metabolic studies conducted earlier by Institute-supported investigators in Peru had suggested that convalescent malnourished infants and children might thrive on a diet containing cottonseed flour as the only source of protein. Prolonged feeding trials conducted by Drs. Graham and Baertl now have established that properly processed cottonseed flour, at adequate levels of intake, can serve as the main or sole source of protein for rapidly growing infants and children, at least for short periods of time.

ENDOCRINOLOGY

Endocrinology concerns itself with the endocrine glands, internally-secreting, hormone-producing glands like the pituitary, thyroid and adrenal glands, or the ovary and testis, and with the effect of hormones on the metabolism and physiology of man. The endocrine system, together with the nervous system, controls almost all the metabolic, growth, and reproductive functions of man. This rapidly expanding area of biomedical research continues to produce important findings at an ever-increasing rate.

For example, Dr. Choh H. Li of the University of California, San Francisco, has culminated a 32 year research effort by synthesizing human growth hormone, or HGH, the anterior pituitary hormone which controls such life processes as growth and varied aspects of metabolism.

This accomplishment should broaden research on human growth and other life processes; until now such research has been hampered by the minute supply of HGH, which can be derived only from human pituitary glands obtained at autopsy. More specifically, it may later result in more widespread and adequate use of HGH in the treatment of hypopituitary dwarfism, a growth disorder currently affecting an estimated 10,000 Americans, once the new synthetic

material becomes available in larger quantities.

The synthesis of HGH also will permit more definitive studies of the effects of the hormone and, possibly, of specific active portions of the HGH molecule, on carbohydrate, fat, and protein metabolism, and should provide further insight into such disease states as giantism, acromegaly, diabetes and obesity. Current studies are geared toward purification of the synthetic material in order to increase its potency.

It was reported last year that two groups of Institute-supported scientists had simultaneously synthesized the hypothalamic hormone, thyrotropin releasing factor (TRF). This hormone stimulates the pituitary gland to release thyrotropin, which in turn stimulates the production of thyroid hormone by the thyroid gland.

Continued studies by one of these groups, headed by Dr. Roger Guillemin of Baylor University, now have revealed that TRF administration stimulates a rise in plasma thyrotropin levels in normal individuals, but not in subjects with pituitary gland failure. Thus, synthetic TRF might provide a convenient means of testing the integrity of the human pituitary gland for thyrotropin secretion.

In a remarkably similar series of events, two groups of scientists working independently, one at the National Heart and Lung Institute and the other at the NIAMD and Massachusetts General Hospital have announced the complete structure of parathyroid hormone. In addition, the latter group has succeeded in synthesizing the active portion of the hormone, and has discovered new facets of how it controls calcium metabolism in the body. Dr. H. B. Brewer of the National Heart and Lung Institute reported the complete 84 amino acid sequence of parathyroid hormone just a few weeks prior to a similar announcement by Dr. J. T. Potts of Massachusetts General Hospital, who worked with grant support from the NIAMD. In addition, Dr. Potts reported the synthesis of a substance comprised of the first 34 amino acids of the hormone, the biologically active portion of the molecule of parathyroid hormone.

Dr. G. D. Aurbach and associates of the NIAMD have also resolved an argument going on for many years, as to whether the major effect of parathyroid hormone is on the kidney or on bone. He has found that the hormone activates the enzyme adenyl cyclase in the relevant receptor cells in both bone and kidney; consequent increased formation of cyclic adenosinemonophosphate in these cells is responsible for ultimate effects of the hormone in both organs. This relatively small molecule is found in many tissues and appears to be the agent that mediates many hormonal effects.

Furthermore, Dr. Aurbach has found that the 34 amino acid segment synthesized by Dr. Potts and colleagues is completely active in both kidney and bone. Up until now, pure parathyroid hormone has been in short supply, and availability of the synthetic product will be useful in further studies in basic research and possibly clinically as well. Indeed it may be possible to synthesize a parathyroid hormone more active than the natural product now

available.

Another significant finding by Bethesda scientists involved Drs. J. R. Lefkowitz and J. Roth of the NIAMD and Dr. I. Pastan of the National Cancer Institute. This NIH team has developed a rapid and sensitive technique for measuring biologically active adrenocorticotropic hormone, or ACTH, in human plasma. The basis for specificity in the new procedure is biological, rather than immunological as in currently used radioimmunoassay procedures, and the technique appears to be applicable to all polypeptide hormones.

HEMATOLOGY

Institute scientists in Bethesda and grant-supported investigators elsewhere have made substantial advances recently in the understanding of a number of blood diseases, particularly "bleeding" disorders such as hemophilia.

Dr. S. I. Rapaport of the University of Southern California has shown that standard therapeutic doses of aspirin may result in abnormally prolonged bleeding times in patients with severe hemophilia. Aspirin did not lead to prolonged bleeding times in 24 patients with relatively mild bleeding disorders. Eight patients with severe hemophilia, however, had profoundly prolonged bleeding times after aspirin, and seven patients required plasma or plasma concentrate to control excessive bleeding. This finding points up the potential therapeutic hazard that aspirin may hold for some patients with major blood clotting disorders.

Institute scientists in Bethesda, (Drs. R. J. Hirschman, S. B. Itscoitz and N. R. Shulman) meanwhile have shown that long-term prophylactic treatment with Factor VIII (an anti-hemophilic factor) can markedly reduce the number of spontaneous hemorrhages that occur in hemophilic patients.

Treatment of four hemophilic patients for as long as two years with Factor VIII was found to decrease significantly the number of spontaneous hemorrhages, with only minimal complications. Prior to such therapy, two patients with classical hemophilia suffered spontaneous incapacitating hemorrhages at least once a month and could not retain jobs because of this. The first patient had only one bleeding episode during a two-year period while receiving prophylactic treatment four times a week. The second patient had only one spontaneous hemorrhage during an eight-month period while receiving treatment five times a week.

Although such prophylactic therapy is restricted by the limited supply and the cost of Factor VIII concentrates, it appears justified based on the experience with these four patients. In one patient such therapy arrested the progressive enlargment of a life-threatening inoperable hematoma (a focal tumor-like extravasation of blood which tends to swell and impinges on surrounding tissues). The other three patients illustrate the successful use of short-term prophylaxis which required amounts of Factor VIII no greater than those needed ordinarily in after-the-fact therapy with Factor VIII

when bleeding episodes were a regular occurrence.

Two years ago an Institute grantee at Harvard University produced abundant quantities of antihemophilic factor (AHF) by perfusing pig spleens with human hemophilic blood. Subsequently, he reported preliminary success in "curing" true hemophilia A in dogs via splenic transplantation. Despite these successes, controversy still existed as to whether the spleen actually synthesizes, or merely stores, AHF.

Another Institute grantee at the University of Colorado, Dr. Ben Eiseman, now has shown conclusively that the spleen is a source of AHF synthesis. Perfusion of pig spleens for as long as four days has resulted in production and maintenance of levels of AHF sufficient to control bleeding episodes. It was concluded that the AHF activity represents synthesis by the spleen rather than release of stored material. The data suggest that transplantation of a spleen from a donor into a hemophilic recipient of comparable size could result in production of AHF levels of 15-20 percent of normal, which are sufficient to control hemophilic bleeding episodes.

Sickle cell anemia is a major health problem for Negroes, occurring in about one in 500 births. To date, no form of therapy has been completely satisfactory. Basing their strategy on an Institute scientist's molecular theories of red blood cell sickling, investigators in Michigan and Washington, D. C. now have devised a new form of therapy that is reported to reverse the acute sickling crises of this disease and may temporarily block further sickling of red blood cells (the mechanism which leads to these painful and disabling episodes).

Drs. Robert Nalbandian of Blodgett Memorial Hospital, Grand Rapids, and Paul McCurdy of D. C. General Hospital have employed intravenous infusions of urea and invert sugar in aborting acute sickle cell crises in a large majority of instances in 25 such crises.

Further long-term studies are needed, however, to confirm these preliminary observations. The research teams are now investigating a program of daily oral maintenance doses to prevent the onset, or decrease the severity, of sickle cell anemia crises. This new treatment represents one of the first instances in which a molecular therapeutic strategy has been successfully devised on purely theoretical grounds.

DISEASES FROM INBORN ERRORS

National Institute of Neurological Diseases and Stroke scientists are now able to diagnose before birth certain genetic abnormalities causing neurologic disorders. Fabry's disease has been diagnosed *in utero* by scientists in the NINDS Laboratory of Neurochemistry who had earlier uncovered the enzyme deficit in the disease.

The affected fetus was identified on the basis of

aminocentesis, and assays of cells from the subsequently aborted fetus have confirmed the diagnosis of the rare X-linked disorder of lipid metabolism.

The key to in utero diagnosis by amniocentesis lies in knowing what to look for in the cells of fetal origin drawn out of the fluid surrounding the fetus. Over the past four years, NINDS-supported investigators, and scientists from the NINDS Laboratory of Neurochemistry have forced six rare hereditary diseases to give up their biochemical secrets by discovering the exact missing enzyme in each.

Based on this biochemical work, it is now possible to monitor pregnancies at risk of producing children with Tay-Sachs disease, Gaucher's disease, Niemann-Pick disease, and now, Fabry's disease. With refinement in technique, the other two diseases in this general group called lipid-storage disorders, Krabbe's disease and metachromatic leukodystrophy, should also soon become diagnosable in utero.

This group of diseases, presently incurable and characterized by the buildup of a fatty material called sphingolipid in tissues, causes severe mental retardation and greatly shortened life-span in children.

At the NINDS-sponsored Conference on the Torsion Dystonias, scientists reported that dystonia musculorum deformans--a hereditary disorder characterized by involuntary movements and postures--has autosomal dominant and recessive modes of inheritance. This finding is of importance to physicians engaged in genetic counseling of patients and their families, for previously this disorder was thought to be passed on solely as an autosomal dominant form.

NINDS-supported scientists in Warsaw, Poland, have discovered abnormal beta-1-globulin in the blood streams of patients with progressive muscular dystrophy and their carrier mothers. Control patients with other types of muscular dystrophy did not have this abnormal globulin. If this finding can be incorporated into a screening test, it may be possible to alert a woman to her probability of giving birth to a child with progressive muscular dystrophy.

NEUROMUSCULAR DISORDERS

Inflammatory Myopathy. Two muscle diseases, characterized by inflammation of the muscle and/or skin, have been successfully treated at the NINDS Medical Neurology Branch. Because the usual therapy for these disorders--a daily regimen of glucocorticoids--frequently causes untoward side effects, NINDS investigators have been treating patients with an alternate-day glucocorticoid program, usually after they have failed to be adequately controlled on a program of daily glucocorticoids.

Scientists have found that the alternate-day regimen can

effectively control inflammatory myopathy in several of its clinical forms and maintain the same or a better degree of remission as is achieved by high doses of daily glucocorticoids, with fewer undersirable side effects.

Some of the unpleasant and serious side effects avoided in these patients have been: gastro-intestinal ulceration, hypertension, fluid retention, osteoporosis, psychiatric disorders, and cataract and muscle atrophy, all of which may limit treatment or be even more serious than the disease itself.

Myasthenia Gravis. Alternate-day treatment with prednisone has caused dramatic and sustained improvement in myasthenia gravis without observable side effects. This treatment regimen, initiated in the NINDS Medical Neurology Branch, affirms that clinical benefit without drug-related initial worsening can be attained in myasthenia gravis. This alternate-day mode of treatment is superior to the short, intensive course of daily adrenocorticotrophic hormone (ACTH), the common therapy for the disease, because it avoids several drawbacks of daily ACTH treatment.

During daily ACTH treatment, most patients have a decrease in strength for several days before they improve and the improvement lasts only weeks, or a few months at most. The ultimate goal of the NINDS investigators in treating myasthenia gravis with alternate-day therapy is to produce sufficient suppression of the disease until symptoms remain absent even after slow withdrawal of corticosteroid therapy.

Peripheral Neuropathies. Histochemical characterizations of muscle and the recognition of its two principal fiber types in the Medical Neurology Branch have provided much impetus to differential diagnosis of neuromuscular disease. The ability to differentiate disease entities in this vast group of disorders is important if proper therapy is to be initiated. Scientists can now differentiate a familial peripheral neuropathy in adults and the denervating diseases in children from simple peripheral neuropathies in adults and from amyotrophic lateral sclerosis.

PARKINSON'S DISEASE

L-Dopa. Development of L-Dopa therapy, which has brought relief to thousands of people suffering from Parkinson's disease, now promises even greater dividends in terms of new research opportunities. Several new projects have been launched utilizing L-Dopa to open up unexplored territory in the chemistry, physiology and pharmacology of the brain. It is possible that scientists may learn, within the next few years, what causes parkinsonism, and what measures might prevent it.

At Brookhaven National Laboratory, Dr. George Cotzias is extending and enlarging his pioneering work with L-Dopa in a broad NINDS-supported study of parkinsonism, including experiments with both animals and humans. He is breeding strains of mice with high and low sensitivity to L-Dopa; searching for compounds having

effects similar to L-Dopa; and attempting to determine how trace metals affect the action of L-Dopa in the brain. Dr. Cotzias has found that one strain of mice does not absorb manganese efficiently, and is also highly resistant to toxic quantities of L-Dopa. This relationship is of particular interest because the effects of manganese poisoning in humans closely resemble parkinsonism.

The Brookhaven investigators are also studying long-term effects of L-Dopa in several groups of patients, one with Parkinson's disease, and another with such movement disorders as dystonia, Wilson's disease, and Huntington's chorea. The question of whether L-Dopa offers hope for sufferers from diseases other than parkinsonism remains open. At a meeting of neurological scientists in December 1970, the concensus was that L-Dopa's effectiveness would prove to be greatest in parkinsonism and parkinsonism-dementia. Trials in other disorders will continue, however, and may provide new clues to treatment, if not effective treatment itself.

Surgery. Although L-Dopa has materially reduced the need for surgery in parkinsonism, it has by no means eliminated it. L-Dopa is most effective against the rigidity and slowness of movement caused by parkinsonism, and the percentage of good results with tremor is much lower. Thalamic surgery, in which the small area of the brain where the tremors originate is inactivated by heat, freezing, or chemical methods, is most effective against the tremor, and less so against the other two principal symptoms. NINDS neurosurgeons reported this year that their follow-up studies have shown the chance of abolishing tremor with surgery is in the range of 80 to 90 percent. Thus, in some cases, the combined use of L-Dopa and surgery offer the most hope for control.

Epidemiology. A major question in the field of Parkinson's disease is whether L-Dopa affects the natural history of the disorder, or is merely symptomatic treatment. Institute scientists are collecting data on patients who had the disease between 1958 and 1964 to determine life expectancy and specific cause of death. This data will be matched with identical information on a series of patients who had received L-Dopa.

Valuable information is expected from an NINDS study of records of members of the Mormon Church in Salt Lake City who died with a diagnosis of Parkinson's disease between 1930 and 1940, together with a check of incidence among their descendants. This group is particularly valuable for such a study because they maintain accurate, up-to-date genealogical records.

STROKE

Diagnosis--Hydrogen Saturation. New refinements in technique have enabled scientists at Baylor College of Medicine to detect small disturbances in cerebral circulation which are not discernible in angiograms. Although angiography (injection of dye and subsequent X-ray of the head) is still generally the best way of detecting flaws in the complex circulatory system of the brain,

it is far from being entirely satisfactory, and scientists in many centers are attempting to improve other methods. The work at Baylor entails injection of hydrogen-saturated saline into the carotid (neck) arteries and subsequent calculation of blood flow and oxygen metabolism from catheter-drawn samples taken from the cerebral transverse sinus. The samples, which are pumped through curvettes containing hydrogen, p02, Pco2, and pH electrodes, enable calculations to be made from a previously developed formula using the clearance curve of hydrogen in the sinus, and a new formula for estimating hemispheric oxygen, glucose, lactate and pyruvate metabolism.

The study, which included 22 patients, all having infarctions on one side, and nine having normal angiograms, demonstrated the hemispheric blood flow and oxygen metabolism on the affected side were reduced in every case. The reductions also occurred on the unaffected side during the acute phase of stroke, despite normal angiograms. The findings suggest the possibility of supplementing conventional angiography with a substantially more sensitive method.

Isotope Clearance. Detection of diminished blood flow within a specific region of the brain can be a valuable means of assessing various neurological diseases, including epilepsy and brain tumors, as well as stroke. Grantees at the University of Pennsylvania have demonstrated a new application of the isotope clearance method developed by Lassen and Ingvar for locating focal alterations and for obtaining measurements which correlate with angiographic and clinical findings.

Regional cerebral blood flow (rCBF) studies were performed in 100 neurological patients at the Philadelphia General Hospital. The rCBF was measured by injecting xenon 133 into the internal carotid artery and monitoring the arrival and clearance of the isotope by 8 scintillation detectors enclosed in a block placed at the side of the patient's head. Each detector contained a small sodium iodide crystal which recorded the clearance of the xenon from a 1.5-inch diameter core of brain tissue. Clearance curve data were analyzed by computer.

Focal diminutions of flow were detected in nearly all cases examined. Decreases in blood flow were found surrounding tumors, subdural hematomas, and some cerebrovascular lesions. In presenile dementia the rCBF data showed a marked decrease in overall blood flow, though this had not been evident from angiograms. Also noted were significant decreases in gray matter blood flow in 11 of 13 epileptics.

Thermography. Thermography, a method of detecting circulatory defects in the carotid arteries by finding asymmetries in the pattern of heat radiating from the face, has been limited in its usefulness by a number of factors, one being the rapid development of collateral circulation when an artery has become blocked. NINDS grantees at the University of Minnesota have designed a head clamp which reduces this problem by occluding the superficial temporal artery just in front of the ear. Normally, obstruction of

this artery results in an increased flow through the supraorbital and frontal branch arteries, accompanied by a slight warming of the supraorbital skin area. In patients with blockages on one side, even when nothing shows up on routine thermograms, use of the clamp usually results in a "cold spot." The scientists report that the device increases the detection rate in these patients from 58 to 88 percent.

Epidemiology. NINDS grantees have determined that differences in stroke mortality among geographic areas of the United States are directly related to stroke incidence, rather than to case fatality rates following stroke. This finding would rule out the supposition that regional variations in the quality of medical care of stroke patients might affect mortality rates.

Previous studies have revealed that large differences in stroke mortality exist among various geographic areas, and that these differences are not due to variations in the practices of physicians preparing death certificates, or to different diagnostic criteria.

A total of 2,619 stroke cases were studied. The incidence of stroke was higher in the high stroke death rate areas (North Carolina, South Carolina, and Savannah), as compared with the low areas (Miami, Denver, and Kansas), especially for men. Considering the known risk factors in stroke, high blood pressure, elevated lipids, and high blood sugar or diabetes, the scientists hypothesize (1) that populations having a high prevalence of hypertension but low lipid levels have high rates of intracranial disease, but little extracranial atherosclerotic heart disease, as appears to be the case with the Japanese; (2) that populations with a high prevalence of both elevated blood pressure and lipids have high rates of both intracranial and extracranial disease as well as atherosclerotic heart disease (U.S. Negroes), and (3) that populations with a high prevalence of elevated lipids (U.S. whites) would tend to have more extracranial disease and high rates of atherosclerotic heart disease. Further studies are planned to test the hypothesis.

MULTIPLE SCLEROSIS

Epidemiology. Populations migrating from high incidence areas of multiple sclerosis (MS) to low incidence areas retain the high rate of the country of origin. A new study provides corollary data about migration from low risk areas to high risk and about MS rates among first generation migrants. As a rule, temperate zone regions are high risk areas while the warmer regions are low risk. However, there seems to be a big exception to the geographic pattern in Asia, where the disease is rare.

In the latest study, incidence data on MS were compiled on American, Japanese and Chinese migrants to California and the State of Washington. It was found that death rates with MS were higher among native-born whites in Washington than in California. Death rates among migrants from high risk areas were also higher in Washington than in California. However, rates among migrants from low risk areas did not differ between California and Washington and

in fact were similar to the rates in their area of birth. The finding of high rates from MS among native-born Washingtonians and intermediate death rates among native-born Californians supports the previous finding of others that the cause of MS is related to latitude.

Antibody Levels in MS Serum. A number of investigators have noted that measles virus antibody levels are more frequently and more consistently elevated among MS patients than among controls. In a recent study, it was found that serum titers of MS patients were higher than those of carefully matched unrelated controls for measles, influenza C, herpes virus hominis, parainfluenza type 3, mumps and varicella. However, serum titers among MS patients were not higher for any of these agents than those of their siblings of the same sex born within three years of the patients, suggesting a familial effect on these responses. The observed pattern indicates that viruses and immune responses somehow play some indeterminate role in the causation of MS.

EPILEPSY

In 1969, Drs. Daniel A. Pollen and Michael C. Tractenberg, Institute grantees at Massachusetts General Hospital, advanced and mathematically verified a new hypothesis that brain glial cells are electrical storage areas where potassium ions go while neurons are discharging in normal brain operation and that damaged glia (as in epilepsy) may hold fewer potassium ions, forcing them to build up on neuron walls and possibly helping them to trigger abnormal discharge activity. In the past year, Dr. Pollen and another co-worker, Dr. Edward P. Richardson, Jr., went a step farther. They measured potassium-ion content of normal and sclerotic glial tissue in cat brains. Although technical difficulties limited the amounts of data obtained, results were encouraging enough to warrant further efforts in the same direction.

Two grantees, Dr. Gilbert H. Glasser and Dr. E. C. Zuckermann, Yale University School of Medicine, also working with cat brains but using different techniques, studied the influences that ions and amino acids may have on the activities of chronic epileptogenic foci. Their results agree with those of Drs. Pollen and Richardson as far as potassium's probable roles in epilepsy mechanisms are concerned.

Diagnostic Tools. Data which affirm the reliability of the electroencephalograph (EEG) machine used to locate and measure epileptic electrical activities in afflicted brains resulted from experiments by two Institute grantees at Stanford University, Dr. D. A. Prince and Dr. K. J. Futamachi. Using monkeys in which epilepsy had been induced by applying alumina gel directly to the brains to cause lesions which react like human epilepsy, they measured brain electrical activity extracellularly at the cortex surface and intracellularly with deeply implanted microelectrodes. The recordings correlated well, indicating that EEG electrodes at the surface are indeed picking up and recording the electrical activity which is going on deeper down in the cells.

Enzyme Changes. At the University of Washington Epilepsy Center, while studying a surgical method for creating animal "models" for epilepsy research, Dr. J. R. Green and associate, Dr. L. M. Halpern, found important changes in the amounts of three specific enzymes, considered important in epilepsy initiation, in cat brain cortex after it had been separated from the midbrain. After undergoing the brain separation operation, called "undercutting," the cats lived two months before they were sacrificed and their cortex tissue studied. Large increases in amounts of one enzyme and large reductions of two other enzymes were found. The information is considered important in understanding why epileptic brain tissue behaves as it does electrically.

Drugs. Two experiments shed light on how diphenylhydantoin (Dilantin) acts as an anticonvulsant drug for epilepsy therapy.

In one experiment, grantees at Duke University, Dr. A. V. Escueta and Dr. S. H. Appel, induced epilepsy attacks in rats with one-a-day electrical shocks for two, four, and six days. Post-mortem examination of brain-cell tissue showed that potassium content within specific brain cells called synaptic terminals was less after two days of the induced attacks than in animals not shocked. At four days, the amount of potassium was down 27 percent and down 40 percent after 6 days. Administration of Dilantin was shown to have corrected the most severe potassium deficiency within four days.

The other related experiment, by investigators at the Denver Veterans Administration hospital, probed the effects that Dilantin and phenobarbital have on epilepsy induced in cats by freezing their cortexes with an ethyl chloride spray. In animals not given the drugs before freezing, there was an increase in the activities of specific enzymes which are believed to affect epilepsy susceptibility. The animals that were treated with Dilantin and phenobarbital before freezing damaged their brains exhibited no increase in activities on the subject enzymes.

A long-standing controversy over the value of the drug primidone in epilepsy therapy was helped by experiments completed by Dr. H. E. Booker and co-workers at the University of Wisconsin. Because many medical scientists believed that primidone, used in epilepsy treatment, was completely metabolized to phenobarbital, they questioned why it should be used. The grantee investigators, using gas chromatography to measure drug levels in the blood of patients taking primidone, found that a percentage of the drug is not changed to phenobarbital and that the amount remaining in the blood in its original state is effective in controlling epilepsy attacks.

Also at Wisconsin, another grant-supported study probed previous reports of adverse interaction between phenobarbital and Dilantin serum levels in animals receiving both for treatment of induced epilepsy. The results of these experiments showed that no significant interference occurs in human clinical patients taking the two drugs on a continuing basis. The results agreed with other experiments recently reported by other investigators.

Can Stress Trigger Epilepsy Attacks? Psychological data on epilepsy was developed when Dr. Richard H.Mattson and co-workers at Yale found that some epilepsy patients tend to overbreathe during periods of stress or anxiety, lower the carbon dioxide levels in their lungs and blood, and suffer epilepsy attacks as a result. The hyperventilation (overbreathing) was often not clinically obvious and had not been previously suspected as a triggering factor, even though the patients studied had histories of increased frequency of attacks during periods of emotional stress. The study demonstrates that some epilepsy victims can hold down attacks during anxiety by more careful control of their breathing.

Conditioning Therapy for Sensory-Evoked Epilepsy. Dr. Francis M. Forster, University of Wisconsin School of Medicine, reported on continuing work on sensory-evoked (reflex) epilepsy. The report reviewed studies with a relatively small number of patients who were affected adversely by sound stimuli that was not loud enough, or of a type, to be unpleasant or disturbing to the vast majority of citizens of the country, yet was a serious impairment in the patients' lives. Dr. Forster explained the types of sounds which triggered epilepsy attacks in the study patients and how they are ameliorated by a behavioral type of therapy called therapeutic conditioning, wherein the offending sounds are taped then played back often until they become innocuous. The report declared the sound induced epilepsy attacks are pathophysiological and not on an emotional or functional basis.

CEREBRAL PALSY

Researchers at the Laboratory of Perinatal Physiology studying the birth process in monkeys have found that hormones released in pregnant monkeys under psychic or other kinds of stress can result in brain damage or even death to the fetus. These scientists, studying asphyxiation of monkeys to learn about the functioning of the brain and causes of perinatal brain injury, found that infusions of hormones called catecholamines in certain amounts into the maternal blood stream produce fetal asphyxia. This may also result when the flow of blood from the mother to the placenta is reduced through constriction of vessels brought on by release of these hormones from the adrenal glands due to stress. The implications of these primate studies for the human are not yet certain.

A recent Perinatal Project study indicates that antigens inherited by a fetus from the father can place stress on the pregnant woman, and affect not only her health, but that of her offspring. The researchers suggest this may account for evidence which shows that as mothers bear more children, the babies tend to weigh more and are generally more vigorous. This could be because the mothers become increasingly sensitized to the antigens with each pregnancy, and are therefore less subject to stressful effects of the antigens on maternal health. Mothers with normal weight gain and good health tend to bear larger, healthier babies.

Eclampsia, a form of toxemia which causes convulsions and coma,

was found to have occurred remarkably seldom in the Perinatal Project. Hospitals in various countries have reported incidences of one eclamptic out of every 500 to 1,500 pregnancies, but only one out of every 1,804 pregnancies were eclamptic in the Perinatal Project. Equally remarkable, there were no maternal deaths from eclampsia among the 50,500 deliveries in the project. Whether or not this condition is preventable has been a source of controversy in the past. Project scientists say this evidence shows eclampsia is both treatable and preventable with prompt detection of symptoms and proper obstetrical attention.

HEARING DISORDERS

Implantable Hearing Aid. An experimental model of a permanently implantable hearing aid, designed to last a lifetime, has been tested in animals by Institute grantees at the University of Oregon Medical School. The tiny crystal, less than one-half inch long and ten-thousandths of an inch in diameter, is attached to a small wire probe, and implanted in the middle ear. It picks up sound, in the form of electrical impulses, which causes it to vibrate and send these impulses to the brain. Although the aid cannot help patients with nerve damage, it could benefit thousands of people with inoperable otosclerosis. Scientists are working to perfect two essential components--an implantable microphone and power source. When tested on a volunteer with normal hearing, using a tape recorder rather than the microphone, "sounds" were reported to be clear and undistorted--a problem inherent in many currently available aids which amplify sound in the outer ear.

Effects of Noise on Hearing. Recent studies at the Central Institute for the Deaf show exposure to intense noise can indeed cause damage to the inner ear although the damage does not show up on audiograms. Histologic examination on animals exposed to noise showed that sensory receptor loss occurred in the ears of all test animals exposed to low-frequency noise. Their findings strongly suggest that "moderately intense sound can gradually destroy, bit by bit, the integrity of the organ of Corti, and eventually, the ability to hear."

An Institute grantee at the University of Minnesota has found that full recovery from changes in the threshold level caused by noise can take from a few minutes to weeks after cessation of the noise, depending on the intensity of the level. Chemicals and drugs tested for possible preventative value were found to afford no protection, and in fact the mycin drugs have been found to produce destruction similar to that produced by noise-induced permanent threshold shifts. A subtoxic dose of the drug Kanamycin was found to make the ear more susceptible to damage from noise.

In addition, intermittent exposures to high-frequency, high-energy noise have been found to frequently require more than 16 hours of rest before initial sensitivity is restored. The investigating grantee suggests that since chronic auditory fatigue which can lead to permanent damage may afflict many working in an industrial situation, industrial noise levels should not exceed

100dB, even though periods of quiet may far exceed periods of noise.

Promising Hearing Test. A test shown to be unusually effective in detecting hearing loss and deafness in animals has been developed through some collaborative research with a National Institute of Dental Research geneticist. There are indications that the test may eventually be a reliable indicator of human, as well as animal hearing, and could be especially useful in detecting hearing loss of deafness in infants.

Histological examination of 28 test animals correlated precisely with hearing test results. Using the test, geneticists can now accurately measure deafness and hearing impairment in test animals and can therefore then breed animals specifically for genetic deafness, hearing impairment, and normals. Their offspring can then be studied at a very early age to determine the causes of genetic deafness and hearing impairment, and how normals first begin to hear.

The test method consists of an adapted lock-in amplifier which measures directly the ability of the animal's ear to convert sound waves into electrical impulses by detecting and measuring electrical signals of known frequency that are buried in high amplitude background noise. It is these electrical impulses which are interpreted by the brain, enabling the subject to "hear." When the wave pattern of the ear's electrical signal is the same as that of the sound wave, the subject is not deaf. When the electrical signal is smaller than that of the sound wave, the subject is considered to have hearing impairment.

Inner Ear Fluid Test. A method for early differentiation of Meniere's disease and acoustic nerve tumor by chemically testing inner ear fluid has been developed by scientists at the University of Michigan Medical School and the Massachusetts Eye and Ear Infirmary. Previously, because both produce such similar symptoms as sudden hearing loss and dizziness, exploratory surgery was often necessary to determine the cause. The treatment of the two disorders differs significantly, however, and an early diagnosis is imperative because acoustic nerve tumors can be removed successfully only when diagnosed early. Failure to remove the tumor can result in deafness and even death. Meniere's disease, on the other hand, can cause great discomfort but is not fatal.

The scientists found that the fluid of patients with Meniere's disease contained an electrolyte (sodium and potassium) imbalance, while the fluid of those with acoustic tumor had an elevated protein concentration. This method may considerably reduce the instances where potentially dangerous exploratory surgery is needed.

Sudden Deafness Related to Systemic Disorders. A five-year study by scientists at the University of Michigan Medical Center shows that sudden deafness can be related to systemic diseases, and is not necessarily a localized problem. They found that 40 patients experiencing onset of sudden deafness had systemic diseases, including fat embolism and hypercoagulation as well as infection

from mycoplasma pneumoniae, adenovirus and parainfluenza virus. The ear, therefore, as well as the eye, is a sensitive indicator of vascular and intravascular pathology.

SPEECH DISORDERS

Larynx Transplant Research. Larynx transplants, to be practical substitutes for the use of esophageal speech following the removal of the larynx, must be safe, offer a high chance of cure, and provide functional results. To date, transplant procedure has presented two problems: tissue rejection and regeneration of laryngeal nerves. Scientists at the Washington University School of Medicine have recently perfected two techniques for improving nerve regeneration which should greatly aid transplant success.

They have found that an experimental drug speeds regeneration time of severed larynx nerves in dogs by accelerating protein and RNA synthesis, while producing no intoxicating effects. This is vitally important since restoration of function depends heavily on fast regeneration of severed nerves. Nerve recovery time in dogs who received the preparation exceeded that of untreated dogs by 32 days, as measured by functional restoration of the vocal cord.

Scientists have also initiated a technique which bypasses the problem of having the regenerating nerve fiber "find" its proper pathway to the correct muscle. By leaving the nerve attached to muscle tissue surrounding the removed larynx, they need only resuture the muscle back to the transplanted larynx, rather than suture the nerve itself. Regenerating fibers have only a short distance to go to innervate the appropriate nerve motor units this way.

Partial Laryngectomy. Grantees at Washington University have developed types of partial removal of the larynx in patients who have cancer which has not infected the cords themselves. Termed conservation surgery, the cordal function of the larynx and essential components of the pharynx remain intact, preserving normal speech, while only surrounding malignant tissue is removed.

Collaborative Study Defines Communication Development Trends. A comprehensive understanding of the development of hearing, speech, and language is being gained through the Institute's Collaborative Perinatal Research Program. Results of a battery of 12 tests administered to 4,400 children (at six participating medical centers) at age three and again at age eight has uncovered some startling trends. Only 10.5 percent of the children were reading orally at their proper grade level, while one-quarter of the children in silent reading tested at least one year below their age level. Vocabulary test scores seemed to correspond quite closely with IQ scores; 2.5 percent of the children had difficulty discriminating speech at an acceptable level (children were able to remember strings of numbers better than strings of syllables); and, 4 percent of the children were found to have defective articulation, while 15 percent were found to have articulation problems warranting attention

These and other study results are providing scientists with a better understanding of the extent and nature of early communication problems, and should greatly aid research in helping children with communication problems.

A NEW TEACHING DEVICE FOR MEDICINE

A new teaching device called a cinemicrotone has been developed at the University of California under the sponsorship of the NINDS and the National Library of Medicine. The device consists of a microtone used to make very thin sections of the whole human brain and a movie camera for photographing each slice. When projected these pictures give one the sense of moving slowly through the brain. Sections of the brain are made in three planes--coronal, sagittal, and horizontal. The student is thus able to view the brain from any of the three directions. A major problem in the development of the device, now partially overcome, has been in staining the brain as it is being sectioned to show the differences between white and gray matter.

The cinemicrotone has already been used successfully to make teaching movies. The films made with this new technique are expected to make an important contribution to neuroscience education.

VIROLOGY

INFECTIOUS MONONUCLEOSIS

In 1970 National Institute of Allergy and Infectious Diseases scientists and grantees made further progress in clarifying the role of the Epstein-Barr virus (EBV) in a variety of diseases. It is accepted that EBV is probably responsible for a tumor of African children known as Burkitt's lymphoma. More recently, evidence has accumulated linking this virus with the common ailment, infectious mononucleosis (IM). However, some scientists have expressed the opinion that EBV may be merely a "passenger" virus, flourishing in IM patients because of the proliferation of certain white blood cells which characterizes this disease. To test this possibility, Neil R. Blacklow and Albert Z. Kapikian of NIAID's Laboratory of Infectious Diseases studied blood samples from 10 children with infectious lymphocytosis, another disease in which white blood cells proliferate. The investigators found that antibody to EBV did not increase during the illnesses of any of the children. This finding tends to support the idea that the occurrence of EBV antibody rises during bouts of infectious mononucleosis is of real significance.

Two other groups of scientists (Werner Henle and associate, University of Pennsylvania School of Medicine; James C. Niederman, et.al. Yale University School of Medicine), working with the National Institutes of Health's support, have shown that individuals who reach late adolescence without immunity to EBV and who then become infected are more likely to develop clinical mononucleosis than children infected with EBV at an earlier age. The epidemiologic pattern parallels that seen in polio and infectious hepatitis -- viral diseases which are mild or inapparent

when contracted early in life, but which tend to become more severe with increasing age.

HEPATITIS

Along with many other investigators, NIAID scientists and grantees have been actively following up recent breakthroughs in the area of serum hepatitis. This disease is transmitted by blood and occurs in as many as 1% of patients following transfusion. It is estimated that such transfusion-associated hepatitis kills a minimum of 1500 Americans each year.

Until very recently, it was impossible to identify blood carrying the hepatitis virus. Now, however, scientists have found a substance--called the Australia or hepatitis-associated antigen (HAA)--whose presence in blood indicates that the blood is very likely to transmit infection.

It is believed that exclusion of all HAA-positive blood from use in transfusions will greatly reduce the incidence of post-transfusion hepatitis. First, however, it is necessary that one or more tests be developed which can be applied to mass screening of blood for the telltale antigen.

Recently, NIH scientists Robert H. Purcell, Paul V. Holland, John W. Walsh, Doris H. Wong, Andrew G. Morrow, and Robert M. Chanock reported on their use of a standard immunologic technique called complement fixation to detect and quantitate HAA. This test is far more sensitive than the commonly used agar gel diffusion method. It also can be used to measure antibodies to HAA, thus providing additional information of interest to researchers.

Yet another technique--called immunoelectroosmophoresis (IEOP) was applied by NIH-supported scientists in 1970 to the detection of HAA. Alfred M. Prince and an associate at the New York Blood Center found IEOP to be more sensitive than gel diffusion while retaining the specificity of the latter. In addition, the new test can be completed within one to two hours, making its use feasible in the screening of perishable blood products, including fresh whole blood.

ANTIVIRAL SUBSTANCES

Of course, few subjects are of as much interest to virologists as the development of agents active against viral infections. One such agent--idoxuridine or IDU--achieved striking results when used by Wayne State University School of Medicine investigators (A. Martin Lerner, et.al.) in treatment of six patients with a devastating form of encephalitis caused by Herpesvirus hominis. This disease is not only characterized by a high mortality rate but also leaves many of its surviving victims permanently impaired. In general, fewer than 20% of patients emerge from their illness intact. In Dr. Lerner's study, four of six IDU-treated patients, including three in coma, recovered completely. In contrast, only one of seven patients not receiving IDU is relatively (though not completely) well, and none of the three comatose patients in this

group recovered. Other studies have not shown such consistent results and further study of the potential role of IDU in herpes encephalitis is needed.

Interferon and interferon inducers are the antiviral substances which have attracted most attention in recent years. Interferon is a natural product, manufactured by cells in response to viral invasion. It acts to limit spread of virus, causing the infection to die out.

In an attempt to assess the importance of interferon in recovery from viral infections, NIAID grantee George G. Jackson of the University of Illinois College of Medicine and his associates at Case Western Reserve School of Medicine measured blood levels of both interferon and specific antibody following infection of volunteers with Asian influenza. The investigators found that symptoms improved as interferon reached peak titers. They suggest, therefore, that interferon may have played an active role in the recovery process, especially the initial symptomatic improvement between the third and sixth days following inoculation. After six days, however, levels of virus-neutralizing antibody increased significantly, and the investigators believe that this antibody played the major role in effecting final recovery from the disease.

Since interferon itself is not available in sufficient quantity for clinical use, interest has focused on the interferon inducers--substances which, by mimicking viral components, stimulate cells to produce their own interferon. One of the most effective inducers is a specially synthesized chemical known as poly I.poly C, and in a recent study investigators at the Universities of Toronto and Pittsburgh obtained more evidence of this substance's clinical potential.

The scientists, working under an NIAID grant to the University of Pittsburgh's Monto Ho, demonstrated that a single injection of poly I.poly C protected rabbits from lethal effects of rabies virus administered shortly before or after the interferon inducer. All of 39 rabbits receiving poly I.poly C from 24 hours before to three hours after virus challenge survived, as did 9 of 10 animals receiving the inducer six hours post-challenge and 10 of 15 receiving it after 24 hours. In contrast, all of seven animals who were challenged with virus but received no poly I. poly C succumbed to rabies infection.

Conditions in this study resembled those of human rabies infection. The investigators believe, accordingly, that their observations may suggest a possible new approach to post-exposure treatment of rabies in man.

VACCINES

Despite the great current interest in antiviral substances, from a clinical point of view they represent a hope for the future rather than a present-day reality. Right now, vaccines remain our most potent weapon against viral diseases.

62-645 O - 71 - pt. 3 - 13

Recent work in vaccine development offers a ray of hope for cold-sufferers--that is, almost all of us. NIAID scientists John C. Perkins, David N. Tucker, Harry L. S. Knopf, Albert Z. Kapikian and Robert M. Chanock, and their coworkers at the University of Maryland, found that an inactivated rhinovirus type 13 vaccine induced immunity in recipients when inoculated intranasally. Rhinoviruses--of which there are more than 90--are believed responsible for one-fourth to one-third of all colds. Although the large number of rhinovirus types presents a major difficulty, the investigators believe that their approach offers some hope of eventually eliminating a significant proportion of colds through preventive vaccination.

In addition to attempting to develop safe and effective vaccines against a number of viral diseases, scientists in 1970 undertook further assessment of vaccines already in widespread use. Of particular interest to specialists in this field has been the question of whether the attenuated virus strains used in live rubella vaccines are transmissible from person to person to any significant degree. Since scientists do not know whether or not the vaccine viruses share the natural virus' potential for causing birth defects, it appears possible that transmissibility of the vaccine strains might present a hazard to pregnant women in contact with vaccinated children.

Working under a contract from NIAID's Infectious Disease Branch, Jorge A. Veronelli of Case Western Reserve University School of Medicine conducted an open community trial of three live rubella vaccines. He found no instances of virus transmission in any of the families studied, members of which had been inoculated with two of the vaccine types. All of 347 unvaccinated susceptible children exposed to vaccinated siblings remained susceptible at the end of eight weeks, indicating that they had not been infected. Almost half of these children had been exposed to more than one successfully vaccinated sibling.

Earlier work has indicated that rubella vaccine virus is unlikely to infect the fetus even when present in the mother. In view of the present findings, it appears that vaccination of children during early pregnancy in their mothers is quite unlikely to be hazardous to the unborn.

BIOLOGICAL CONTROL OF VECTORS

A number of viral diseases (yellow fever, for example, or many types of encephalitis) are caused by organisms that are transmitted by insects. For many years, insecticides have been the most successful means of destroying these disease vectors, but the toxic effects of these chemicals on both man and his environment have become of increasing concern. Now, a patent for a new technique for mosquito control by sterilization has been awarded to an NIAID grantee, George B. Craig, Jr. and his associate, Morton Fuchs, University of Notre Dame. Dr. Craig's patent describes a method of sterilizing female mosquitoes with a hormone extracted from the accessory gland of male mosquitoes. This substance, called

"matrone", can be added to the food of mosquito larvae or sprayed on surfaces where young mosquitoes feed.

DEFECTIVE VIRUSES

Some scientists believe that viruses themselves may, at times, limit their own spread. NIAID grantee David Baltimore and his associate at the Massachusetts Institute of Technology think that defective virus particles--seen in a variety of viral infections--may play such a role. The "crippled" particles have a normal protein coat, but they contain only a portion of the usual genetic material. When they infect a cell, they cannot replicate on their own. However, they can reproduce if normal virus is also present. When they do so, they interfere with reproduction of the normal virus, thus tending to limit the infection or to drive it underground. The MIT scientists believe that defective virus particles may serve to explain some common patterns of viral illness as well as certain rare and puzzling syndromes.

VIRUSES AND CANCER

Few subjects are of as much interest to both scientists and laymen as the relationship between viruses and cancer. One discovery gave this subject particular impetus in 1970. Working with grant support from NIH, Howard M. Temin and his associate at the University of Wisconsin, and David Baltimore of the Massachusetts Institute of Technology found a new enzyme -- RNA-dependent DNA polymerase -- in RNA tumor viruses. (Viruses, including those producing tumors, contain either RNA or DNA as their genetic material and are classified accordingly.) The new enzyme can transfer genetic information from RNA to DNA -- thus reversing the usual process -- and its presence in RNA tumor viruses offered a welcome explanation of how such viruses could permanently alter or "transform" normal cells, rendering them cancerous.

Discovery of the new enzyme was rapidly followed up by other scientists, who identified the enzyme in additional RNA tumor viruses but failed to find it in non-tumor-causing RNA viruses. It is hoped that this work, which is continuing at a rapid pace, may have significant clinical application to the virus-cancer problem.

DNA tumor viruses also continued to receive their share of attention in 1970. NIAID career awardee Andre J. Nahmias and his associates at Emory University Medical School, supported in part by an NIAID research grant to Oscar L. Frick, found a definite association between cancerous and pre-cancerous conditions of the cervix, on the one hand, and presence of antibodies to type 2 Herpesvirus hominis (HVH) -- a DNA-containing virus -- on the other. Women with the most severe types of disease were most likely to possess such antibodies.

Whether the association found in this study is one of cause and effect remains to be determined. However, the findings, considered along with others, are highly suggestive.

In addition to HVH, several other viruses of the herpes family--including the EB virus mentioned earlier -- have been implicated in tumor causation. Also, one herpes-type virus (HTV) has been associated with a cancerlike syndrome of chickens (Marek's disease) which is of considerable economic as well as theoretical importance. NIAID investigators M. Katherine Cook and Johnna F. Sears recently succeeded in obtaining HTV in relatively pure form for the first time. This development paves the way for experiments to clarify the virus' role in Marek's disease.

Another recent achievement of NIAID scientists promises to aid researchers hunting for leukemia viruses in animals. Vaclav Klement, Wallace P. Rowe, Janet W. Hartley, and Wendell E. Pugh have developed a method for detecting the presence of mouse leukemia viruses in tissue culture by means of visible changes in "indicator" cells. Previously, techniques for detecting these viruses were indirect or required special materials. The investigators believe that their new simpler procedure will prove useful in the search for leukemia viruses in several species.

IMMUNOLOGY

The immune system of man plays a uniquely important role in his existence. In addition to warding off infections of all types, immune mechanisms may well constitute the first line of defense against cancer. On the other hand, these same mechanisms account for the phenomenon of graft rejection, which so severely restricts use of organ transplants. Moreover, aberrations of the immune system may themselves give rise to diverse disease states ranging from various forms of allergy to fatal autoimmune illness.

The basic immune interaction involves combination of specialized molecules (antibodies) or immune cells with microorganisms or substances recognized as "foreign" by the body. Scientists have devoted much attention to this interaction as well as to the mechanism by which each of a vast number of different foreign substances (antigens) can induce production of specifically corresponding immune cells and antibodies. In addition, knowledge of immune interactions has been utilized to develop better means of diagnosing, treating, or preventing disease.

DIAGNOSIS

NIH scientists and a grantee (Theodore Pincus and James A. Rose, NIAID; John L. Decker and Norman Talal, NIAMD; Peter H. Schur, Robert Breck Brigham Hospital) recently reported development of an improved immunologic test for systemic lupus erythematosus (SLE) -- an autoimmune disease with serious consequences. Like earlier diagnostic tests for this disease, the new method detects characteristic abnormal antibodies capable of combining with DNA (genetic material). However, the new test is distinctive in being based on the direct binding of antibodies to radioactive DNA, and is, therefore, more accurate than those in common use. In addition, since levels of anti-DNA antibody are associated with extent of SLE manifestations, this test has particular value for

assessing the stage of disease in an individual case at a given time.

A discovery by scientists at the New York University School of Medicine may help physicians to diagnose congenital rubella (German measles). NIAID grantee Saul Krugman and his associates found that, in contrast to normal children, those who contract rubella before birth fail to develop antibodies in response to rubella vaccine administered several years later. Accordingly, the character of a child's response to rubella vaccine can help determine whether infection with rubella occurred before birth. Such information is of importance in genetic counseling of parents and in studying patterns of rubella spread.

VACCINES

Perhaps the most important application of knowledge of immune reactions has been the development of effective vaccines. As knowledge of immunology becomes increasingly refined, new discoveries are continually being applied to development of improved means of immunization.

Increased awareness of the importance of "local" or "secretory" antibodies is having particular impact on vaccine development. These antibodies differ structurally from their counterparts in the circulating blood, and they remain confined to particular areas of the body. Secretory antibodies directed against influenza virus, for example, are found in the lining of the nose and throat. They evidently act to stop the virus invader at its point of entry.

NIAID investigators Harry L. S. Knopf, John C. Perkins, Dinah M. Bertran, Albert Z. Kapikian and Robert M. Chanock reasoned that induction of local antibodies in tears should furnish protection against eye infections, including those causing blindness. The scientists vaccinated volunteers intranasally with a killed virus vaccine and infected controls with the corresponding live virus. After an appropriate time interval, tears were cellected from both groups of volunteers and tested for antiviral activity and presence of secretory and other antibody.

Significant levels of secretory antibody -- and antiviral activity -- were found in tears collected from both groups. Although the virus used was one which does not cause eye disease, the scientists hope that their method will aid in development of more effective means of vaccinating against those viral infections which do pose a threat to vision.

In an effort to clarify the mechanism by which production of secretory antibody is stimulated, NIAID career awardee David T. Karzon of Vanderbilt University and grantee Pearay L. Ogra of the State University of New York at Buffalo studied the effect of immunization at one body site on production of local antibody at a distant site. Tests were made on twelve pediatric patients whose colons had been rendered externally accessible by surgery to correct a congenital defect. The scientists demonstrated that polio vaccine administered into the colon elicits production of secretory

antibodies at the colonic site but not in the nasopharynx. In contrast, in natural poliovirus infection--which is usually initiated by the victim's swallowing the virus--secretory antibody is found in both nasopharynx and alimentary tract. Secretory antibody thus appears to be produced locally, its production depending upon local stimulation by antigen.

TRANSPLANTATION

Immunology has assumed greater importance with the advent of transplantation as an accepted form of therapy. Rejection of foreign tissue remains a tremendous obstacle, but this problem is being dealt with more effectively as information accumulates.

The preferred means for avoiding graft rejection is to select donors whose tissues closely match the recipient's. A recent discovery by NIAID grantee Norman Ende of the Emory University School of Medicine may help to improve such tissue-matching. Dr. Ende reported that lymphocytes (a type of white cell) from abdominal lymph nodes contain antigens not found on lymphocytes from the blood. Since lymphocytes from blood are generally used in tissue typing, the additional lymph node antigens may be involved in cases where an organ which appears to "match" a recipient's tissues is rejected soon after transplantation. If so, modification of typing procedures may be indicated for improved results.

Even in situations where an optimal tissue match is not possible, graft rejection can often be combated successfully, especially if it can be anticipated. Scientists at the University of Texas and at Baylor College of Medicine, supported by NIH grants and an NIAID contract (Evan M. Hersh, University of Texas), recently described a new test which appears able to predict episodes of rejection. The test uses radioactive tracers as a means of detecting lymphocyte activation--a process which plays an important part in graft rejection. Sudden increases in the number of activated lymphocytes, as determined by this test, precede clinical evidence of rejection by 24-48 hours. During this time interval, therapy to suppress immune responses and avert rejection can be instituted or intensified.

Since generalized immunosuppression greatly increases the risk of infection, scientists are interested in developing methods which will suppress graft rejection selectively without compromising an individual's overall immune capabilities. A phenomenon known as specific immunological tolerance offers hope that such alternatives can be found. Specific tolerance can be produced in experimental animals by exposing them to either very small or very large amounts of an antigen (foreign substance). As a result of such exposure, the animals lose their ability to respond immunologically to that particular substance, but not to other unrelated antigens. They are then said to be tolerant or unresponsive to the antigen in question.

NIAID investigators (Phillip J. Baker, Philip W. Stashak, Diana F. Amsbaugh and Benjamin Prescott), and a colleague at the

University of Kansas have obtained evidence, in mice, that two types of cells sometimes play an important role in regulating antibody responses. One cell type suppresses while the other cell type enhances the magnitude of the antibody response following immunization with certain antigens. Further study of these cells may provide scientists with the necessary tools for inducing tolerance and preventing graft rejection.

ALLERGY

Kinins are naturally occurring chemicals which, in minute doses, cause dilatation of small blood vessels, increased capillary permeability, and contraction of certain smooth muscles. Evidence suggests that kinins may be responsible for some of the symptoms encountered in allergic conditions.

NIH grantees (Nathan Back and Carl E. Arbesman, State University of New York at Buffalo) and an associate have now detected significant kinin activity in nasal secretions of ragweed-allergic patients following challenge with ragweed pollen extract. Nasal secretions of non-allergic patients with colds showed little or no activity. This finding of kinin-like activity in secretions of allergic patients immediately after challenge tends to support the possibility that kinins play a role in producing allergic symptoms.

IMMUNE SYSTEM AND CANCER

There is increasing evidence that immune mechanisms may normally function to prevent establishment of cancer. A variety of tumor cells have been shown to carry special markers or tumor antigens which distinguish them from normal cells. Since the immune system should identify such marked cells as foreign and act to destroy them, clinically observable cancer may well represent a relatively uncommon breakdown of ongoing immune surveillance.

A number of NIH investigators and grantees have recently garnered evidence to support this concept. Harry G. Bluestein and Ira Green of NIAID's Laboratory of Immunology confirmed that croton oil, known to promote tumor formation in laboratory animals, is also a potent suppressor of immune responses. They demonstrated that this chemical, in addition to suppressing antibody formation, also inhibits cellular immunity -- the immune function involved in cancer surveillance. Additionally, they showed that poly I.poly C--which counteracts the cancer-promoting activity of croton oil--also counteracts its immunosuppressive effect. Taken together, these findings support the hypothesis that the cancer-promoting effect of croton oil is correlated with its capacity to inhibit normal immune surveillance.

NIAID grantee Fritz H. Bach and his associates, working also with support from NIGMS, have found evidence that leukemia-associated markers may be present on white blood cells from some patients with the disease. Using tissue-matching techniques commonly employed in organ transplantation, the University of Wisconsin scientists obtained anomalous results in two out of six

tested patients with active leukemia. In these two cases, cells from the patient reacted to a sibling's cells as though they were compatible with his own, but the sibling's cells appeared to perceive those of the patient as "foreign". Such nonreciprocal reactions are extremely rare among normal sibling pairs. Their occurrence in this study suggests that leukemia cells may develop new markers (tumor antigens) which render them foreign even to formerly compatible cells.

If normal and cancerous cells can indeed be distinguished immunologically, new kinds of therapy will become possible. For example, leukemia patients might be given transfusions of immunologically active white blood cells well-matched for the patient's normal tissue, but reactive against his leukemia cells and capable of selectively destroying them.

NIAID grantee Sidney R. Cooperband and a colleague at Boston University School of Medicine have been trying to develop therapeutic techniques exploiting immunologic differences between normal and cancer cells. As a model, the investigators used cells infected with mumps virus, and carrying an abundance of viral antigens (immunologic markers) on their surfaces. Antibodies directed against the mumps virus antigens were produced in guinea pigs and coupled with diphtheria toxin -- a potent cell poison. The antibody-toxin conjugate was then added to virus-infected tissue cultures and to uninfected control cultures. Mumps-infected cultures displayed extensive disruption within 24 hours of exposure to the conjugate. Identically treated control cultures, in contrast, showed no ill effects within this time period.

These findings suggest that antibodies conjugated with a cell toxin could act as "magic bullets", delivering toxic chemicals to specific cell populations with great selectivity. The investigators hope that this technique, with appropriate modifications, will prove effective against malignant cells bearing tumor antigens.

PARASITOLOGY

Toxoplasmosis

Toxoplasmosis is an important disease of worldwide distribution. Infection during pregnancy may cause abortion or serious birth defects. Postnatal infections, in contrast, are usually so mild as to be inapparent, though in exceptional cases severe illness, blindness, or death may result.

Although it has been accepted for many years that Toxoplasma gondii, a protozoan parasite, causes toxoplasmosis, the nature of this organism's life cycle and its mode of transmission to humans have remained unclear. In the past year, however, in independent reports, three groups of NIAID scientists and grantees set forth evidence that T. gondii falls into the parasite group called coccidia, members in turn of a larger group known as Sporozoa. In addition, the domestic cat has been identified as a possible reservoir of the parasite, although the studies do not conclusively

incriminate the family pet as a direct transmitter of the disease to humans.

One of the groups reported feeding T. gondii-infected mouse brains to healthy cats. Five to six days after the feeding, typical coccidian reproductive forms were seen in cats' intestines. In addition, oocysts, or fertilized eggs, were shed in the animals' feces (J. Chr. Siim, Statens Seruminstitut, Copenhagen).

Similar studies were reported by NIAID investigators Harley G. Sheffield and Marjorie L. Melton and by grantees at the University of Kansas School of Medicine (Jacob K. Frenkel). Although the Kansas group fed T. gondii to 14 kinds of birds and small animals, completion of the life cycle with production of oocysts was confined to cats. It nevertheless remains possible that oocyst formation can occur in other animals -- perhaps even in man.

These findings shed new light on the mystery of how toxoplasmosis is contracted. It had been supposed that the major means of transmission might be ingestion of the parasite in raw or undercooked meat from infected animals -- much like the situation in trichinosis. It is now clear, however, that infected cats may seed the environment with large numbers of oocysts which might infect humans.

Malaria

Malaria is still one of the major diseases of the world and, in an age of jet travel, poses a threat even to non-endemic areas such as the United States. Research on this disease is thus a major concern of NIAID.

In recent years, strains of malaria resistant to the commonly used drugs have emerged. Scientists have been seeking, therefore, new effective antimalarial agents which differ from older ones chemically and in mode of action. For example, Kendall G. Powers, NIAID, has been studying compounds related to the antibiotic lincomycin. He and his colleagues have shown that chlorinated analogues of lincomycin can cure one form of blood-inoculated malaria in rhesus monkeys.

Since the lincomycin-type compounds are different from the more commonly used antimalarials, and their mode of action may also be different, these findings provide clues to potentially useful new antimalarials.

Schistosomiasis

Some 200 million persons throughout the world are afflicted with chronic schistosomiasis. This parasitic disease of the tropics and semi-tropics is frequently serious and disabling and greatly reduces human vitality in endemic areas.

One approach to control of schistosomiasis involves elimination of those snail species which serve as intermediate hosts

for the parasites and enable them to be transmitted to man. Commonly this is done by chemical poisoning of the snail host; but the possible environmental complications of poisoning are well known from the DDT story. The Institute has encouraged, therefore, diverse lines of research in an area labelled "Biological Regulation of Vectors". Recent work by an NIAID investigator provides an example of research along these lines which might make it possible to supplant snail vectors by parasite-resistant stocks.

Charles S. Richards of NIAID's Laboratory of Parasitic Diseases performed his studies on the snail Biomphalaria glabrata -- intermediate host and vector of Schistosoma mansoni. Beginning with a cross between a susceptible and a resistant snail of this species, the scientist developed a variety of snail stocks, some susceptible and some refractory to infection with S. mansoni. He found that susceptibility is a complex characteristic, determined by several distinct genetic factors. In addition, stocks which were susceptible in their juvenile stages often proved refractory when tested as adults.

If stocks of refractory snails were introduced into areas endemic for schistosomiasis, they might be expected to interbreed with local susceptible populations, leading to reduced transmission of parasites. It would be important, however, to select snails displaying resistance at all ages and carrying as many refractory genes as possible. The effectiveness of a program to control schistosomiasis through introduction of resistant snail stocks might be further enhanced if the resistant stocks were so bred as to contain traits especially favorable to their survival and proliferation.

Although Dr. Richards has resistant snail stocks, they are genetically impure. However, progress already achieved in clarifying the complex factors involved makes it seem possible that useful stocks can eventually be developed.

Test for Amebiasis

Amebiasis is a disease of the large intestine caused by ingestion of the protozoan parasite Entameba histolytica. It is encountered throughout the world and is remarkably common, even in temperate areas. Although many cases are asymptomatic, mild to severe gastrointestinal symptoms frequently accompany infection. Occasionally, the parasites spread through the bloodstream, producing abscesses in liver, lungs and other organs. Invasive amebiasis is almost always curable, but if diagnosis is unduly delayed, mortality may be appreciable.

An NIAID grantee, Ronald Elsdon-Dew, and his associates at the Institute for Parasitology in Durban, South Africa, have now developed a simple and rapid test for invasive amebiasis. Material for the test may be prepared in a central laboratory and distributed as a kit, use of which requires little training or equipment. Previous tests, in addition to being quite slow, required a high level of skill for interpretation, rendering them unsuitable for the

underdeveloped areas where amebiasis is most prevalent.

The antigen used in the test kit is prepared from amebae cultured in the absence of other microorganisms. This culture technique, developed by Louis S. Diamond, an NIAID investigator, is also being used to prepare antigen for use in skin testing. Studies underway at the NIH Clinical Center and the All-India Institute of Medical Sciences, New Delhi, (using PL-480 funds) show that this skin test is valuable in the diagnosis of invasive amebiasis.

BACTERIAL AND FUNGAL DISEASES

The classic epidemic infectious diseases caused by bacteria no longer threaten this country but microorganisms are still the cause of many diseases that end in death or extend and complicate expensive stays in hospitals. Medical care is immensely more effective and sophisticated than ever before; it is also considerably more expensive. Control of infectious disease is one assured way of reducing the socio-economic impact of disease without building more hospitals or significantly increasing the number of medical care personnel.

A major technique for control of bacterial and fungal infectious diseases is use of antibiotics, and the search for new and better antibiotics goes on unceasingly. This search is needed, particularly, due to the ability of many bacteria to develop resistance to commonly used antibiotics.

Tuberculosis

In 1970, William Lester and his associates at Denver's National Jewish Hospital and Research Center reported highly encouraging results in use of rifampin to treat patients with far-advanced, multiple-drug-resistant tuberculosis. Patients were treated with this semi-synthetic compound, in combination with other drugs, for 4 to 12 months. No toxicity attributable to rifampin was observed and, within 10 to 90 days of the initiation of treatment, the illness of 21 of 30 patients, all with stubborn disease, achieved a stable quiescent status, as shown by repeated cultures. Resistance to rifampin developed in 7 of the 9 failures, all but one of whom received no satisfactory companion drug because of previously acquired resistance to all available agents.

Rifampin appears to represent a significant addition to the armamentarium of anti-tuberculosis drugs. Although it is not yet possible to decide whether rifampin is superior to isoniazid (currently the favored drug in treatment of tuberculosis), it appears to offer at least three clear advantages over another old standby, streptomycin. It acts more rapidly than streptomycin, has much lower toxicity, and can be administered orally rather than by injection.

Although rifampin proved effective in more than half of those patients in whom it was used as the only active agent, in the future, it will undoubtedly be employed along with other drugs

whenever possible, since such multiple drug therapy has been shown to be by far the most effective procedure for treating tuberculosis.

Strep and Staph Infections

NIAID grantee Donald Kaye of Women's Medical College of Pennsylvania and his associates at the New York Hospital-Cornell Medical Center recently demonstrated that cephalexin -- a new antibiotic -- is effective in treating streptococcal and staphylococcal soft tissue infections. The same group of scientists earlier showed the drug to be useful in treating urinary tract infections. In the present study, 24 of 25 patients with severe soft tissue infections had an excellent clinical response to cephalexin, with elimination of the causative microorganism by the seventh day after initiation of therapy. Penicillin-resistant as well as penicillin-sensitive staph strains were inhibited by moderate concentrations of the new antibiotic.

Cephalexin has minimal side effects and low toxicity, and it can be administered orally. It promises to be a useful addition to the list of safe and effective antibiotics.

Actinomycosis

Drug allergies in patients often interfere with treatment of infections. For example, actinomycosis -- a fungal disease frequently localized in the jaw or lungs -- is very difficult to treat effectively without penicillin. Patients with serious penicillin allergy thus present a considerable medical challenge.

Recently, investigators at the University of Oklahoma School of Medicine, working under an NIAID training grant, reported success in using linocomycin -- a relatively new antibiotic -- to treat actinomycosis in four patients with penicillin allergy. Two of the patients had lung involvement, while the other two had infected jaws. All responded rapidly to administration of linocomycin and remained symptom-free throughout the period of maintenance medication (5 to 12 months) and as long as followed thereafter.

Pyelonephritis

The role of bacterial infection in development of chronic pyelonephritis (inflammation of the kidney) has been questioned in recent years. Failure to elicit a history of symptoms consistent with renal infection and failure to detect bacteria in the urine has suggested to some a possible autoimmune origin for this type of progressive renal disease.

In order to clarify the role of bacteria in pyelonephritis, and to evaluate use of a new technique for this purpose, NIH-supported scientists (William R. McCabe, et.al.) at Boston University Medical Center obtained renal (kidney) tissue from 23 patients with kidney disease and from 20 controls. Seven of the patients had typical bacterial pyelonephritis, while 7 others had pyelonephritis with no clear indication of bacterial infection.

The scientists stained sections of each kidney with antibodies known to react with many of the bacteria most commonly involved in renal disease. These antibodies had been coupled with a chemical that fluoresce in ultra violet light. Microscopic examination of thin sections of fluorescent antibody-treated kidney showed no evidence of bacteria in the 20 specimens from subjects without renal disease nor in 8 of the 9 specimens from patients with chronic renal disease other than pyelonephritis. However, traces of bacteria were found in 6 of the 7 patients with bacterial pyelonephritis and also in 6 of the 7 patients with pyelonephritis of undetermined origin.

These results indicate that absence of a history of urinary tract infection and absence of bacteria in the urine at the time of examination do not rule out prior infection as a cause of progressive kidney damage. In addition, these findings show that the fluorescent antibody test may furnish evidence of such infection and thus aid diagnosis.

BASIC RESEARCH

Protein Synthesis

A "candid camera" view of bacterial genes in action was reported in 1970 by NIH grantees. Barbara A. Hamkalo and Charles A. Thomas, Jr., of Harvard Medical School, along with a coworker at the Oak Ridge National Laboratory, used an electron microscope to directly glimpse cellular protein synthesis -- an essential life process which, until now, has usually been studied by indirect means.

The scientists' achievement was made possible by their use of a special mutant strain of Escherichia coli -- a common intestinal bacterium and favorite experimental tool of molecular biologists. While normal E. coli have tough outer cell walls, walls of the mutant strain are fragile. Thus, these bacteria can be broken open with unusual ease, leaving their interior contents relatively undisturbed.

Exploiting this weakness, the investigators gently opened mutant cells, immediately preserved them, and, using an ingenious preparative technique, subjected them to electron microscopy. The resultant micrography -- much like candid snapshots -- caught cells in the act of protein synthesis.

Protein synthesis ultimately determines the nature and behavior of all living cells. Thus, increased understanding of this function should pay rich dividends -- for example, in helping detect and eliminate genetic defects and aiding control of such "molecular" diseases as viral infections and perhaps even cancer.

Prostaglandins

Prostaglandins are a family of hormone-like chemicals which occur naturally throughout the human body. Their remarkably wide spectrum of biological activity ranges from nasal decongestion to induction of uterine contractions. The list of possible

therapeutic applications reads like the label on a bottle of old-fashioned patent medicine. It includes control of blood pressure, prevention and treatment of blood clots and of stomach gastric ulcers, correction of male infertility, and control of asthma. Two members of the prostaglandin family have already been successfully employed to induce both therapeutic abortion and labor at term.

Recently, Elias J. Corey of Harvard University -- an NIAID grantee -- described a procedure for synthesizing prostaglandins which has significant advantages over other methods. The new procedure permits synthesis of pure prostaglandins of all three major types from a single precursor compound. Some pharmaceutical companies are already utilizing the method -- which Dr. Corey has elected to keep free of patents -- to produce prostaglandins for research. Since the new procedure promises to adapt well to scaling-up, it is expected that it will eventually be used in commercial production of these wonder chemicals for medical use.

Applications of Basic Research

One of the strongest arguments in favor of fundamental or "pure" research is that this type of endeavor frequently and unpredictably yields very practical results. In 1970, a number of NIAID grantees were among those scientists who produced striking examples of the practical potential of basic research.

Intrigued by observations that carotenoid pigments prevent photo-sensitization in bacteria, plants, and mice, a group of scientists, supported in part by grants from NIH, decided to study the effect of such pigments in patients with erythropoietic porphyria (EPP) -- an hereditary sensitivity to light.

Three patients -- a father and daughter and an unrelated man -- were fed carrot-oil or beadlets of beta-carotene. Prior to therapy all three patients experienced itching, redness, burning, swelling and eruptions after even brief exposure to sunlight. Following treatment to develop and maintain adequate blood levels of carotene, the first two patients (father and daughter) were able to carry on fully normal activities out of doors. The third patient also showed considerable improvement, though his response was less complete. (Thomas B. Fitzpatrick, Massachusetts General Hospital; Leonard C. Harber, New York University; Edward H. Kass, Boston City Hospital.)

In another example of a basic research finding being applied successfully to treatment of a disease, NIH grantee H. Hugh Fudenberg and his associates at the University of California Medical Center used an extract of white blood cells called transfer factor to correct an hereditary immune deficiency in a young boy. Transfer factor, prepared from white blood cells of one individual and given to a second, confers upon the latter the donor's pattern of cellular immunity.

At the time of its discovery, transfer factor, like cellular immunity itself, was primarily of academic interest. More recently,

however, cellular immunity has emerged as critically important in many types of infection, in graft rejection, and probably in the natural control of cancer. Since transfer factor transmits cellular immunity, its potential usefulness has become increasingly apparent as the importance of cellular immunity has been made clear.

The nine-year-old boy treated by Dr. Fudenberg and his coworkers was a victim of the Wiskott-Aldrich syndrome, a sex-linked hereditary disease characterized by severe recurrent infections and, usually, death at an early age. Since the age of nine months, this patient had experienced numerous episodes of illness, including 24 bouts of pneumonia.

Like other victims of Wiskott-Aldrich syndrome, the present patient had defective cellular immunity, as confirmed by tests, and transfer factor from a normal adult male volunteer was administered in an attempt to remedy the deficit. Results were dramatic. The boy's chronic seborrhea, eczema, and ear infection all improved greatly or disappeared, and no new infections occurred in the five months elapsing between treatment and report. Laboratory tests and physical examination also indicated significant changes toward normal. The investigators believe that transfer factor deserves further study as a potential treatment for several immune deficiency diseases that are associated with impaired cellular immunity.

BASIC AND HUMAN GENETICS

Genetics is a scientific discipline receiving strong emphasis and support from the National Institute of General Medical Sciences. In only a few years this field of inquiry has produced many exciting advances that lead toward the treatment and prevention of human genetic disease.

Genetic disease, inherited from one or both parents, is an important medical problem. It has been estimated conservatively that genetic disease adversely affects the lives of some 15 million Americans, and that approximately 25 percent of all hospital beds are occupied by persons suffering from some aspect of hereditary disease. These include anemias, severe neurological diseases, psychiatric disorders and mental retardation, a large group of metabolic diseases, and a wide variety of birth defects. Although many diseases are entirely genetic in origin--sickle cell anemia, hemophilia, Rh blood disease, and mongolism, for example--others result from an interaction between genetic factors and environmental influences, as with diabetes mellitus, schizophrenia, and manic-depressive psychosis. Although some genetic defects are apparent at birth and may be fatal in the first few years of life, others do not present clinical symptoms until quite late in life.

It should be emphasized that not all congenital diseases--diseases present at birth--are of genetic origin but may also result from malnutrition, infectious disease, or from drugs and other toxic substances taken in by the mother during pregnancy. One of

the vital tasks of the clinical geneticist, in collaboration with physicians and clinical investigators, is to sort out which congential diseases are truly genetic in origin, and which result from environmental influences that if identified and prevented would eliminate the grief and economic burden that would otherwise be borne by the family of a defective child.

DETECTION OF GENETIC DISEASE

The Institute stimulates and supports research on new screening techniques to detect carriers of genetic disease. In marriages between persons who carry the same genetic disease trait, the probability that one or more of their children will display the full-blown disease is markedly increased. On the other hand, in many so-called "recessive" conditions, genetic disease may not be outwardly observed in parents, and these persons may be unaware of their carrier status until after the birth of a defective child. Unfortunately, carriers of defective genes can now be identified for only a few genetic diseases. New methods of genetic screening would permit physicians and genetic counselors to search for carriers of serious forms of genetic disease and advise them on problems related to family planning.

An accomplishment along these lines is that of Institute grantee Barbara I. Brown, of Washington University, St. Louis, who with co-workers developed a simple but ingenious biochemical blood test which potentially can be used to identify carriers for as many as 40 different genetic anomalies. The test measures cellular levels of enzymes required for carbohydrate metabolism and has been used to recognize carriers of genes for several kinds of glycogen storage diseases, and the disease galactosemia, which is marked by a basic inability to metabolize milk sugar and usually leads to severe mental retardation. The national incidence for galactosemia alone is one in 18,000 births, and the proportion of carriers in the population is believed to be one in 134 persons. When diagnosed within a few hours after birth, mental retardation can be minimized by restricting milk sugar from the diet of the infant. Carrier parents and attending physicians can now be alerted to the risks involved, and rapid diagnosis of the disease will be facilitated.

Grantees J. Edwin Seegmiller, John O'Brien, and Shintar Okada of the University of California at San Diego discovered this past year the basic biochemical and clinical measures to identify carriers of Tay-Sachs disease and to diagnose this condition before birth. Their findings also were independently confirmed by NINDS intramural investigators, Drs. Roscoe O. Brady, Jr., and Edwin H. Kolodney. The disease--which produces severe brain damage, paralysis, blindness, and early death--is found predominantly among Jewish people. It is estimated that 500,000 persons within the United States are carriers of the defective gene responsible for this disease. The California investigators determined first that the enzyme hexosaminidase A is missing in Tay-Sachs patients and is the fundamental cause of disease. This discovery enabled the investigators to (1) identify carriers by showing that the

enzyme is present but in reduced amounts in cultured connective tissue or skin cells; (2) demonstrate the presence or absence of the enzyme in the cells of unborn infants, obtained through amniocentesis--prenatal sampling of cells--early in the pregnancies of carrier mothers. In such a situation parents in many states can elect to terminate the pregnancy so as not to bring gravely defective children into the world.

Because of the above developments, plans are being made in one large eastern city to conduct a community-wide screening program to identify and counsel carriers of Tay-Sachs disease. It is forecast that the total cost of the proposed screening program will be no greater than the expense of caring for just one affected child during its short lifetime.

GENE THERAPY

Whereas progress has been made in treating inherited disorders by dietary means, drugs, and surgical procedures, there still is no broadly applicable cure for genetic disease by replacing missing genetic materials directly or otherwise correcting basic gene defects in the cells of affected persons. The prospects for gene therapy nonetheless gained importantly during the past year, and the possibility of its application to man now seems likely to come much sooner than had previously been anticipated.

Scarcely six months ago a group led by Dr. H. Ghobind Khorana at the University of Wisconsin completed the total laboratory synthesis of a gene. The gene in question was pieced together in a test tube, the links consisting of two chains, each having a length of about 80 nucleotides--the basic building blocks of genes. The Wisconsin feat followed by only a few months the isolation of a single, intact gene by an Institute grantee, Dr. Jonathan Beckwith, and his co-workers at Harvard University. The Harvard team also showed that its gene, derived from a bacterium, controlled a specific biological function involved in the cellular breakdown of the sugar lactose. Such work with lower organisms admittedly is far removed from the much more complex genetic makeup of man. But few doubt any longer that methods currently evolving will in time make it possible to create or obtain human genetic materials for therapeutic purposes.

Laboratory geneticists thus are seeking ways to place and reactivate missing genetic material within defective cells and to determine whether these materials are incorporated into chromosomes and can direct the production of a missing or deficient enzyme. It should be added, however, that investigators in this field are aware of potentially serious ethical problems involved in the work to manipulate human genetic materials, and they are further aware that an informed public and a consenus are needed before the technology now evolving can be extended to man.

Considerable attention is being paid to viruses as potential carriers of therapeutic genetic information, because viruses are essentially composed of nucleic acids, the basic hereditary

62-645 O - 71 - pt. 3 - 14

substances, and a protein coat to protect the nucleic acid from destruction upon entering the host organism. One gene delivery study involving viruses and cultured mammalian cells is that of Dr. Vasken Aposhian at the University of Maryland School of Medicine, Baltimore. Dr. Aposhian and co-workers are pursuing, with Institute support, a novel scheme to package the DNA of normal mouse cells in a virus coat and to infect other mouse cells, carrying a gene defect, with these particles. Their goal is to demonstrate that the mouse "passenger DNA" is accepted by the host cell genome, and to prove its viability through biochemical analysis. The Maryland group is taking advantage of a property of the polyoma virus in which the virus, while reproducing itself inside a cell, produces not only its own kind but also false viruses (psuedovirus) which contain not viral DNA but that of the host cell. In less than a year the investigators successfully produced pseudoviruses containing radioactive labeled mouse DNA and exposed them to other mouse cells. They have shown, almost certainly, that the pseudoviruses enter the target cells, lose their protein coats upon entry, and thereby deposit their mouse DNA "cargo" within the host cell. In the coming year they will try to determine if the bit of transposed DNA actually enters the mouse cell nucleus and becomes functionally incorporated into the chromosomes.

Another, similar effort is that of Dr. Theodore Friedman at the University of California, San Diego, who is working with cultured cells from patients with the genetic defect known as Lesch-Nyhan syndrome. This disease is a relatively rare but nearly always fatal condition marked by mental retardation, movement disorder, and peculiar self-mutilation. Dr. Friedman is attempting to repair these genetically defective cells by supplying them with DNA from normal cells. He has found that on treating these mutant cells in tissue culture with "normal" DNA the treated cells begin to produce the missing enzyme. Thus far the effect can be sustained for only a short time. The reason for the transitory nature of the phenomenon remains a question for further investigation. The speculation is that an enzyme within the mutant cell degrades or breaks down the new DNA. Dr. Friedman is attempting to find ways of protecting the normal DNA within the mutant cell until it can be incorporated into the chromosomes--which usually occurs during cell division.

MUTANT CELL LINES

Many geneticists, molecular biologists, biochemists, virologists, and kindred investigators are finding human mutant cell culture techniques indispensable to the solution of genetic disease problems. Until recently only a few human mutant cell lines characterized by enzyme deficiencies or inborn errors of metabolism had been established on a permanent basis. The Institute is vitally concerned in making a wide variety of cell lines representing genetic diseases more available to qualified investigators.

Thus a welcome accomplishment is that of grantee Arthur D. Bloom, who with co-workers at the University of Michigan has established permanently in culture two lines of mutant lymphocytes obtained from blood samples from two young Lesch-Nyhan patients.

One advantage of lymphocytes over skin cells is that they can be stimulated biochemically to divide and grow more easily. Because of their more rapid growth rate, a sufficient number for study can be cultured in a few days, compared to the several weeks previously required--thus speeding the early diagnosis of this disease. Since the mutant lymphocytes can be maintained in culture, it is possible to make them available to other investigators and clinicians for further propagation and study.

CELL STRUCTURE AND FUNCTION

Genetic disease can be expressed in the cell by one of two routes:

-- An altered genetic message
leads to an altered protein structure
leads to altered cell function
leads to disease.

-- A failure of gene expression
leads to a deficiency of a given protein
leads to altered cell function
leads to disease.

Disease resulting from an altered genetic message is nearly always hereditary, but may occur from environmental causes through a process called "mutagenesis," in which the structure of DNA within the genes is altered through exposure to toxic chemicals, drugs, or radiation.

Disease due to a failure of gene expression may result from an altered structure or function of the so-called "regulatory genes" which control the transcription of genetic information from its point of storage in the DNA to RNA "messengers" which carry the information to the "ribosomes" within the cell where protein is synthesized. Recently Dr. Harvey Itano, working on an NIGMS grant with a team of human geneticists at the University of California, San Diego, has shown that failure of gene expression can also result from interference at any point in the complex process by which information on the RNA messenger is translated into the structure of a protein. Dr. Itano is widely known for his work with Dr. Linus Pauling in 1949 which led to the discovery of sickle cell anemia as the first "molecular disease" in which an apparently minor change in the structure of the hemoglobin molecule results in a devastating disease. Subsequent research has shown that this structural change was caused by the substitution of the amino acid valine for glutamic acid in the sixth position of the beta hemoglobin chain, which in turn resulted from the substitution of a single nucleotide, adenine for thymine, in the DNA of the gene directing the synthesis of the beta chain. Dr. Itano's present work suggests that in sickle cell anemia the incorporation of valine into the beta chain may require an unusual form of "transfer RNA" which if not present in adequate amounts leads to deficient synthesis of sickle cell hemoglobin. He is now using cultures of immature human red cells to explore in greater depth the precise mechanisms by which the synthesis of

hemoglobin is controlled within these cells.

Research on the control of gene expression is a particularly "hot" field among scientists seeking ways to alleviate the painful "crises" of sickle cell anemia. It has been observed clinically that some sickle cell patients escape the most severe aspects of this disease due to the persistence into adult life of a type of hemoglobin known as fetal hemoglobin, or hemoglobin F, normally found in unborn infants. Scientists would like to find ways of prolonging the synthesis of fetal hemoglobin in young sickle cell anemia patients and continuing this synthesis as they grow into adulthood--as a regular mode of therapy.

An important clue may arise from the studies of Dr. Marks at Columbia University on another genetic disease called beta-thalassemia, in which the red cells synthesize the alpha chains of hemoglobin at a normal rate but the beta chains, only slowly if at all. This is a serious disease common among people from the Mediterranean area. Dr. Marks has been able to develop cell-free preparations for hemoglobin synthesis from the red cells of normal and thalassemic patients. He finds that ultra filtration removes a substance which inhibits hemoglobin synthesis in the cell-free preparations from normal cells. Furthermore, after removal of the inhibiting substance by filtration, the thalassemic preparations have an accelerated rate of hemoglobin synthesis, a rate which is again depressed upon addition of the ultra filtrate. It appears that in thalassemic patients an inhibitor of hemoglobin synthesis is formed in an unusual amount. Whether this substance normally has a role in the regulation and control of normal adult hemoglobin synthesis is not yet known. It is conceivable that similar substances are involved in turning off the formation of fetal hemoglobin; and if so, their discovery may lead to a new approach to the treatment of sickle cell disease.

Although many of the proteins of the body are enzymes whose deficiency or altered structure leads to an altered cell function and to disease, other proteins form important structures in the cell; e.g., the cell wall, the mitochondria, and other subcellular organelles. Many of these structures are actively being studied by scientists under NIGMS support. The past score of years has seen many advances in the understanding of cell structure and function, and one of the most interesting has been the discovery of so-called "microtubules." These structures had been seen and reported to occur in cells only a few times prior to 1963, when an Institute grantee developed a new method of fixing tissues for electron microscopy. The new method, which uses gluteraldehyde as a fixative, preserves the delicately structured microtubules for examination whereas they previously had been destroyed. Subsequent extensive studies by numerous scientists, largely supported by NIGMS, have produced considerable understanding of the structure, function, and occurrence of these structures. For example, it is now known that:

- Microtubules are ubiquitous among both plant and animal cells.

. Structurally, they are long, flexible cylindrical tubes about 250 Angstrom units--or one-millionth of an inch--in diameter with a low-density, possibly hollow central core (100 A^{o} in diameter).

. Microtubules form the primary structures in the tail of sperm, which is composed of nine pairs of outer tubules surrounding a varying number (0, 1, or 2) of central tubules. Whether they are "active" in imparting motion to the sperm tail, or whether they are simply "passive," serving as long, flexible structures to keep the sperm tail extended, is under active investigation. This area of research has considerable significance in the search for a male contraceptive.

. In cell division, microtubules form in a "spindle" shape around the dividing chromosomes and act, in some as yet unknown way, to pull the chromosomes apart, after which the cell divides into two daughter cells. Formation of the microtubular spindle is a critical event in this process. Since a singular characteristic of cancer cells is that they continuously undergo uncontrolled division, the events surrounding cell division are of great interest and concern. It is important in this regard that certain chemicals--notably colchicine, vincristine, and vinblastine--bind rather specifically to the microtubules. This may well serve as the basis of action of vincristine and vinblastine as cancer chemotherapeutic agents, in that these drugs bind to the spindle proteins, disrupting spindle formation and blocking cell division. Equally of interest is the possibility that some malfunction of microtubules in the spindle apparatus may be involved in those genetic diseases marked by an abnormal number of chromosomes, as in mongolism or Down's syndrome, where affected persons have 47 chromosomes instead of the normal complment of 46.

. Microtubules appear to have, in addition, an important role in maintaining the structure of cells. Thus the red blood cell, or erythrocyte, has a series of microtubules just inside the outer margin, and it is these microtubules that give the red blood cell its flat, disc-shaped appearance. Similarly, microtubules have been observed lying just under the surface of many other cells where they appear responsible for the maintenance of shape and structure. As a cell moves, the microtubules appear and disappear constantly, thus forming a continuously changing internal scaffolding or "cytoskeleton" for the cell as it moves from one place to another. Further research on this is critically important because a major characteristic of the cancer cell is its ability to leave its normal position and move to other loci in the body, there to grow, divide, and start new foci of cancer.

. Microtubules further appear to have an important role in the

functioning of nerve cells. If one cuts through a nerve axon, or fiber, one sees several hundred microtubules rather evenly dispersed through the "axoplasm." Their purpose and function is poorly understood--whether they carry materials to the distant end of the axon or whether they are simply resilient, structured "stiffeners" to keep the axon in place is not yet known. Recently, scientists supported by the NINDS have found that an important group of neurological diseases known as senile dementia is accompanied by marked degeneration of the microtubules. This is important because "senile dementia" is a common disorder that contributes to a significant proportion of the disability and hospitalization among the elderly. Continued study of this microtubular degeneration and its origin in these neurological conditions is a matter of urgent priority.

TRAUMA

Research on trauma, or accidental injury, is another area of investigation given strong emphasis by the Institute. Accidental injury is one of the neglected problems of modern society. It is the leading cause of death in the first half of life's span. Currently the annual toll of trauma for all age groups is about 115,000 lives; in addition, 11 million persons each year are injured and 400,000 are permanently disabled. In 1969 the economic costs of trauma totaled $25 billion, and injury victims used 22 million hospital bed days--more than all heart patients or obstetrical patients and four times as many as all cancer patients. One out of every eight hospital beds is occupied by a trauma victim.

Accidental injury is now frequently viewed as a disease entity. In this light it is not only the wound--or site of injury--that must be studied but even more importantly, the body's response--or lack of needed response--to the injury. Through this approach, NIGMS-supported studies are changing present concepts of treatment and are enabling severely injured patients to recover more promptly.

For example, pulmonary complications are very common after severe injury, and the "Post-Traumatic Respiratory Distress Syndrome" is a frequent cause of death in trauma. Investigators at the Albany Medical College Trauma Center, using computers and electronic monitors, have shown that this syndrome begins very soon after injury, even when patients show no evidence of impending respiratory distress by physical examination or routine laboratory procedures. Their work is significant because such changes usually are not diagnosed until 36-48 hours after injury, at which time irreversible damage may have occurred. By contrast, the combination of early diagnosis, intensive therapy, and careful evaluation has virtually elminiated deaths at this Center from respiratory failure.

A research team at the University of Pennsylvania Hospital in Phildelphia is studying traumatic shock, especially septic shock, at the cellular level. This group is particularly concerned with the effects of shock on the red blood cell's ability to transport and release oxygen. Because mortality from septic shock remains

at about 50 percent at even the best treatment centers, a new clinical approach to treatment is needed. Studies of oxygen utilization during the body's response to overwhelming trauma or infection indicates that an organic phosphate substance, 2, 3-diphospho-glycerate (2,3 DPG), within the red blood cell affects the ability of hemoglobin to take up oxygen in the lungs and release it to tissues. This substance may provide a therapeutic means for red cells to respond more actively to changes in oxygen requirements of tissues. Patients who receive large volumes of stored blood, patients in septic shock, and premature infants with infection or respiratory distress syndrome have great need for increased oxygen delivery, but are unable to respond to this need by increasing 2, 3 DPG levels. Thus, an already precarious situation is compounded by the consequent increased difficulty in oxygen delivery to tissues. These observations may offer an explanation for some of the late or delayed secondary organ failures which frequently kill trauma victims.

An estimated 70,000 patients with severe burns are admitted to hospitals each year, and the annual death toll is 12,000. Better life-saving techniques are obviously required for burn victims, as are better ways to reduce disfigurement and scarring. The trauma team at Parkland Hospital in Dallas, Texas, has pioneered the use of strips of fresh pigskin as a biologic dressing for burns. The temporary pigskin covering the raw wound prevents fluid loss, eases the pain of the burn, lessens the danger of infection, and permits greater movement by the patient, thereby helping the patient progress to the point where he can accept permanent skin grafts.

Also of major interest to these investigators is the study of changes in body fluid spaces after injury. A knowledge of these fluid shifts is important to the accurate restoration of blood volume after injury, since improper fluid therapy increases complications and impairs wound healing. Using an ultra-microelectrode, this group has been able to show alterations in cell membrane permeability in undamaged cells at a distance from the injury. Abnormal function of overtly uninjured cells may help to explain the severity of the circulatory derangements, the marked metabolic upsets, and the susceptibility to infection which follow injury. The investigators have also noted that red blood cells show abnormal cell membrane function following injury; the degree of this abnormality can provide an indication of the severity of the injury.

PHARMACOLOGY-TOXICOLOGY

Clinical and basic studies in pharmacology and toxicology are supported by the Institute to solve serious problems posed for both physicians and their patients by the multiplicity of drugs and what these drugs do or may not do in the body.

One problem of great concern is the effect on their unborn children of drugs taken by women during pregnancy. The urgent need for such investigations has been apparent since the disaster with thalidomide, where drug injury was grossly manifest. Unfortunately, few definitive studies on the effect of drugs in children have been

done at the clinical level, partly because the required analytical technology has been lacking.

Until very recently it was not possible to assay the blood of newborn infants for the suspected presence of drugs. This, in part, was because of the relatively large amounts of blood that were needed for laboratory testing, amounts that could not be obtained safely from the infant. Drs. Reba M. Hill and Marjorie Horning at Baylor University's College of Medicine have overcome this problem by the use of two highly sophisticated analytical techniques called mass spectrometry and gas chromatography. Using them together, Drs. Hill and Horning have been able to identify with great accuracy trace amounts of drugs and their metabolites (by-products) in a single drop of blood.

The Baylor studies have focused on obstetrical patients and their infants in three Houston hospitals--Methodist, St. Luke's, and Texas Children's. Drug histories are taken and periodic analyses--up to the time of delivery--are done on blood and urine samples from the prospective mothers. At birth, umbilical cord blood of the infant is analyzed. Thus far the doctors have examined more than 100 infants born to mothers who received drugs during their pregnancies. Nine percent of the infants were found to have major defects at birth, including cleft palates, hernias, and incomplete kidney development, while another 18 percent had deformities of a lesser nature. Most significant is the fact that a cluster of congenital malfunctions occurred in infants born to mothers who received certain categories of drugs. Furthermore, the evidence accumulated by Drs. Horning and Hill makes it clear that many more drugs cross the placenta than previously realized and may be harmful to the infant at any time during pregnancy.

The technologies used by Drs. Hill and Horning are also being used by Drs. Monroe Wall and Keith Palmer at the Research Triangle Institute in North Carolina to identify the products to which drugs are converted within the body. These products, or drug metabolites, may be more potent or less potent, more toxic or less toxic, than the administered drug. Such knowledge is exceedingly important for designing safer, more effective drugs.

Of special interest are steroid drugs which are used to treat a variety of diseases and are contained in various types of birth control pills. Over the past year, Drs. Wall and Palmer learned that norethynodrel, a component of some contraceptive pills, causes a variety of fetal or birth defects when administered to pregnant mice. They also found that administration of two specific metabolites of the drug caused more defects in mice offspring than did the parent drug. Three different groups of pregnant mice totaling 300 animals were tested, some with the steroid itself and others with pure forms of one or another of the metabolites. Examination of their litters revealed that up to 64 percent of the fetuses displayed severe developmental abnormalities. Among the birth defects observed were malformed brains and skulls, cleft palates, and a variety of anomalies in the development of eyes, ears, and sex organs. Less than one percent of the mice in normal litters

have such abnormalities. These findings show the need for better understanding of the metabolic fate and the physiological effects of metabolites of steroids in clinical use.

Studies at the University of Pittsburgh are concerned with effects from long-term administration of such commonly used drugs as reserpine, chlorathiazide, digitoxin, and chlorpromazine. Dr. Joseph Buckley and co-workers have noted that the extended administration of reserpine significantly reduces the amount of substances called catecholamines which regulate and control the force of the heart in response to the different demands placed upon it. Undue reduction of the catecholamines causes the heartbeat to deteriorate to the point of failure.

Schistosomiasis--caused by a parasitic blood fluke or worm harbored by snails and commonly called "snail fever"--is estimated to afflict 200 million people in the world. In tropical and semi-tropical countries it often surpasses malaria as a major public health problem. The principal control weapons are pesticides which destroy the carrier snails but at the same time pollute the waterways for other animal species. A satisfactory drug is badly needed. Dr. Paul Talalay and his associates at Johns Hopkins University have prepared and tested a series of compounds which appear to be effective against established infections of various strains of schistosomiasis in mice.

In the collaborative drug surveillance project covering four Boston-area hospitals, Tufts University scientists found that patients with low levels of serum albumin, a protein, had an increased incidence of adverse effects from the steroid immunosuppressive drug, prednisone, compared to patients with high serum albumin concentrations. Side effects among these patients included hemorrhagic complications, psychoses, and elevated blood sugar levels. The findings by Dr. Hershel Jick and his colleagues suggest that--in the presence of low albumin levels--the degree of binding of prednisone to serum proteins is decreased, thereby allowing a greater amount of the drug to be free, active, and thus toxic to the patient.

AUTOMATION IN THE CLINICAL LABORATORY

The burgeoning requirements of the American people for better, and less expensive, health care dictate that each physician's capabilities be augmented with competent medical and technical personnel working with efficient and dependable diagnostic instruments, organized into systems designed to provide valid data upon which to base clinical diagnosis.

The past 20 years have seen striking advances in fundamental research at the cellular and molecular levels and in the development of new laboratory approaches to the diagnosis of disease. The program in the automation of clinical laboratories is an attempt to bridge the gap between these new discoveries and their practical application in patient care.

The Institute previously has reported on the development of the modular units which can be incorporated into an automated system. One of these is the GeMSAEC--a radically new fast analyzer developed by scientists and engineers at Oak Ridge National Laboratory. This unit has progressed steadily for three years from initial concept to prototype, to commercial production, and field testing to become a clinical reality. The first commercial model of GeMSAEC was placed in routine use in December 1970 in the Department of Clinical Chemistry, Georgetown University Hospital, Washington, D. C. This instrument represents a successful product of cooperative developmental effort between industry and the basic and applied sciences. Dr. Martin Rubin, Director of the Department of Clinical Chemistry there, states that GeMSAEC has cut the analytical time required to perform many of the routine blood chemistry tests by one-third. Moreover, by using the improved methodologies concurrently developed with the instrument, the amount of analytical variation (often called laboratory error) has been reduced from the usual 15 percent to less than five percent.

The use of enzymes in therapy may have great implication for improved treatment of certain disease conditions. For example, it is known that the enzyme asparaginase is present in most human cells, but is absent in leukemic cells. There is good evidence that leukemic cells cannot exist in the presence of the enzyme. On the basis of this finding, asparaginase has been used to treat some leukemic patients, and in a few instances remission of the disease has been claimed. Therapeutic doses of the enzyme, however, are very expensive, and there is the further problem that it disappears from the blood stream in an hour or two. Dr. Stuart Updike, working at the University of Wisconsin, has developed a technique which entraps the enzyme in very tiny beads of polyacrylamide gel without changing the activity of the enzyme. When this gel has been administered to animals it remains active in the blood for weeks. The success achieved in these animal studies to date is encouraging. In the future it may be possible to develop these resin-enzyme complexes in forms or devices that are appropriate for use in human patients.

One of the basic requirements of an automated system for clinical chemistry is an accurate list of normal values upon which the computer can act to either reject or accept a patient's data. At the present time this is done by visual inspection, and abnormal or early variations in a person's individual "profile" (each person's normal set of values) which may portend disease are often overlooked. Dr. George Z. Williams, at the Pacific Institute of Medical Sciences, is working to establish normal biochemical profiles for a large group of individuals. The primary objective is to find out how stable the biochemical profile is over the average life span. The influences of sex, race, season, nutrition, physical condition, stress and age; changes which precede overt disease, and the predictive value of profiles in health management and preventive medicine are being studied. By accumulating data on the ranges and profiles of blood chemistry values in normal subjects, Dr. Williams has found that the individual's normal range of blood constituents is much narrower than that previously established for

the average population. This suggests the possibility of early detection of significant, persistent abnormal trends of physiology or chemistry within an individual before they reach a grossly abnormal range.

COMPUTER RESEARCH

RESEARCH AND DEVELOPMENT

The Computer Center Branch, under the direction of Mr. Joseph Naughton, is successfully meeting the diverse needs of the Bureaus, Institutes and Divisions at NIH. Constant investigation into the most advanced but economical techniques of computing have helped administrators and researchers use Division of Computer Research and Technology's IBM-360 Computers effectively. Three thousand jobs are processed each day by the Computer Center Branch. At present 120 remote terminal users can communicate directly with the central system at any one time using DCRT's interactive time-sharing facilities. The number of users increases continually.

DRUG IDENTIFICATION

Computers connected to sophisticated analytical instruments can collect and process data quickly and accurately. One of several such systems has been designed by a Computer Systems Laboratory Project Team, led by Mr. Marvin Shapiro. It is a special-purpose system which analyzes data collected from the mass spectrometer located in the laboratory of Dr. Henry Fales of the National Heart and Lung Institute.

The system has been used to identify possible poisons in emergencies. An unknown substance, often obtained from gastric lavage or a blood sample, is introduced into the spectrometer and its mass spectrum is determined. The component peaks of the unknown are matched with information the computer already holds in its memory, leading to an almost immediate identification of the substance.

ION MOVEMENT THROUGH BIOLOGICAL MEMBRANES

Dr. Michael Mackey of the Physical Sciences Laboratory has developed a theory, the purpose of which was to provide a physical explanation of how charged particles move across a nerve cell membrane. In nature, one sees such movement in terms of pulsations of activity. Dr. Mackey observed that there is a "conductivity reversal" as a charge builds up. That is, the flow of current tends to cut itself off after many particles have collided with the cell membrane. This cut-off is dependent upon the number, rate and intensity of the collisions. After a relatively quiescent state, movement again increases until the next conductivity reversal occurs.

CHEMICAL INFORMATION SEARCH

In chemistry, as in all sciences, there is a formidable amount

of literature which is not easily accessible to the researcher. Manual searches of primary and secondary (abstract) journals are expensive and time-consuming. A computer, however, can access vast files of chemical information quickly.

In order to make the computer an easy to use and familiar tool, Dr. Stephen Heller, Mr. Kenneth Shapiro, Mr. Richard Feldmann and Miss Deena Koniver, have designed computer programs which allow the chemist to communicate with the machine in his own language. Sitting at a remote terminal he can query the files in one of three ways. He can enter subject words and obtain references to the chemical literature. He can draw a structural diagram of his compound using a specialized graphics technique. Or, he can enter any data he has on the compound (such as the mass spectrum) and find materials having the specified characteristics.

The system is run experimentally using a time-sharing PDP-10 computer which allows interaction between the chemist and the machine. When the scientist asks his question, he gets his information back in real-time, or almost immediately. He is thus able to reformulate his query on the spot if the information extracted is not what he is looking for.

"FUZZY SETS"

The concept of fuzzy logic is an important one in the field of artificial intelligence. The human mind works in such a way that it can recognize unclear pictures as belonging to one or another set of objects. The ability to do this is based on previous experience and the fact that certain indefinite characteristics are recognized as being "like" something else.

A computer, however, cannot handle fuzzy or uncertain information. It cannot draw upon previous experience nor can it recognize the "likeness" of things without the intervention of the human programmer.

Dr. Chin Liang Chang and Dr. Richard Lee of the Heuristics Laboratory have proposed that "fuzzy" or many-valued logic be used in problem-solving systems. Using this concept, they have devised computer programs which will allow the machines to make intelligent decisions. Such programs can be applied, for example, to the examination of photomicrographs where the determination of cell normality or abnormality must be made by the machine.

ELECTROCARDIOGRAM ANALYSIS

Arrhythmia is often an immediate lethal consequence of a heart attack. If arrhythmia can be controlled by prompt treatment, the patient's chance for survival is greatly increased. Cardiologists are trying to learn more about what kinds of drugs can stabilize the heart rhythm. One way of doing this is to analyze an electrocardiogram, beat-by-beat, both before and after a heart attack, and after drug administration. Such analysis involves voluminous data which can more easily be handled by a computer than

a human being.

Electrocardiograms on patients who have suffered heart attacks at home are collected by the Montgomery County Heartmobile, which is sent out in emergencies. These ECG's in addition to being relayed to a hospital by telephone, are stored on magnetic tape for computer analysis. Computer programs, designed by Dr. James Bailey and Mr. Martin Miller of DCRT, analyze heartbeats and determine the effects on the beat of any drug given to control arrhythmia. The same kind of data is collected and analyzed on dogs, in which heart attacks have been experimentally induced. Information on the efficacy of certain experimental drugs is thus compiled and made available to the cardiologist.

The project is conducted in collaboration with Dr. George Beiser, Dr. David Redwood, Dr. Richard Karsh, Dr. Stephen Epstein and Dr. Eldon Smith of the National Heart and Lung Institute.

TUESDAY, MAY 4, 1971.

DIVISION OF BIOLOGICS STANDARDS

WITNESSES

DR. RODERICK MURRAY, DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. SAM T. GIBSON, ASSISTANT DIRECTOR, DIVISION OF BIOLOGICS STANDARDS
GEORGE A. BRUST, EXECUTIVE OFFICER, DIVISION OF BIOLOGICS STANDARDS
MRS. ELIZABETH GRUBBS, BUDGET OFFICER, DIVISION OF BIOLOGICS STANDARDS
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
GERALD F. MEYER, CHIEF, HEALTH BRANCH, DIVISION OF BUDGET

Biologics Standards

Object Classification (in thousands of dollars)

Identification code 09-30-0845-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	2,831	3,102	3,182
11.3	Positions other than permanent	35	47	47
11.5	Other personnel compensation	73	70	70
	Total personnel compensation	2,939	3,219	3,299
12.1	Personnel benefits: Civilian employees	289	303	303
21.0	Travel and transportation of persons	100	122	122
22.0	Transportation of things	15	15	15
23.0	Rent, communications, and utilities	44	50	53
24.0	Printing and reproduction	114	10	10
25.0	Other services	3,707	4,401	3,849
26.0	Supplies and materials	943	922	905
31.0	Equipment	84	85	80
99.0	Total obligations	8,235	9,127	8,636

Personnel Summary

Total number of permanent positions	273	273	273
Full-time equivalent of other positions	6	5	5
Average number of all employees	269	268	268
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

	Identification code 09-30-0845-0-1-651	1970 actual	1971 est.	1972 est.
	Program by activities:			
	Biologics standards (program costs, funded)[1]	6,347	9,127	8,636
	Change in selected resources [2]	1,888		
10	Total obligations	8,235	9,127	8,636
	Financing:			
25	Unobligated balance lapsing	2		
	Budget authority	8,237	9,127	8,636
	Budget authority:			
40	Appropriation	8,225	8,838	8,636
40	Portion withdrawn (Public Law 91-204, sec. 410)	−2		
40	Pay increase (Public Law 91-305)	14		
41	Transferred to other accounts		−19	
43	**Appropriation (adjusted)**	8,237	8,819	8,636
46.10	**Proposed transfer for wage-board pay increase**		19	
46.20	**Proposed transfer for civilian pay act increases**		257	
46.30	**Proposed transfer for military pay act increases**		32	
	Relation of obligations to outlays:			
71	Obligations incurred, net	8,235	9,127	8,636
72	Obligated balance, start of year	2,770	2,563	2,750
74	Obligated balance, end of year	−2,563	−2,750	−2,237
77	Adjustments in expired accounts	−89		
90	Outlays, excluding pay increase supplemental	8,353	8,647	9,134
91.10	Outlays from wage-board supplemental		18	1
91.20	Outlays from civilian pay act supplemental		243	14
91.30	Outlays from military pay act supplemental		32	

[1] Includes capital outlay as follows: 1970, $30 thousand; 1971, $85 thousand; 1972, $80 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1968, $755 thousand; 1969, $2,643 thousand; 1970, $2,643 thousand; 1971, $2,643 thousand.

NOTES

Includes $116 thousand in 1971 and $116 thousand in 1972 for activities previously financed from: Research resources, 1970, $116 thousand.

Excludes $552 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	*1971*
Office of the Director	453	28
National Institute of General Medical Sciences	48	
National Institute of Environmental Health Sciences	---	135
Research resources	---	94
Health manpower	---	295

INTRODUCTION OF DR. MURRAY AND ASSOCIATES

Mr. FLOOD. We continue with the National Institutes of Health, and will now take up the Division of Biologics Standards. Dr. Roderick Murray will make the presentation. We have your biographical sketch.

Is there anybody with you that you would like to introduce?

Dr. MURRAY. I have Mr. Brust, Dr. Gibson, and Mrs. Grubbs.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH OF RODERICK MURRAY, M.D.

Name: Roderick Murray, M.D.

Position: Director, Division of Biologics Standards, National Institutes of Health.

Birthplace and date: Christchurch, New Zealand, August 12, 1909.

Education: B.S., University of Witwatersrand, South Africa, 1930; M.Sc., University of South Africa, 1931; M.D., Harvard Medical School, 1941.

EXPERIENCE

1956—present: Director, Division of Biologics Standards.

1949–1956: Assstant Chief, Laboratory of Biologics Control, National Institutes of Health.

1947–1949: Laboratory of Biologics Control, NIH.

1947: Commissioned Officer, USPHS.

1946–1947: Research Fellow, Thorndike Memorial Laboratory, Boston City Hospital.

1942–46: U.S. Army Medical Corps (major).

1942: Assistant residency, second medical service, Boston City Hospital (interrupted by military service).

1941–42: Medical internship, second medical service, Boston City Hospital, Boston, Mass.

1931–37: Biochemist, South African Institute for Medical Research, Johannesburg.

Association memberships: Alpha Omega Alpha; American Medical Association; American Public Health Association (Fellow); American Association of Immunologists; American Academy of Microbiology (Fellow).

Special awards, citations, or publications: Cullen Medal, Faculty of Science, University of Witwatersrand, 1930; Distinguished Service Medal U.S.P.H.S., 1965; and 47 publications.

GENERAL STATEMENT

Mr. FLOOD. Doctor, you have a prepared statement. Do you want to read it?

Dr. MURRAY. I would like to present the prepared statement if I may.

Mr. FLOOD. Suppose you do.

Dr. MURRAY. Mr. Chairman and members of the committee, I would like first to outline, if I may, the 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. These products include all vaccines, antitoxins, therapeutic serums, allergenic products, and human blood for transfusion, as well as products prepared from human blood. There are presently 263 biological products licensed, all of which are under constant surveillance and study by the DBS.

The basic instrument for the control of biological products provided in the Public Health Service Act is the issue of licenses. 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 to determine continued compliance with standards. In addition, each manufacturer must submit to the Division, for testing and review, samples and test reports of batches or lots of the product he proposes to distribute as required. 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.

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. 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.

Division scientists must be constantly aware of advances in research, and must 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. The aim is to make possible the early application of these new products to public health and medical practice, while insuring conformance to adequate standards for safety and potency on the basis of current knowledge. This is aptly pointed up in the Division's research interest in hepatitis.

CONTROL OF SERUM HEPATITIS

The control of hepatitis has been a major challenge in medical virology for many years. In the field of biologics, the disease constitutes a serious risk in the administration of blood and some blood products. Transfused blood is estimated to cause more than 30,000 cases of overt hepatitis and 1,500 to 3,000 deaths every year in the United States. Because of this risk, and the hope for possible development of a vaccine against the serum hepatitis agent, the Division has for many years maintained an exploratory research program in this field.

In testimony before the committee in the last couple of years we have referred to the Division's role in this effort to conquer hepatitis. In the way of progress we are pleased to report that during the past year, the Division has evaluated the efficacy of test procedures for detection of hepatitis associated antigen (HAA) or Australia antigen and the practicality of the tests for blood donor screening. Solid information has also been acquired on HAA-positive blood donors, and a panel of blood donor serum specimens has been established for use in evaluating sensitivity and specificity of other test techniques for the detection of HAA as they are developed. These studies have shown that by identifying and eliminating donor bloods which are positive for HAA, it may be possible to reduce the number of cases by as much as 25 percent.

In addition to the assessment of all practical methods for HAA antigen testing, the DBS has been involved with standardization of the antisera which are subject to licensure through the Division. Federal regulations for specific standards of safety, purity, and potency for hepatitis-associated antibody (anti-Australia antigen) have been deveoped by DBS this past year. Two manufacturers are licensed and several more are expected to be licensed in 1971 for commercial distribution of the reagent. When materials to perform these tests become available in sufficient quantity, it will be required that all human blood collected for transfusion purposes or for further processing in licensed establishments be tested for Australia antigen and that only negative blood be used.

REEVALUATION OF YELLOW FEVER VACCINE

Although newly developed biological products create the heaviest and most urgent demands on the Division, problems often arise concerning long-established products. For example, yellow fever vaccine has been licensed for many years and its effectiveness in inducing solid immunity to "wild" yellow fever virus is undisputed. However, the vaccine, which is produced in chick embroys, was developed in the early 1940's when little was known about avian leukosis viruses. During the 25 years that yellow fever vaccine has been in use, there has been no observation of any relation between avian viruses and human disease; nevertheless, DBS scientists have been working to purify yellow fever vaccine virus without altering the efficacy of the vaccine as an immunizing substance. This has been accomplished and as soon as the field evaluation is completed it will be possible to release the particular virus strain for commercial yellow fever vaccine production.

ADVENTITIOUS AGENTS

Of special concern to the Division in relation to the virus vaccines is the development of methods for the detection of tumor viruses and adventitious agents, including mycoplasma. Viruses must be grown on living cells, for example, eggs and animal tissue cell cultures.

Evidence of the implication of mycoplasma in human diseases has occurred with increasing frequency since these organisms have been subjected to study by laboratory techniques.

The DBS for the past several years conducted research on the detection, isolation, and identification of mycoplasma in cell cultures. These studies have resulted in the establishment of cultures free from these agents, and in the introduction of test procedures to insure the exclusion of mycoplasma from vaccines.

CELL STRAINS

The matter of the cell strains used in the production of viral vaccines is important. As a result of the Division's concern with this matter, research projects under contract directed toward the development of nonhuman diploid cell strains have been organized. It is generally considered that such cell strains will be important alternatives for primary cell cultures in the production of viral vaccines and will in-

crease the assurance of safety of such vaccines. To date, two promising subhuman primate diploid cell strains have been developed which meet the criteria of acceptability for cytogenetic and growth characteristics, as well as freedom from adventitious agents, and the ability to support the growth of viruses from which vaccines presently are produced. These two cell strains are being made available for further evaluation to all interested virologists and commercial establishments involved in the production of viral vaccines.

If further studies of these cell strains by other workers in the field indicate that they are acceptable, it is anticipated that these cell strains could be used in the production of viral vaccines.

FISCAL YEAR 1972 BUDGET

The Division is requesting $8,956,000 in 1972 compared to $8,725,000 available for obligation in 1971. This will enable the program to continue at approximately the same level of operation, allowing the increase of $231,000 to be applied to mandatory cost items.

Mr. FLOOD. Doctor, this would be a pretty short hearing if we just talked about your program increases wouldn't it?

Dr. MURRAY. Yes.

Mr. FLOOD. This $50,000 program cut shown in the justifications is actually understated since there are some cost-of-living increases that aren't reflected in your budget. Isn't that so?

Dr. MURRAY. Yes, that is true.

INFRACTIONS OF DBS REGULATIONS

Mr. FLOOD. Have there been any significant infractions of your law and your regulations in the past year?

Dr. MURRAY. We had one problem which has been partly solved in connection with the hepatitis associated antigen test. One of the manufacturers decided this was not subject to the provisions of the Public Health Service Act and started marketing material for which no standards had been adopted.

Eventually through a number of procedures this material was withdrawn from the market when it was shown that the manufacturer could produce a product which met standards, it was eventually licensed. That is one example.

SUCCESSES AGAINST HEPATITIS

Mr. FLOOD. What has been your role in research on hepatitis during the last 2 or 3 years. It appears to me you have something to brag about don't you? You appear to be very modest this morning.

Dr. MURRAY. I think there are two or three things that could be mentioned. First of all is the increasing interest in the question of so-called Australia antigen and antibody to Australia antigen. Many different people have developed testing methods. These have been evaluated and refined in our laboratories and we have used these methods for testing blood serum from cases of hepatitis which we have had in storage for as long as 18 years.

From this has come a good deal of information about how the illness evolves in man, and how some of the individuals who develop hepatitis become positive for the antigen and thus become potentially dangerous blood donors. This is a very valuable bit of information.

We have supported under contract a rather large program carried out by the New Jersey State department of health which has been very actively following the epidemiology of hepatitis in that State for many years.

This particular contract program was designed to provide us and the country with basic information on the rate of occurrence of hepatitis associated antigen in blood donors in different communities, and to find out how this compares with voluntary donors and with donors who donate in various commercial blood banks.

Mr. FLOOD. Is hepatitis infectious or contagious?

Dr. MURRAY. It is infectious. The organism must be introduced into the body. There is some suspicion that rare cases may be contagious by contact.

AUSTRALIAN ANTIGEN

Mr. FLOOD. You refer to the Australian antigen. How does this come to be identified that way?

Dr. MURRAY. That is a curious story and interesting one. Dr. Blumberg in Philadelphia has been interested for a number of years in the serology of different population groups throughout the world and in the course of this he identified an antigen in the blood of some Australian aborigines which he gave the name of Australia antigen.

Subsequently it was found this antigen also occurred in other populations throughout the world and in fact it occurred in people in the United States.

Mr. FLOOD. Is it inherent, can it be transmitted?

Dr. MURRAY. It is now related to serum hepatitis.

Mr. FLOOD. But it is not confined to the aborigines in Australia, is that right?

Dr. MURRAY. It seems to be present in the blood of people in many parts of the world. It is not confined to Australia. The word Australia comes in because this was the first time it was found, when various groups of patients with different diseases in this country were examined, it was found there was a high degree of association with the presence of this antigen and serum hepatitis in man.

Mr. FLOOD. What conditions exist or are peculiar to the people of the area where you have discovered this condition?

Dr. MURRAY. Curiously enough there is little information about increased incidence of hepatitis in those areas.

Mr. FLOOD. Can it be transmitted?

Dr. MURRAY. Dr. Blumberg's original thought was that it might be a genetic factor. But as far as we are concerned the interesting thing is that about 98 percent of the people with serum hepatitis we studied had Australia antigen present in their blood.

Mr. FLOOD. Does the law of Mendel apply in this?

Dr. MURRAY. If this is a genetic factor, I am sure it might apply.

DISCOVERY RESULTING FROM UNRELATED RESEARCH

Dr. MARSTON. Mr. Chairman, I have two points to add to what Dr. Murray has said.

First, Dr. Blumberg was working on the intramural staff of the National Institutes of Health when a fair amount of this work was done by him. He subsequently moved to Philadelphia.

The second point is that this is another one of those very striking examples where a considerable amount of effort, over a number of years, had been directed toward this serious disease, with the morbidity and mortality figures you have heard, and yet the answer came from a study that was completely unrelated to the question of hepatitis from a gifted investigator interested in differences among populations and people of blood antigens.

This is often the way we make our advances in research and this is perhaps as striking an example as one can find. We all worked for many years trying to make some progress in hepatitis with very, very little result, and then from this unrelated discovery the whole field of hepatitis has opened up not only as far as the Australia antigen is concerned but as you will hear, with this ability to identify the antigen, the work in other areas has just blossomed and gone forward.

HEPATITIS VACCINE

Mr. FLOOD. Is a vaccine to attack it the answer?

Dr. MARSTON. As I mentioned in my opening statement yesterday, there is even some hope that a vaccine might be produced. Now that we are able to identify at least some of the blood that may transmit hepatitis, the possibility of the development of a vaccine for some forms of hepatitis is real.

Mr. FLOOD. Is it based primarily upon the liver?

Dr. MURRAY. There is very little known actually about the pathogenesis of hepatitis, other than it is related to the presence of this antigen. I am talking about serum hepatitis.

The end result is damage to the liver which can be either temporary or permanent. But whether the liver is the primary point of attack of the virus or whether this is the result of something else that goes in the body is not known.

As a matter of fact examination for the virus in portions of the liver from patients who have succumbed to hepatitis has shown very little.

HEPATITIS MORTALITY RATES

Mr. FLOOD. Is the mortality rate high after an infection?

Dr. MURRAY. This is a very difficult question to answer. As more information is gathered about hepatitis, I think the figures will change. It varies according to age. In younger people who are better able to withstand the onslaught of the disease, the mortality is not very high. But in older people, and this is the tragic part because these are the ones who have to undergo the most surgery, the mortality can get up as high as 20 percent from figures which we have seen.

Mr. FLOOD. Does it recur after treatment?

Dr. MURRAY. Yes, it can recur in the sense that the patient never really recovers from the disease.

Mr. FLOOD. Is it a prolonged condition once it develops?

Dr. MURRAY. Serum hepatitis is rather a serious illness. The incubation period from the time of the administration of the blood, the infected blood, can vary from as little as 25 to 30 days to as long as 5 to 6 months, so that sometimes in the past, the disease was never associated with the administration of blood.

MANIFESTATIONS OF HEPATITIS

Mr. FLOOD. What are the most obvious external manifestations of the disease?

Dr. MURRAY. Jaundice is the main one. Weakness, a feeling of malaise, loss of appetite.

Mr. FLOOD. What is the manifestation of jaundice?

Dr. MURRAY. Yellowing of the eyeballs and the skin. Also the demonstration of increased levels of bilirubin in the blood and the presence of bile in the urine, which makes it dark in color.

Mr. FLOOD. Is diet of any help in the treatment?

Dr. MURRAY. That is a debatable point. It is believed, and we did some studies on this years ago, that certain forms of diet may be helpful.

Mr. FLOOD. Is alcohol when consumed a contributory factor? First, is it a cause and secondly, does it contribute materially?

Dr. MURRAY. Alcohol can be a cause of toxic hepatitis, but it can be a contributing cause to the severity of the illness.

Mr. FLOOD. There are other kinds of hepatitis?

Dr. MURRAY. Yes, for instance, toxic hepatitis caused by toxic chemicals. I think other witnesses might testify on this later on because this is a matter of interest in other parts of the NIH.

DEVELOPMENT OF DIPLOID CELL CULTURE

Mr. FLOOD. On page 11 of your justification there is a paragraph regarding your research on "diploid cells". When I finished reading your justifications I had no more idea what a diploid cell was than when I began. What is important in this?

Dr. MURRAY. As I mentioned earlier, many virus vaccines are produced in tissue cultures. Some of these are prepared from primary tissues of animals like monkey kidneys in the preparation of polio vaccine. But there has been a feeling that a much better method of producing vaccine from the point of view of standardizing its production would be to use cells which are standard in their properties and could be propagated through a number of generations. Then from one source of cells which could be carefully standardized one could eventually develop enough cell culture material to produce the vaccine. Thus we are not dealing with a different animal every time but are dealing with the same cell source. A characteristic of cells as they go through generations is that some of them become apparently like cancer cells, they develop characteristics of malignancy. Others, however, may be maintained in their original condition in which the chromosomes are in pairs. This is called the state of diploidy.

Mr. FLOOD. Why?

Dr. MURRAY. The chromosomes are paired. It is derived from the Greek word for two.

Mr. FLOOD. Is there chain reaction in the reproduction of these cells?

Dr. MURRAY. We don't know that. They develop this malignant transformation spontaneously. So, part of the program we are developing is to obtain lines of monkey and other cells which are diploid in character and maintain this character up to a point at which they can be useful for preparing virus vaccines.

Human diploid cells have been used experimentally here in some instances and in other countries for the production of vaccines. There are a number of people in this country, however, who have felt that diploid cells may have some disadvantages. Whether these are theoretical or not we don't know.

However, human diploid cells I am sure will be used in this country for vaccine production and in due time some of these other diploid lines which we are developing.

Dr. MARSTON. The general thought in the present state of knowledge is that, the diploid cell is the normal and naturally occurring cell, and when it becomes changed as we see in the case of cancers and under other circumstances, this then becomes an abnormal type of cell.

So the diploid is usually equated with the normal conditions.

EFFECTS OF HEPATITIS

Mr. FLOOD. How does hepatitis affect the infected person other than the jaundice? What does it do to the physical body, weakness?

Dr. MURRAY. Weakness, loss of weight, sometimes the patient may develop coma due presumably to the production of ammonia and like compounds. They can succumb to this very easily and, of course, the ultimate thing it does to the body, some 20 percent of elderly people, is to bring about their deaths.

Mr. FLOOD. Mr. Michel.

TREND IN HEPATITIS INCIDENCE

Mr. MICHEL. Dr. Murray, in what time reference are these statistics given on hepatitis? You say the transfused blood is estimated to cause more than 30,000 cases of overt hepatitis and 1,500 to 3,000 deaths. That is every year?

Dr. MURRAY. Yes.

Mr. MICHEL. Has that been pretty static over a period of years, going up or coming down or what?

Dr. MURRAY. The figures we have seen indicate it has been going up. This is in the case of serum hepatitis. But hepatitis in general, at least of viral origin, which includes so-called infectious hepatitis, shows a cyclical tendency over the years; it goes up and comes down and goes up and comes down.

Mr. MICHEL. Is that tied to anything at all?

Dr. MURRAY. Nobody knows. But part of the reason why the figures for serum hepatitis appear to be going up seems to be more awareness of hepatitis and better reporting of cases.

(The following was subsequently submitted:)

HEPATITIS IN THE UNITED STATES

Prior to 1966 serum hepatitis and infectious hepatitis were not reported separately. Since that time the number of cases reported by year were as follows.[1]

	1966	1967	1968	1969
Serum hepatitis	1,497	2,458	4,829	5,909
Infectious hepatitis	32,859	38,909	45,893	48,416

[1] Extracted from CDC Morbidity and Mortality Weekly Report Annual Supplement, September 1970.

Mr. MICHEL. A couple of years ago we had an outbreak of it caused by eating shellfish, I guess.

Dr. MURRAY. Yes.

Mr. MICHEL. Has there been any repetition of that outbreak?

Dr. MURRAY. There have been many such outbreaks reported in this country and abroad. I think one of the most famous was at Pascagoula, Miss. There have been some in New Jersey and elsewhere. One was reported in Stockholm, Sweden, from oysters. These are related apparently to contamination with human waste by being harvested too close to sewage outlets.

Mr. MICHEL. Has that been pretty well established?

Dr. MARSTON. With the realization of this hazard and the greater restrictions on harvesting shellfish that might be contaminated, some of the problems we had before we knew this have disappeared.

Now that we understand how the disease was transmitted through the contamination of shellfish by human waste, we can minimize the risk when the controls are followed.

Mr. MICHEL. In these 30,000 cases that crop up each year, would there be any difference related to blood type?

Dr. MURRAY. It would be my guess, no, because I don't think there is any connection between this kind of hepatitis and blood type.

DANGER OF HEPATITIS IN BLOOD TRANSFUSIONS

Mr. MICHEL. Would someone who might come from a family that would be subject to having a number of blood transfusions have cause for alarm or concern?

Dr. MURRAY. I don't believe so. I don't think there is any connection in adults with jaundice due to serum hepatitis and blood types.

In young children who have had Rh disease, this is a different thing. That is definitely related to blood type.

Dr. BERLINER. I wasn't quite sure whether you were asking whether there was a hazard to other members of the family.

Mr. MICHEL. Not really, but that could very well follow. I was more concerned about those who had the transfusions.

Dr. BERLINER. There is a hazard in transfusion, a hazard of hepatitis. There is not a very major one. But people who have a large number of transfusions are very likely to get hepatitis eventually.

DONOR SOURCES OF HEPATITIS

Mr. FLOOD. We have heard reports in the eagerness of some groups to collect blood that they sweep through the ghettos and through the poorer areas of town where the wino's hang out. This is a great source of funds for the wino who sells blood when he needs funds. It has been suggested that these people for many reasons are the source of much of the hepatitis coming into the blood banks.

Dr. MURRAY. I can't give a definite answer.

Mr. FLOOD. You are aware of this talk?

Dr. MURRAY. I am aware of the talk and that is part of the study which we have been supporting in New Jersey. We are finding that the blood from voluntary donors, family donors and people who volunteer for a particular patient does have a definite low level of positive-

ness with respect to the antigen. So there is a hazard even there. Blood which comes from commercial sources collected in the cities, presumably from donors who have given a history of not having had hepatitis, and who meet the standards and are accepted by the blood bank under medical supervision have a higher level of positiveness. So, they will be involved in more hepatitis. The aim of this is to be able to screen out those who are positive and therefore reduce the hazard from blood transfusion.

The figures we have thus far would indicate that the number of cases can only be reduced by about 25 percent. Seventy-five percent will still remain. The reasons for this are not fully understood. Some of it may be due to lack of sensitivity of the tests available, and may also be due to the fact this kind of hepatitis may be caused by other viruses which we know nothing about.

Dr. BERLINER. We ought to make one thing clear and that is it is not the Red Cross that uses the commercial approach. The Red Cross donors are volunteers. There are a number of commercial blood banks who pay their donors for the blood. It is in this group that the incidence of hepatitis-carrying blood is so much higher than blood from volunteers.

I might say, as Dr. Murray has said, at present we are only able to detect about 25 percent of the contaminated blood and therefore even under the best circumstances there is going to continue, for the foreseeable future, to be hepatitis induced by blood transfusions.

We hope to be able to gradually reduce the incidence as we learn more about the various causes. Meanwhile there are certain legal problems. There have been a couple of court cases in which people who developed hepatitis following transfusions have brought suit against the hospitals and the courts have affirmed their right to collect damages even though there was no way at the time they received the blood to rule out the possibility they might get hepatitis. There is a major problem in this regard.

MONONUCLEOSIS

Mr. MICHEL. Have you any thoughts on why there seems to be an increase of mononuclesosis among the young people.

Dr. MURRAY. No, I won't speculate on that. I think mononucleosis like many other infectious diseases comes in waves. Some years there is more of it, other years less. But since we are able to identify it now and to do some virological investigations, I think much more information on this line will be available in coming years.

Mr. MICHEL. That is all.

ENFORCING SANITATION STANDARDS FOR BIOLOGICAL PRODUCTS

Mr. FLOOD. Mr. Natcher.

Mr. NATCHER. Dr. Murray, I was very much interested in your statement to the committee concerning the basic instrument for the control of biological products which of course is the issue of licenses. Further you stated to the committee:

> In addition, each manufacturer must submit to the Division, for testing and review, samples and test reports of batches or lots of the product he proposes to distribute as required.

In Kentucky we have a gentleman who is a pharmacist and a right qualified and right able pharmacist. He told me several months ago that on one of his vacation trips with his wife he decided to pass through one of our cities where a large drug manufacturing firm is located.

He went in and identified himself and they let him go through. He was absolutely amazed at the system that was in use in the large drug manufacturing firm from the standpoint of cleanliness and from the standpoint of the way they were putting up their particular drugs and products. This gentleman was simply amazed.

Doctor, after the license and after the approval of the product and the samples and the batches that are submitted, what about the drug manufacturer that then sells this particular drug? Where do we have inspection?

Dr. MURRAY. I can't answer for the whole of the pharmaceutical industry. I can only answer for that small part of it which manufactures biological products subject to the Public Health Service Act and under license.

In general that part of the establishment is separate from the general drug manufacturing. As we have testified in previous years, it is incumbent upon our staff to go out and inspect each of these licensed establishments manufacturing biological products, those that have been licensed or will be subject to license, at least once a year.

If we suspect there is anything unusual going on, we may inspect more often than that.

As far as licensed biological manufacturers are concerned, I think this type of inspection together with the requirements for submission of samples of most of the products involved assures that the public is getting materials which meet the standards.

LICENSING AND ENFORCEMENT PROCEDURES

Mr. NATCHER. Dr. Marston, generally speaking what system do we use as far as the drug manufacturer is concerned? This particular drug has been approved by the Food and Drug Administration.

What system do we use now from the standpoint of some inspection concerning manufacture and sanitation.

Dr. MARSTON. I think there are two things we can do that might be helpful, Mr. Natcher. One, and I don't know whether you want to do this or not, we can certainly talk to Dr. Edwards about any specific problems there may be.

We can also obtain, for insertion in the record at this point, a statement in answer to your question. This would come from the Commissioner of the Food and Drug Administration and not the National Institutes of Health.

If you would like, I can get for you and also for the record an answer to this question generally and also to expand on Dr. Murray's statement of what we do in the Division of Biologics Standards which is the only regulatory responsibility we have at NIH.

Mr. NATCHER. With your permission, Mr. Chairman, I would like to have that inserted in the record.

Mr. FLOOD. Without objection.

(The information follows:)

STATEMENT RELATING TO THE DIVISION OF BIOLOGICS STANDARDS MODE OF OPERATION

As part of the DBS Licensing and control activities the facilities and equipment used for manufacturing products comply with high standards of sanitation and cleanliness by applying the following procedures: (a) conformance with The Establishment Standards of the Public Health Service Regulations, (b) prelicensing onsite inspections (c) at least one and frequently two post license onsite inspections each year by two technically qualified inspectors (d) conformance with the good manufacturing practice regulations adopted under the Federal Food, Drug, and Cosmetic Act and (e) liaison with the scientific community through personal contacts, scientific meetings, and seminars.

STATEMENT PROVIDED BY THE FOOD AND DRUG ADMINISTRATION

The Food and Drug Administration establishes good manufacturing practices to insecure that adulteration of drugs does not occur. To assure high standards of sanitation and cleanliness in drug manufacturing plants, the Food and Drug Administration conducts programs of factory inspection and industry education to promote voluntary compliance. Educational activities include seminars, films and slides for the training of drug industry employees.

IMPORTANCE OF SANITARY PRODUCTION

Mr. NATCHER. The Food and Drug Administration is before another subcommittee now. Mr. Michel and I serve on that subcommitee. We have had the Administrator of the Food and Drug Administration before the other subcommittee.

I do think this is a right important matter. It never occurred to me a firm the size of this particular firm would operate as it seems to do. They complain about meat inspection and other matters. According to the report that this man gives me, it is simply outrageous, the conditions that exist in this particular plant.

Dr. MURRAY. Was this in the State of Kentucky?

Mr. NATCHER. No; this firm is not in the State of Kentucky. It is one of the large ones in the United States.

INCIDENCE OF HEPATITIS IN THE MILITARY

Mr. FLOOD. Hepatitis was just a funny word for years around here, then all of a sudden there is a great public interest in it. Is it transmissible and infectious? What kind of hepatitis, what does it do, can it be cured and how long does it take? It is now of public moment you see.

Dr. MURRAY. This patricular form of hepatitis has been recognized as such since about 1937. I think that was the first report. It was quite a problem during World War II because nothing was known about the agent that caused it. And the great public interest at the present time is due to the fact that we can actually see and measure this antigen. This has given the scientists involved what is commonly referred to as a breakthrough leading to expanded interest in studying hepatitis.

Mr. FLOOD. You mentioned World War II. We have noticed in our mail in the last 25 years many letters from families and from members of the Armed Forces and veterans that they have hepatitis.

Could you get in touch with the Surgeon General and see what the incidence is in the Armed Forces? Why is this peculiar to the Armed Forces as against any other segment of society? What kind of hepatitis is this?

Dr. MURRAY. I would think that most of the hepatitis they are talking about is infectious hepatitis. This is the main problem the military have at the present time with hepatitis.

While it occurs in this country in outbreaks mainly among schoolchildren, it is endemic in certain other parts of the world and when the troops go abroad they are exposed to this infection and develop outbreaks of hepatitis.

I think this is the Army's main concern. I personally can't answer in specific terms of numbers but it can readily be gotten from the Office of the Surgeon General of the Army.

(The information follows:)

The incidence of Hepatitis in the armed services during 1970 was reported as follows:

Army: 371 per 100,000.
Air Force: 120 per 100,000.
Navy: 130 per 100,000.

Mr. FLOOD. Mr. Patten.

DRUG MANUFACTURERS IN NEW JERSEY

Mr. PATTEN. Doctor, am I right in the impression the largest concentration of drug manufacturers is in New Jersey?

Dr. BERLINER. Yes.

POSSIBILITY OF R. & D. OVERLAP WITH HSMHA

Mr. PATTEN. Dr. Sanozaro testified you are spending $62 million for research and development. Is this a duplication of your work?

Dr. MARSTON. No, sir. Dr. Sanozaro's division in the Health Services and Mental Health Administration is concerned with research and development in methods of the organization and delivery of health services. It is a completely separate type of activity from the research that is done at NIH which is medical research on disease problems and prevention of disease.

In the case of Dr. Murray, his is the one part of NIH that has the responsibility for actually assessing, maintaining standards, and regulating in the area of biological products. The research his division does is that research that is necessary to carry out this function, that is of regulating, maintaining standards, having the information that is needed to intelligently carry out the laws of the Nation concerning biological standards.

I can't think of any overlap at all between his activities and Dr. Sanozaro's.

RELATIONSHIP OF DBS WITH FDA

Mr. PATTEN. Doctor, there is a Federal Drug Administration, a separate department from yourself.

Dr. MURRAY. That is right, the Food and Drug Administration.

Mr. PATTEN. They apparently made some ruling about products that have a combination of drugs and we are getting some letters on it. We were being flooded with requests to take a look at the ruling. They are going to have a public hearing. It is not clear in my mind where

their work starts and yours ends. These people seem to pass on whether a drug manufacturer can put a drug on the market. Isn't that work similar to yours?

Dr. MURRAY. We maintain close cooperation with the Food and Drug Administration as to whether the food and drug laws, apply to all products, in some instances might apply to biological products.

But the specific law under which our activity is carried out applies to specified biological products which as I indicated are vaccines, serums and the like. There is no overlap in that area, except that we do, in the case of products which are under course of development and have not yet reached the point of commerce, use the Food and Drug Administration's regulations under the investigation of new drug provisions.

Mr. PATTEN. What do you think of the birth control pills. They did that research not you.

Dr. MURRAY. Right.

Mr. PATTEN. If we are going to stop selling cranberries, FDA will make the ruling.

Dr. MURRAY. That clearly comes under the Food and Drug Administration; yes, sir.

Dr. MARSTON. The reason for the difference is that the problems are different. We are not involved at NIH and DBS in the problems of pharmaceuticals which is a different set of problems.

The problems we are involved in are in the use of biological products, that is things that are derived from living systems such as vaccines, and the problems of transfusion that have been described here.

Mr. PATTEN. Thank you, Mr. Chairman.

VARIETIES OF HEPATITIS

Mr. FLOOD. Doctor, in the course of your testimony you have made it clear that there are various types and kinds of hepatitis just as there are various types and kinds of cancer.

The average man has the idea if you have hepatitis, something is the matter with your liver. First of all, you have been drinking too much or second, eating the wrong things—anyhow it is the liver and hepatitis is just one thing.

You make the distinction by talking about serum hepatitis and stating there are certain other types and kinds of hepatitis. I wish the record would show something of that.

Dr. MARSTON. We will provide that.

(The information follows:)

Hepatitis is an inflammation of the liver caused by infectious agents or by toxic substances. The chief features of hepatitis are jaundice, enlargement of the liver, frequently fever, loss of appetite together with a number of systemic effects.

The commonest form of hepatitis is the so-called viral hepatitis of which there are two kinds, (1) serum hepatitis, which is transmitted by blood from an infected person either by administration of blood or certain blood products, or by inadvertent transfer by means of contaminated needles, instruments, by tattooing, and so forth, and (2) infectious hepatitis transmitted by consuming presumably contaminated material. This occurs in outbreaks and is sometimes referred to as epidemic hepatitis. It is seen most frequently in children, but occurs among such people as foreign service personnel and military personnel stationed in countries where the disease is endemic.

Other forms of hepatitis may be due to infection by bacteria, protozoa such as amoebae, spirochetes as well as by toxic substances such as arsenical compounds, carbon tetrachloride, and under certain conditions by a number of drugs.

CLINICAL RESEARCH AT NIH

Mr. PATTEN. Do you have enough patients to carry on your work? Because you know every time a fellow feels at the end of the rope, he says get me to NIH, maybe they can help me.

Dr. MURRAY. To answer your question, the work being done by our Division will not require very much in the way of patients. This will be done by other people who have clinical interests and clinical responsibilities. Most of the work we, in DBS, will be doing will be in the laboratory in an attempt to cultivate the virus, attempts to define the methods of detecting it, and studies in the population at large.

Dr. MARSTON. In answer to your more general question, we have a very small research hospital in which the patients are selected entirely on the basis of the needs of research. And you are quite right, there is no way in the world that the small clinical center can serve the needs of large numbers of people.

Mr. PATTEN. You are not surprised that many people say get me into NIH and maybe they can help me?

Dr. MARSTON. That is right, but as you probably know this is less than a 500-bed hospital. It is highly specialized. In the research we are working on, we do a superb job in the care of patients. But there are large areas not under active research at NIH.

Quite frankly, we don't even have the competence to take care of patients in the way a general hospital is prepared to meet all of the needs. We have never tried to take care of broken legs and automobile accidents and normal sicknesses. It is a research unit, and that is its purpose and the basis on which we have justified it before this committee over the years.

Mr. FLOOD. Mrs. Reid?

LEUKEMIA VACCINE

Mrs. REID. Has your division become involved in research regarding possible use of vaccine for leukemia? If so, what progress has been made?

Dr. MURRAY. This division is not involved in research related to a vaccine for leukemia. If such a vaccine were ever to become a feasibility, there would be division involvement. However, the division is involved with the development of standards for asparaginase, which has been used under clinical investigative conditions for several years.

SIDE EFFECTS OF SMALLPOX VACCINE

Mrs. REID. Have there been any new studies made regarding ill effects of smallpox vaccinations?

Dr. MURRAY. The division itself is not engaged in the studies to which you refer. It is concerned with the establishment of standards for the product as it exists. Information on the nature and frequency

of side effects is obtained by State health departments and by the Center for Disease Control, Atlanta, Ga.

INFLUENZA VACCINE EFFECTIVENESS

Mrs. Reid. It has been said that the vaccine for influenza is one of the least effective. Do you know of any research that is being done in reference to this vaccine?

Dr. Murray. The effectiveness of influenza vaccine is limited by a number of factors, including the fact that influenza viruses are not highly antigenic, and because the strains causing illness change unpredictably from time to time. Research on various aspects of influenza vaccination are a continuing activity under the auspices of the Commission on Influenza of the Armed Forces Epidemiological Board. This work has been going on since World War II. The National Institute of Allergy and Infectious Diseases has recently announced a program of research in this area. This division conducts research related to the standards applicable to the safety, purity, and potency of influenza vaccine.

Mrs. Reid. Thank you.

Mr. Flood. Mr. Conte?

SUSPENSION OF MANUFACTURING LICENSE

Mr. Conte. For how long a period of time can a manufacturer's license be suspended for not complying with DBS regulations?

Dr. Murray. Upon suspension of a license for failure to comply with standards a manufacturer has 60 days or such other time period as specified in the suspension notice to correct the deficiencies before proceedings will be initiated to revoke the license.

PROBLEMS UNSOLVABLE BY DBS

Mr. Conte. Would you elaborate on your statement that the Division is often confronted with problems that may never be completely solvable? What are these problems?

Dr. Murray. This statement is meant to imply that biological products have their limitations. For instance, smallpox vaccine causes serious reactions in a small number of people. This is an inherent feature of this vaccine, and while these reactions may be reduced as new research findings indicate how this can be accomplished, it is doubtful that they will ever be eliminated. Other examples of such vaccines are typhoid vaccine and pertussis vaccine.

DETECTION OF HEPATITIS ASSOCIATED ANTIGEN

Mr. Conte. Have you come up with a method for identifying donor bloods which are positive for HAA? If not, how long do you estimate it will take to do this?

Dr. Murray. Two manufacturers have now been licensed to distribute the reagent needed to do the test for hepatitis associated antigen. It is anticipated that others will be licensed in the near future. It is impossible to tell at this time how soon the required materials will

be available in the quantity necessary to perform the test on all blood donors in the United States.

Mr. CONTE. Have you any estimate as to what percent of persons have blood which is positive for HAA?

Dr. MURRAY. Surveys for hepatitis associated antigen indicate that approximately 0.2 percent of the general population in the United States is positive. The figure differs for different population groups, however, and percentages many times greater have been reported for different parts of the world.

NEW DATA ON YELLOW FEVER

Mr. CONTE. When will the field evaluation of the new yellow fever virus strain be completed?

Dr. MURRAY. Actually field evaluation has just been completed. Data have been provided to the World Health Organization for accreditation of the strain for use in manufacturing yellow fever vaccine meeting international quarantine requirements.

NIH MANAGEMENT FUND SERVICES

Mr. CONTE. What are the centrally furnished services for which $50,000 will be paid to the NIH management fund in fiscal 1972?

Dr. MURRAY. This $50,000 is for mandatory items. The management fund provides the Division with such services as data processing, engineering, alteration, housekeeping, personnel and other such services which could be considered as overhead costs.

PRODUCT LABELING VIOLATION INCIDENCE

Mr. CONTE. How many product labeling violations did your Division discover last year?

Dr. MURRAY. It is standard operating procedure that all new product labeling, before licensing, and therefore before marketing, must be reviewed and corrected for conformance to both the PHS and FDA regulations. For products already licensed no labeling changes may be made by the licensee, as prescribed in regulations, until reviewed by the DBS. Thus no product labeling violations were discovered or brought to the attention of the division last year.

Mr. CONTE. How many trained inspectors are engaged in investigating law and regulations infractions?

Dr. MURRAY. Presently, there are 42.

DANGERS OF FREQUENT BLOOD DONATION

Mr. CONTE. How serious a problem is too frequent blood donations?

Dr. MURRAY. If a person gives blood too frequently, he could become anemic because of the slow rate of restoring the red blood cells that have been removed. This is readily remedied by discontinuing blood donation and taking iron to speed replacement of the lost cells. Licensed blood banks are required to insist on an 8-week interval between blood donations and must always measure the blood donor's hemoglobin before blood can be taken. These precautions prevent the donor from having harmful effects as a result of donations.

SHORT SUPPLIERS

Mr. CONTE. By how much would the workload of the Division increase if the "short suppliers" described on page 10 of your justification were brought under direct supervision?

Dr. MURRAY. Currently there are approximately 100 short suppliers. If they were required to be licensed, the Division would need as many as 10 additional persons to handle the details of licensing, inspection, and control and up to $150,000 additional funds.

CONTROLLING HEPATITIS

Mr. CONTE. What effective control measures are needed to minimize the chance of contracting hepatitis following a blood transfusion?

Dr. MURRAY. The chances of contracting hepatitis following a blood transfusion cannot be eliminiated, but can be minimized by careful selection of volunteer blood donors with no history of having ever had hepatitis or close contact with it for the preceding 6 months, and whose blood is not reactive when tested for the presence of hepatitis associated antigen.

Mr. CONTE. Thank you, Mr. Chairman.

Mr. FLOOD. Thank you, Dr. Murray.

Dr. MURRAY. Thank you very much, Mr. Chairman.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Biologics Standards

Amounts Available for Obligation

	1971	1972
Appropriation	$8,838,000	$8,956,000
Real transfer to:		
"Departmental Management"	-19,000	---
Real transfer from:		
"National Institute of Arthritis and Metabolic Diseases" (Proposed transfer for increased pay costs)	150,000	---
"National Institute of Neurological Diseases and Stroke" (Proposed transfer for increased pay costs)	308,000	---
Comparative transfer to:		
"Office of Director"	-28,000	---
"National Institute of Environmental Health Sciences"	-135,000	---
"Research Resources"	-94,000	---
"Health Manpower"	-295,000	---
Total obligations	8,725,000	8,956,000

Obligation by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
9	Biologics standards (Total obligations).	273	$8,725,000	273	$8,956,000	---	+$231,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	273	273	---
Full-time equivalent of all other positions	5	5	---
Average number of all employees	268	268	---
Personnel compensation:			
Permanent positions	$3,189,000	$3,379,000	+$190,000
Positions other than permanent	48,000	49,000	+1,000
Other personnel compensation	71,000	73,000	+2,000
Subtotal, personnel compensation	3,308,000	3,501,000	+193,000
Personnel benefits	309,000	317,000	+8,000
Travel and transportation of persons	122,000	122,000	---
Transportation of things	15,000	15,000	---
Rent, communications and utilities	50,000	53,000	+3,000
Printing and reproduction	10,000	10,000	---
Other services:			
Project contracts	1,933,000	1,933,000	---
Payment to NIH management fund	1,555,000	1,605,000	+50,000
Other	416,000	391,000	-25,000
Supplies and materials	922,000	929,000	+7,000
Equipment	85,000	80,000	-5,000
Total obligations by object	8,725,000	8,956,000	+231,000

Summary of Changes

1971 estimated obligations	$8,725,000
1972 estimated obligations	8,956,000
Net change	+231,000

	Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase costs	---	---	---	+$148,000
2. Within-grade pay increases	---	---	---	+70,000
3. FTS rate increase	---	$8,000	---	+3,000
4. Extra day of pay in 1972	---	---	---	+10,000
B. Payment to "National Institutes of Health management fund" for centrally furnished services	---	1,555,000	---	+50,000
Total, increases	---	---	---	+281,000
Decreases:				
A. Program:				
1. Direct operations	273	7,162,000	---	-50,000
Total, decreases	---	---	---	-50,000
Total, net change	---	---	---	+231,000

Explanation of Changes

Built-in increases -- These increases will provide: $148,000 for annualization of 1971 pay increase costs; $70,000 for within-grade pay increases in 1972; $3,000 for increased cost for using the Federal Telecommunications System and $10,000 for an extra day of pay in 1972.

Direct operations -- The decrease of $50,000 is to reduce supply, equipment and other services items.

Authorizing Legislation

	1972	
	Authorization	Appropriation requested
Legislation		
Public Health Service Act Section 301-Research and Investigation, in general.....	Indefinite	$8,956,000
Title III, Part F-Licensing-Biological Products.....	Indefinite	8,956,000

PUBLIC HEALTH SERVICE ACT

The legislative authority which provides for the conduct of research is included in Section 301 of the Public Health Service Act.

The Public Health Service Act, Title III, Part F, Subpart I - Biological Products --

Sec. 351. (c) Any officer, agent, or employee of the Department of Health, Education, and Welfare, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession. (d) Licenses for the maintenance of establishments for the propagation or manufacture and preparation of products described in subsection (a) of this section may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations, and licenses for new products may be issued only upon a showing that they meet such standards. All such licenses shall be issued, suspended, and revoked as prescribed by regulations, and all licenses issued for the maintenance of establishments for the propagation or manufacture and preparation, in any foreign country, of any such products for sale, barter, or exchange in any State or possession shall be issued upon condition that the licensees will permit the inspection of their establishments in accordance with subsection (c) of this section.

Sec. 352. (a) The Service may prepare for its own use any product described in section 351 and any product necessary to carrying out any of the purposes of section 301. (b) The Service may prepare any product described in section 351 for the use of other Federal departments or agencies, and public or private agencies and individuals engaged in work in the field of medicine when such product is not available from establishments licensed under such section.

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer to:		
Departmental Management	-$19,000	To establish the Facilities Engineering and Construction Agency.
Real transfer from:		
National Institute of of Arthritis and Metabolic Diseases	150,000	Proposed transfer for increased pay costs.
National Institute of Neurological Diseases and Stroke	308,000	
Comparative transfer to:		
National Institute of Environmental Health Sciences	-135,000	To provide an equitable distribution of the Management Fund in 1972.
Research Resources	-94,000	
Health Manpower	-295,000	
Office of the Director	-28,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director.

Biologics Standards

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1964	$4,817,000	$4,787,000	$4,787,000	$4,787,000
1965	4,969,000	4,969,000	4,969,000	4,969,000
1966	6,406,000	6,406,000	7,206,000	6,806,000
1967	7,905,000	7,904,000	7,904,000	7,904,000
1968	8,649,000	8,649,000	8,649,000	8,649,000
1969	8,499,000	8,499,000	8,499,000	8,499,000
1970	8,225,000	8,225,000	8,225,000	8,239,000
1971	8,640,000	8,838,000	8,838,000	8,838,000
1972	8,956,000			

Justification

Biologics Standards

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	273	$3,617,000	273	$3,818,000	---	+$201,000
Other expenses	---	5,108,000	---	5,138,000	---	+30,000
Total	273	8,725,000	273	8,956,000	---	+231,000

General Statement

Biologics Standards was officially established in 1955 as a Division of the National Institutes of Health charged with administering a program for the control of biological products in interstate commerce and for the conduct of a program of related research.

Program Plans for 1971 and 1972

The major program objectives of this Division are to keep abreast of the latest research advances and to maintain progress in testing and control techniques. The attainment of these objectives is essential to assure the safety, purity, and potency of biological products used for the prevention, diagnosis, and/or treatment of human disease.

The Division staff is involved in the following control and regulatory areas:

Licensing of manufacturing establishments and biological products -- Presently there are 235 establishments licensed with 113 subsidiaries and 260 blood bank donor centers representing 1,251 product licenses. These establishments are inspected at least annually to assure high quality in the manufacture of the 263 licensed products and to determine that prescribed standards are being met. Over 40 members of the scientific staff serve as inspectors.

Examination of manufacturer's protocols and performance of control tests -- Each protocol submitted is reviewed by knowledgeable scientists to determine if the manufacturer's test results conform to established standards. Depending upon the products, these protocols are reviewed and evaluated by various expert staff members.

Control tests are conducted on eight thousand samples per year prior to release of the products for use. Additionally, tests are performed on random samples obtained at the time of inspection. These chemical, sterility, general safety, pyrogen, residual moisture and potency tests are also conducted on biological products submitted in support of license applications. Total tests performed annually exceed 31,000.

Another very important facet in the release and/or licensing of a product is the review of labelling. Careful and critical examinations of all labels and package inserts are made to ascertain whether they comply with regulations pertaining to nomenclature, expiration dates set for each individual product, dosage, methods of use, warnings as to possible hazards, etc.

Reference standards -- Biological standards, reference and control materials, and reagents necessary for the testing of products to determine compliance with standards are developed, maintained and distributed. Approximately 14,000 of these standards were made available.

Investigational New Drugs -- The scientific staff participates in the evaluation of "Notices of Claimed Investigational Exemption" for new biological products. Presently, there are 294 active cases which are being monitored. Information contained in these "Notices" indicates to the Division the paths in which research should be directed for the purpose of obtaining knowledge to be used in developing Regulations.

Investigations -- Infractions of the law and regulations occur occasionally and must be investigated promptly. These investigations are conducted by specially trained inspectors from the Office of the Director and usually require extensive interviews in the course of assembling complete and accurate evidence. Since these investigations frequently involve other Government Agency jurisdictions, continuing liaison is maintained with the Justice Department, Customs Bureau, Department of Agriculture, Post Office Department, Federal Trade Commission, and the Food and Drug Administration.

These inspectors also conduct special studies in such areas as the practice of blood donation to determine the extent of inaccurate donor identification, too-frequent blood donations, and hepatitis incidence.

Regulations -- Scientific staff of each laboratory, according to their area of scientific activity, participate in the drafting of regulations for new products and amendments of regulations to reflect advances in science and technology. The efforts involved in the acquisition of the information needed to develop written standards are extensive and often time-consuming and based upon an active research program conducted by the Division. When a new vaccine appears achievable, the Division strives to develop standards that will be ready at approximately the time the product is brought to the final stages of manufacture and evaluation. It is necessary during this period to maintain close contact with the manufacturers and with scientists working in the particular field, so that problems related to standards can be rationalized during the developmental phases.

Inspections -- It is estimated that there are some 100 major firms who are currently providing source material such as serums, plasma or blood to licensed manufacturers - manufacturers of biological products under the so called "short supply provisions" of the regulations. Most of these firms were established essentially to serve this purpose and operate without license, and with a minimum of supervision, collecting large volumes of plasma from paid donors by a procedure called plasmapheresis.

Presently, it is incumbent upon the licensed manufacturer to register these facilities with the Division and to assure himself through written agreements, inspections, and tests performed on the source materials that all applicable regulations relating to the manufacturing of his final licensed product have been complied with by the "short supplier."

To provide more standardized and consistent supervision it is deemed desirable for the Division to require that these establishments be subjected to the same licensing procedures and direct supervision now required for other manufacturers who engage interstate sale, barter or exchange of biologics. This would add to the work load of the Division.

Research:

The research program of the Division is focused on improving methods for measuring potency and efficacy and for assuring the purity, potency, and safety of all biological products both established and new. Because the Division's interests in this area are of such scope only a few examples of current endeavor are set forth below:

Adjuvants -- Studies are being conducted on mineral and vegetable oils and aluminum adjuvants by Division scientists and others to examine their purity and safety for use in man.

These immunologic adjuvants are substances which are incorporated in vaccines and toxoids to enhance the immune response to these antigens. Adjuvants may increase or prolong the production of antibody. A variety of substances have been used as adjuvants in man and animals. The adjuvants which have been most commonly used in man are aluminum compounds such as alum, aluminum phosphate or aluminum hydroxide. Mineral and vegetable oil adjuvants incorporating emulsifiers and stabilizers have been used in water-in-oil emulsified antigens only under conditions of clinical investigation. These latter adjuvants have not received approval for general use in man in the United States as the long term safety of oil adjuvants has not yet been established.

Hepatitis -- Hepatitis has long been a problem because of the seriousness of disease, particularly following blood transfusion and lack of effective control measures. Investigators in the Division have had an important role in a series of hepatitis research investigations during the past two years. Studies here and elsewhere have demonstrated that two or more agents bear an etiologic relationship to acute hepatitis. Progress to-date has been with an antigen (termed hepatitis-associated antigen) which is thought to be the virus responsible for "serum hepatitis" or closely related to it. Standards for reagents to be used for the detection of this antigen have recently been published.

Diploid cells -- The Division is supporting research contracts on cell strains used in the production of viral vaccines. The research is directed towards the development of non-human diploid cell strains. To date, two promising strains have been developed and are being made available for further evaluation to interested virologists and commercial establishments. If further studies indicate that they are acceptable, it is anticipated that these cell strains could be used in vaccine production.

Current programs will continue into 1972 with emphasis dependent upon future developments by manufacturers and the scientific community.

The increase of $231,000 includes $148,000 for annualization of 1971 pay increase costs; $70,000 for within-grade pay increases; $3,000 for increased cost in 1972 of using the Federal Telecommunications System; $10,000 for an extra day of pay in 1972 and $50,000 for research-related services and support furnished through the National Institutes of Health Management Fund. These increases are partially off-set by several minor decreases totaling $50,000.

NATIONAL INSTITUTES OF HEALTH

Biologics Standards

Program Purpose and Accomplishments

Activity: Biologics standards. (Public Health Services Act, Title III, Part F)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
273	$8,725,000	Indefinite	273	$8,956,000

Purpose: Activities include establishment of standards for preparation of biologics, testing of vaccines and their preparation and research related to development, manufacture, testing and use of vaccines and analogous products.

Explanation: Exercises controls on the safety, purity, and potency of biological products through a system of licensing of manufacturing establishments and of products which involves control testing, label review, annual inspections and investigations. Related research is product-oriented. The appropriation's funds are for direct operations.

Accomplishments in 1971: The blood-clotting factor essential for the control of hemophilia was made commercially available. Standards were developed by the Division and the first license has been issued. Progress has been made with a hepatitis-associated antigen and a product is expected to be licensed in 1971. Annual inspections were performed at 235 licensed establishments together with 113 subsidiaries and 260 blood bank donor centers. Control tests were conducted on eight thousand product samples prior to release of these products for general use.

Objectives for 1972: Current programs will continue at approximately the same level with specific emphasis dependent upon future developments by both the scientific community and manufacturers.

TUESDAY, MAY 4, 1971.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. CARL G. BAKER, DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. BAYARD H. MORRISON, III, ASSISTANT DIRECTOR, NATIONAL CANCER INSTITUTE
CALVIN B. BALDWIN, JR., EXECUTIVE OFFICER, NATIONAL CANCER INSTITUTE
EARLE L. BROWNING, FINANCIAL MANAGER, NATIONAL CANCER INSTITUTE
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET). NATIONAL INSTITUTES OF HEALTH
GERALD F. MEYER, CHIEF, HEALTH BRANCH, DIVISION OF BUDGET, OS, DHEW

National Cancer Institute

Object Classification (in thousands of dollars)

Identification code 09-30-0849-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	16,792	18,478	19,264
11.3	Positions other than permanent	458	464	464
11.5	Other personnel compensation	221	229	244
	Total personnel compensation	17,471	19,171	19,972
12.1	Personnel benefits: Civilian employees	1,822	1,958	2,062
21.0	Travel and transportation of persons	822	995	985
22.0	Transportation of things	130	140	145
23.0	Rent, communications, and utilities	538	595	613
24.0	Printing and reproduction	451	473	470
25.0	Other services	62,001	88,525	84,753
26.0	Supplies and materials	3,727	4,150	4,254
31.0	Equipment	1,537	1,650	1,650
41.0	Grants, subsidies, and contributions	92,846	114,577	117,330
99.0	Total obligations	181,345	232,234	232,234

Personnel Summary

Total number of permanent positions	1,377	1,410	1,420
Full-time equivalent of other positions	54	54	54
Average number of all employees	1,407	1,441	1,472
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0849-0-1-651		1970 actual	1971 est.	1972 est.
	Program by activities:			
	1. Grants:			
	(a) Research	84,416	10,005	105,624
	(b) Fellowships	4,499	3,798	3,348
	(c) Training	13,066	10,774	8,358
	Total grants	101,981	114,577	117,330
	2. Direct operations:			
	(a) Laboratory and clinical research	18,383	21,272	18,698
	(b) Collaborative research and development	77,484	92,177	91,755
	(c) Review and approval	2,639	2,937	3,112
	(d) Program direction	1,086	1,271	1,339
	Total direct operations	99,592	117,657	114,904
	Total program costs, funded [1]	201,573	232,234	232,234
	Change in selected resources [2]	−20,228	----------	----------
10	Total obligations	181,345	232,234	232,234
	Financing:			
25	Unobligated balance lapsing	12	----------	----------
	Budget authority	181,357	232,234	232,234

Program and Financing (in thousands of dollars)

Identification code 09-30-0849-0-1-651		1970 actual	1971 est.	1972 est.
	Budget authority:			
40	Appropriation	190,362	230,383	232,234
40	Portion withdrawn (Public Law 91-204, sec. 410)	−9,638	----------	----------
40	Pay increase (Public Law 91-305)	124	----------	----------
41	Transferred to other accounts	−96	−28	----------
42	Transferred from other accounts	605	----------	----------
43	**Appropriation (adjusted)**	**181,357**	**230,355**	**232,234**
46.10	**Proposed transfer for wage-board pay increases**	----------	**100**	----------
46.20	**Proposed transfer for civilian pay act increases**	----------	**1,526**	----------
46.30	**Proposed transfer for military pay act increases**	----------	**253**	----------
	Relation of obligations to outlays:			
71	Obligations incurred, net	181,345	232,234	232,234
72	Obligated balance, start of year	112,805	105,889	124,566
74	Obligated balance, end of year	−105,889	−124,566	−129,693
77	Adjustments in expired accounts	−2,002	----------	----------
90	Outlays, excluding pay increase supplemental	186,259	211,742	227,043
91.10	Outlays from wage-board supplemental	----------	95	5
91.20	Outlays from civilian pay act supplemental	----------	1,467	59
91.30	Outlays from military pay act supplemental	----------	253	----------

[1] Includes capital outlay as follows: 1970, $2,061 thousand; 1971, $1,650 thousand; 1972, $1,650 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $83,911 thousand; 1970, $63,683 thousand; 1971, $63,683 thousand; 1972, $63,683 thousand.

NOTES

Includes $687 thousand in 1971 and $695 thousand in 1972 for activities previously financed from: Research resources, 1970, $684 thousand.

Excludes $260 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	*1971*
Office of the Director	576	151
National Institute of Environmental Health Sciences	86	---
Fogarty International Center	---	22
Research resources	---	27
Health manpower	---	54

Excludes $2,416 thousand in 1972 for activities transferred to: Health Manpower 1970, $2,416 thousand; 1971, $2,416 thousand.

INTRODUCTION OF DR. BAKER AND ASSOCIATES

Mr. FLOOD. We continue with the National Institutes of Health and now have the National Cancer Institute. The presentation will be made by Dr. Carl G. Baker, the Director.

We have a biographical sketch of you, I see.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH OF CARL G. BAKER, M.D.

Name: Carl G. Baker, M.D.

Position: Director, National Cancer Institute.

Birthplace and date: Louisville, Kentucky, November 27, 1920.

Education: University of Louisville, 1938–41, A.B., zoology; University of Louisville School of Medicine, 1941–44, M.D.; Childs Fellow, University of California, 1947–48, M.A., biochemistry; University of Chicago, program of executive development for Federal administrators, 1957; CEIR course on advanced projects planning and control systems, 1966.

EXPERIENCE

Present: Director, National Cancer Institute; Assistant Surgeon General, PHS. Director-at-Large, American Cancer Society

1969–70: Acting Director, NCI

1967–69: Scientific Director for Etiology, NCI

1967– : Member, Professional Council—Biological Sciences—Interagency Board of U.S. Civil Service Examiners

1965– : Member, Editorial Advisory Board, *Cancer* journal

1961–67: Associate Director for Program, NCI

1960–61: Acting Scientific Director, NCI

1958–61: Assistant Director, NCI

1958–61: Councillor of the American Chemical Society

1956–58: Assistant to the Associate Director for Intramural Research, NIH

1956–58: Member National Research Council Subcommittee on Amino Acids, Committee on Biological Chemistry, Division of Chemistry and Chemical Technology

1955–57: Secretary, Division of Biological Chemistry, American Chemical Society

1954–55: Associate Editor, *Journal of the National Cancer Institute*

1953–55: Laboratory of Biochemistry, NCI, NIH

1952–53: Research Grants and Fellowships Branch, NCI, NIH

1949–52: Laboratory of Biochemistry, NCI, NIH

1949– : Special Fellow, National Cancer Institute, Bethesda, Md.

1945–46: Medical Officer, Pacific Area, U.S. Navy

1944–45: Intern, Milwaukee County General Hospital, Milwaukee, Wis.

Association memberships: American Society of Biological Chemists; American Association for Cancer Research; American Chemical Society (division of biological chemistry); American Medical Association; Society for Experimental Biology and Medicine

SPECIAL AWARDS, CITATIONS, OR PUBLICATIONS

PHS Meritorious Service Medal; Honorable Order of Kentucky Colonels; Vice-President, 10th International Cancer Congress; Sigma Xi; Phi Kappa Phi; Alpha Omega Alpha

The Special Virus-Leukemia Program of the National Cancer Institute. Scientific Aspects and Program Logic. Academic Press, London, 1965, pages 259–278.

The Chemotherapy Program of the National Cancer Institute: History, Analysis and Plans. Cancer Chemotherapy Reports *50*: 1966, pages 348–540.

The Convergence Technique—A Method for the Planning and Programing of Research Efforts. Management Science *13*: 1967.

Program Planning in Inhalation Carcinogenesis: NCI Plans. AEC Symposium Series 18, 1970, pages 467–481.

And other papers on cancer and biochemistry of amino acids and fatty acids.

Mr. FLOOD. Do you have anybody with you we don't know?

Dr. BAKER. I think you know them, but I should point out we now have selected a new executive officer, Mr. Calvin Baldwin, whom you know since we got him from the Child Health Institute where he served admirably and we feel fortunate in having him as our new executive officer.

Mr. FLOOD. I think we should have a biographical sketch of him.

(The information follows:)

BIOGRAPHICAL SKETCH

Name: Calvin B. Baldwin, Jr.

Position: Executive officer, National Cancer Institute.

Birthplace and date: Radford, Va., December 22, 1925.

Education: Bethesda-Chevy Chase High School, Bethesda, Md., 1943. A.B., University of North Carolina, 1949. University of North Carolina, 1949–51. American University, 1952–53. M.P.A., Harvard University, 1960–61.

Experience: Executive officer, National Cancer Institute, November 1970–present. Executive officer, National Institute of Child Health and Human Development, 1963–November 1970. Assistant chief, grants management branch, Division of Research Grants, NIH, 1962–63. Executive officer, Division of General Medical Sciences, 1961–62. Administrative officer, Division of General Medical Sciences, 1958–61. Administrative officer, Division of Research Services, 1957–58. Budget examiner, Office of the Director, National Institutes of Health, 1955–57. Organization and methods examiner, NIH, 1953–55. Civil service intern, Federal Security Agency, PHS, September 1952–February 1953. Methods examiner, Federal Security Agency, PHS, 1951–53. Research assistant, Institute of Research in Social Science, Chapel Hill, N.C., 1949–50.

Military service: Corporal, U.S. Army, 1944–46.

Honors and other special recognition: Phi Beta Kappa, W.A. Jump Meritorious Award, 1960.

Dr. BAKER. Mr. Browning is financial manager to my left and Dr. Morrison is assistant director.

GENERAL STATEMENT

Mr. FLOOD. I see you have a prepared statement. How do you wish to proceed?

Dr. BAKER. With your permission I would read it. I realize some points were made last week in Dr. Steinfeld's testimony but I have shortened the statement and simplified it and added a few points.

Mr. FLOOD. We will do it your way.

Dr. BAKER. Mr. Chairman and members of the committee, I am pleased to appear before your committee again to share with you the exciting developments in cancer research and to ask you to participate directly in developing an expanded research and development program on cancer research. There is a new ferment which is calling for special considerations, and no better forum for discussion of the appropriate course to take exists than the hearings before this committee. In his state of the Union message to the Congress in January, the President announced that he would ask for the appropriation of an additional $100 million to launch an intensive effort to control cancer, and that he would ask later for whatever additional funds could be effectively used. The President said:

> The time has come when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal.

The conquest of cancer was included in the six major national goals in the state of the Union message after a thorough study had been made of the impact of cancer on the human and economic resources of the Nation and the possibility of making definite progress through a large-scale, carefully designed attack on the problem. The decision was based on information gathered primarily from scientists, physicians, and university advisers who assessed the state of the art in cancer research and evaluated the rapidly emerging promise and opportunities for continued and expanded research.

There is little doubt that we stand today on the threshold of an undisputed opportunity to make great strides against cancer. There is excitement in the air over this prospect. It is felt in the scientific community, in government and industry, throughout our society as a whole.

MAGNITUDE OF THE CANCER PROBLEM

In earlier testimony, Dr. Steinfeld presented the major statistics on cancer. I will only mention that in the 1970's in the United States alone, there will be an estimated 3.5 million cancer deaths, 6.5 million new cancer cases, and 10 million under medical care for cancer unless the present trends are improved.

Although cure rates for cancer patients have steadily improved over the past several years, the mortality is still on the rise—both in actual numbers and in rates corrected for population growth and other changes. This is because new cancer cases are appearing at an even greater rate than the improved rate of cures. Some kinds of cancer are increasing faster than others and a few are decreasing.

CONDITIONS NECESSARY FOR A DECREASE IN CANCER

Mr. Flood. What would there be peculiar about a type of cancer that it would start to decrease?

Dr. Baker. I don't have as good an answer to that question as I would like. Stomach cancer has been going down in incidence for the last 10 or 15 years. Quite frankly none of us have a very good idea at all as to why this is so except perhaps a change in dietary habits.

Mr. Flood. Diet would be an important factor?

Dr. Baker. Yes. We do have some studies underway in Japanese populations where stomach cancer is so high compared to here, looking at that very thing. Uterine cancer mortality is dropping partly because of the effectiveness of the Papanicolaou test, allowing the surgeon to treat it earlier.

NATIONAL UTILIZATION OF THE PAP SMEAR

Mr. Patten. Are you going to put on a big drive to give all women throughout the country that smear test?

Dr. Baker. Not in the Cancer Institute since our responsibilities are research and not straight application of care. Under the other programs in the Public Health Service—the regional medical programs and HSMHA programs—local activities are concerned with the delivery of care. Here the research is already done, and this is not part of the Cancer Institute's direct responsibilities.

Mr. PATTEN. I think some doctors wrote me that the Government should proceed with that uterine cancer smear test and administer it to everybody. It would be a good investment.

Dr. BAKER. Yes, sir, from the standpoint of our interest in cancer even though we are concerned with research, we certainly advocate widespread use of that.

Mr. PATTEN. It is expensive isn't it?

Dr. BAKER. Moderately so.

Mr. FLOOD. How often should the smear be taken?

Dr. BAKER. In women over the age of 30, at least once a year and I would say as they approach the menopause preferably twice a year, but I don't think we have the capacity to do that currently.

FACTORS IN INCREASE OF LUNG CANCER

Mr. FLOOD. Why would cancer of the lung go through the ceiling all at once?

Dr. BAKER. Cancer of the lungs in males has been rising fairly steadily for the last 20 or 25 years. In women it is going up and started up later; until recently it was not rising rapidly, although the rate of change increase in women now is getting almost to the steepness of the curve as compared to men.

We think there is good evidence, although by no means is it completely proven, that cigarette smoking has been the major factor in this. There are suggestions that air pollution is a contributing factor.

Mr. FLOOD. Proceed.

Dr. BAKER. By the year 2000, if present trends continue, cancer of the lung will have increased 52 percent, large bowel 40 percent, leukemias 25 percent, and pancreas 280 percent.

CONQUEST OF CANCER ORGANIZATIONAL PLAN

A plan of organization for a new cancer conquest program has been developed which would place the cancer research program at bureau status within NIH, and the new Bureau Director would also be a Deputy Director of NIH. A Cancer Conquest Advisory Council would be established as well as an Executive Task Force on the Conquest of Cancer to assure that the Secretary of the Department of Health, Education, and Welfare and other Federal officials give increased time and attention to the program. We believe this proposed organizational plan will create an environment in which an expanded research program on cancer can be undertaken efficiently and effectively. It elevates cancer research within NIH, and brings the program routinely before the highest Department officials for review on a frequent basis and before the President on an annual basis.

The proposed pace of the cancer conquest program differs from the past. There is urgent need therefore to develop a more comprehensive scientific and technical plan, taking into account the new national commitment. An outline of such a plan has been under discussion since last year, and we believe a fully developed, comprehensive national plan can now be developed. The need for this type of planning was specified by the National Panel of Consultants. Development time of up to 1 year was called for in S. 34 which would require such a plan "designed to conquer cancer at the earliest possible moment, together

with appropriate measures to be taken, time schedules for the completion of such measures, and cost estimates for the major portion of such a plan." We are in complete agreement about the essentiality of such scientific and technical planning even while the first stages in a greatly accelerated effort against cancer are being undertaken. Large numbers of expert scientists will be asked to participate in the preparation of this plan during 1972. It is essential that these scientists and many others be motivated to join a single cancer effort and to make commitments to the program and its objectives.

ADVANCED STATE OF THE CANCER RESEARCH ART

We are confident that the state of the art in cancer research justifies mounting an enlarged targeted research and development program called for by the President. The signs of progress are numerous and unmistakable. For example, it has now been demonstrated that some advanced cancers can be cured with drugs alone. Some children with leukemia now enjoy long remissions enabling them to return to school and lead practically normal lives for several years, compared to the prospect of a scant 3 months' survival with this disease a few years ago. Not only have active drugs been developed and their effective use determined, but the principles, managerial apparatus and system for clinical evaluation of new treatments have been brought to a mature state.

Largely within the past year a series of related findings have been reported which bring together research in prevention, diagnosis, and treatment of certain cancers. These findings are expected to improve early diagnosis, aid identification of specific factors responsible for the initiation of these cancers, and open up additional approaches to treatment. Interdisciplinary studies toward these objectives are being pursued by top scientists throughout the country in a coordinated attack with scientists within the NCI.

The Surgeon General has already detailed these findings about the detection of certain enzymes present in some 30 cancer-causing viruses.

VIRAL CAUSES OF CANCER

Mr. FLOOD. Do you say that cancer is produced by virus?

Dr. BAKER. In animals we have demonstrated that almost all forms of cancer can be induced by over 110 different kinds of cancer viruses out of approximately 1,000 known viruses we know about totally.

So in man we have major efforts underway to pin down whether any human cancers are virus caused. To date we have not proved that. The evidence is building, the evidence is still consistent in some forms of cancer that they indeed will be viral induced. We think it unlikely that all cancers are produced by viruses. Chemicals produce other cancers, and radiation.

Mr. FLOOD. What is a virus?

Dr. BAKER. A virus is a microorganism, that is an organism so small it can't be seen without the microscope, or with the unaided eye. We must use special electron microscopes, which magnify in the neighborhood of 250,000 times, in order to see these virus particles. There have been some arguments whether a virus is living or nonliving because some viruses can be gotten out in crystalline form but under other

conditions behave as though they are alive. But always they must be grown in living cells.

Mr. FLOOD. Is this type of virus asexually produced?

Dr. BAKER. Yes, sir. Certain enzymes are found in 30 cancer-causing viruses and essentially absent from many viruses not known to produce cancer. These enzymes have also been found in some tumors and some normal tissues, but the characteristics of those from tumors are different from those found in the normal tissues. Detection of the appropriate enzymes should prove useful for screening patients' tumors to learn if they are caused by viruses.

ENZYME INVOLVEMENT IN CANCER

Mr. FLOOD. What is an enzyme?

Dr. BAKER. It is a protein material in living cells which catalyzes special chemical reactions. They are very important in the body because they are very specific, helping control very precisely particular chemical reactions.

So the body elaborates these protein materials in all of the cells, hundreds and hundreds of them.

Mr. FLOOD. These are good guys?

Dr. BAKER. Generally. But occasionally a virus may produce an enzyme which is a bad guy because it leads the cell to be transformed from a normal cell into a cancer state.

REPRODUCTION RATES OF CANCER CELLS

Mr. FLOOD. The asexual reproduction of that type of cell is almost like chain lightning, isn't it?

Dr. BAKER. In some forms of cancer we have rather rapid growth. In other words, about 15 percent of the known human cancers grow rather rapidly. The hair follicles grow most rapidly. New hair is being produced by the cells down in the follicle dividing rapidly. The cells of the lining of the gut, blood forming tissues and skin also divide rapidly.

Mr. FLOOD. The public has the impression that cancer cells reproduce astronomically at great speed.

Dr. BAKER. No, sir; they generally do not divide any faster than the fastest growing normal cells, though cancer cells generally do divide rapidly. I think the reason a number of people feel that way is that they don't notice the tumors until the numbers of cells have already divided into the billions. From that point those billion cells divide in turn; then this later cell division of so many cells at once gives the appearance of very rapid growth sometimes.

DEFINITION OF TUMOR

Mr. FLOOD. What is a tumor?

Dr. BAKER. Literally a tumor is a swelling. Usually in medicine we ordinarily mean a cancer, although there are benign tumors which do not spread and invade surrounding tissue like cancer does and do not set up new growths at other sites in the body called metastasis as cancer does.

IDENTIFIABILITY OF CANCER CELLS

Mr. FLOOD. Are cancers identified with any particular organ of the body?

Dr. BAKER. Yes. If you look at the appearance of cancers in the microscope, there is a direct connection between the appearance and the particular organ in which the cancer originated. When some of the cancer cells split off from the parent original tumor and set up housekeeping in another site in the body, it is often recognizable because it looks like the kind of cells from which the tumor originated rather than the kind of cells into which the spread cells started growing. Rarely, however, the changes in appearance are so drastic that it is not possible to be absolutely sure about the organ in which the cancer originated.

DRUGS TO INHIBIT CANCER-CAUSING ENZYMES

A new series of drugs deriving from a drug that has been used in the treatment of tuberculosis is producing powerful inhibitors of these enzymes. This may prove useful in blocking the formation of cancer-causing viruses and therefore has possible import for prevention. Since there is some suggestion that the genetic information of cancer-causing viruses must continue to be present in cells to keep them behaving as cancer cells—at least for some kinds of cancers—some of these drugs may prove important for treatment. Already in several experiments, for instance, cancer cells from patients with leukemia or sarcoma—which are cancers of the connective tissues like bone and cartilage, general connective tissue of the body—have been killed in the test tube following addition of small amounts of these drugs, whereas normal cells remained unaffected.

An intensive effort is underway to analyze additional types of human cancers, to find and produce drugs of even higher activity against the enzymes, and to evaluate the active drugs, for safety and potency in animals, looking toward successful treatment of cancers in man.

STRUCTURE OF A CANCER CELL

Mr. FLOOD. Is there such a thing as a cancer cell as distinguished from the normal body cell? Is it a different kind of thing? What about its structure? We know the components of a cell in the body. Is there any thing peculiar in the components of a cancer cell which makes it a cancer cell as distinguished from a normal body cell?

Dr. BAKER. Yes, sir, conceptually certainly. But in operational terms the diagnosis of cancer really needs to be made by looking at groups of cells which we call tissues through a microscope after they have been stained with dyes. So you need to look at a specimen of tissue surgically removed from the body to be absolutely sure. We can also usually certainly conclude that particular cells are likely to be cancer when we look at them as in the Pap smear test where, instead of a piece of tissue, we are looking at several isolated individual cells. But to make the proper diagnosis there we need literally to observe several cells at least.

There are differences and this is what much of the research and excitement about the virus induction of cancer is all about, that the virus gets in and changes the nature of that cell so that it has genetic

information in the cell it didn't have before. This in turn changes the characteristics of what that cell does. Cancer cells all have the characteristics of growing fairly rapidly and of being able to invade and destroy other near-by tissues. We also have some fundamental studies that show the surface of these cancer cells have been modified usually.

VIRUS CONVERSION OF CELLS TO CANCER

Mr. FLOOD. A virus can come from some place and change a normal cell to a cancer cell. Is that it?

Dr. BAKER. This is certainly true for most of the kinds of cancers caused by viruses. There are some recent findings that suggest some of the genetic information of some viruses can be transmitted from parent to offspring probably through the germ cells.

Mr. FLOOD. I was speaking only of virus cancer.

Dr. BAKER. This genetic information under some conditions can be converted into a full blown virus. That virus can be gotten out, can be used to then transform other cells in the cancer. It has gotten a little more complicated than the simple old fashioned virology. This offers new possibilities of control of cancer induction and treatment we didn't have when we only thought about the usual infectious diseases kind of virology.

I have two special reports, one on chemotherapy and one on virus in cancer I would like to submit for the record, if agreeable.

Mr. FLOOD. Yes.

(The reports follow:)

LEUKEMIA AND OTHER CANCERS: EVIDENCE FOR VIRUS CAUSATION

There are now over 100 viruses which are known to cause virtually all kinds of cancer in every major group of animals including non-human primates. The probability is very high that viruses responsible for at least some human cancers will be found. When such agents are identified and successfully grown in the laboratory, it should be possible to develop therapeutic and preventive measures (including vaccines) for the control of these diseases. These predictions are based largely on recent findings by scientists working within the Special Virus Cancer Program of the National Cancer Institute.

In 1964, the Congress of the United States provided funds to the National Cancer Institute to conduct an intensified program in virus-leukemia research. The program was enlarged in 1968 to encompass all types of cancer. During these seven years the Institute has developed an effective scientific program which has made rapid, substantial progress in the "virology" of such human cancers as leukemias, lymphomas, sarcomas, and carcinomas. Recently, new approaches aimed at understanding cancer induction by viruses at the subcellular (or genetic) level have provided basic information which may aid the physician in detecting and treating cancers earlier than would otherwise have been possible.

1968 actual	$19,480,000
1969 actual	20,876,000
1970 actual	21,212,000
1971 estimate	38,421,000
1972 estimate	40,913,000

NOTE.—This Special Report excludes the proposed additional $100,000,000 for cancer research initiatives in 1972.

Viruses of one type (Type C) are known to cause leukemias, lymphomas, and sarcomas in chickens, mice, and cats. Particles, which closely resemble Type C viruses, can be found in human patients affected with these same kinds of cancers. Unlike the Type C animal viruses, those from human cases have not been grown successfully outside the body nor have they produced cancer when injected into experimental animals. Viruses of a second type (Type B), but similar to Type C viruses because they contain ribonucleic acid (RNA), produce can-

cers of the breast tissue of mice. Thus far, this is the only animal species in which breast cancer (carcinoma) has been proven to be caused by a virus. Recently, Type B particles, resembling the mouse agent, have been found in human breast cancers and in milk concentrates from patients with breast cancer. Attempts to grow these viruses, if indeed they are definitely shown to be viruses, in the laboratory have just begun. Viruses of a third type (Herpes-type) which are structurally similar but clearly unrelated to viruses causing fever blisters in man, have been shown to be associated with the following human malignancies: Burkitt's lymphoma (a childhood cancer of tropical Africa), nasopharyngeal carcinoma, and uterine and penile carcinomas.

By using the techniques gained from animal tumor virus studies, every effort is being made to determine whether these viruses "cause" human malignancies. During the course of this work, it should be recognized that information on the biological, biophysical and biochemical characteristics of cancer-causing viruses has provided a broad base of knowledge applicable to the isolation and identification of human agents and prevention and control of the disease in man. Some important new discoveries that have been made are: (1) Certain cancer-causing viruses are unable to produce malignancies unless a second "helper" virus is present, thus suggesting that an interplay exists between two viruses. (2) Certain tumor-inducing chemicals, irradiation, (carcinogens) may act as co-factors in activating latent, cancer-causing viruses within cells. (3) Certain cancer-causing viruses contain unique chemical catalysts (enzymes) which are required in the replication of viruses in cells. These and other important developments will be discussed further in this report.

Staff scientists share the responsibility for planning, implementing, and managing the research of the National Cancer Institute on viruses in relation to cancer. The scientific disciplines necessary for an integrated program work together for the broad operational management and in-depth study essential to the attainment of the program objectives.

A special $10 million appropriation by Congress in FY 1965 launched the initial Special Virus Leukemia Program, the main objectives of which were: (1) To determine whether viruses comparable to those known to cause leukemia or lymphoma in many laboratory and domestic animals are causative agents of human leukemia or lymphoma, and (2) to develop a vaccine or other means of control of human leukemia and lymphoma when such agents are found. As evidence accumulated indicating that viruses are associated with other types of cancer, additional funds were appropriated and the program was expanded to the Special Virus Cancer Program having the same main objectives for all types of cancer.

Type C Particles

When the Special Virus Cancer Program was initiated, highest priority was given to the search for human leukemia viruses resembling the Type C viruses causing chicken and mouse leukemias. Since that time, many Type C viruses, the total is now about 85, have been found in a variety of tumors from many species of two vertebrate classes. All of these species continue to be studied intensively under the broader scope of the Special Virus Cancer Program. Several of the Type C viruses are established as the causative agents of leukemias, lymphomas, and sarcomas of chickens, mice, cats and hamsters. Many of these can infect and produce malignancies in other animal species (e.g. a sarcoma virus of the cat produces tumors in marmoset monkeys). Furthermore, some of these viruses can cause malignant changes to occur in animal and human cells grown in the laboratory (e.g. cat leukemia and sarcoma viruses alter embryonic human cells). Type C virus particles have been found in association with malignancies of a spectrum of animal species including rats, non-human primates, cattle, and man. Although electron microscopy is an important method in the search for Type C virus particles, certain newer biochemical, biophysical, and immunological techniques, developed through intensive collaborative studies of animal cancer viruses, are now being directed toward finding viruses present overtly or covertly in the cells of human cancer.

1. Reactions between Type C viruses causing leukemias and sarcomas (solid tumors)

When inoculated into appropriate cell cultures, Type C sarcoma viruses of chickens, mice, and cats produce foci of altered cells. This fundamental discovery provides a readily visible indicator reaction for the detection of sarcoma viruses. On the other hand, leukemia viruses grown in tissue culture do not cause foci or other detectable changes. The finding that leukemia viruses can either inhibit or enhance focus formation by sarcoma viruses of the same

species has led to the development of methods for the detection and quantitation of leukemia viruses indirectly.

Certain of the chicken, cat and mouse sarcoma viruses are "defective" in that they do not produce foci in cell cultures or tumors in animals in the absence of a co-infecting, "helper" leukemia virus. Further, in the presence of a defective sarcoma virus the helper action of leukemia viruses can be used as a specific indicator for their detection and quantitation. It is now believed that defective sarcoma virus—leukemia virus interactions may be more widespread in nature than originally thought and that similar systems may be found in man. A mouse leukemia virus which has been adapted to grow in human cells is now available to search for defective human sarcoma viruses, if they exist. An alternative approach has been developed for the detection of possible human leukemia viruses. A defective mouse sarcoma virus and its leukemia virus helper can be made to form tight functional aggregates, which behave as one virus. Using a mixture of a mouse sarcoma virus and a cat leukemia virus, a hybrid aggregate which could be grown continuously in cat cells was produced. Because the aggregate is defective, it requires the simultaneous presence of a cat leukemia virus for producing altered foci in cat cells. Thus a focus forming sarcoma virus of the mouse, artificially changed to one possessing infectivity for cat cells, can now be used in cultures for the detection of cat leukemia viruses.

This hybrid virus, as well as the cat leukemia virus, will also grow in human embryonic cells in tissue culture. If sufficient amounts of the Type C particles found in association with human leukemia can be obtained, the possibility exists that the cat-adapted mouse sarcoma virus can be hybridized with the human agent to produce an indicator system for the detection of human leukemia viruses.

2. Ubiquitiy of C-type viruses and their possible transmission in nature as part of the genetic inheritance

By developing highly sensitive immunological methods for detecting Type C viruses of chickens, mice and cats, an extensive program to determine the occurrence of Type C viruses throughout the life span of different animals has begun. Studies in mice revealed that no strains are wholly free of Type C virus involvement. In strains subject to a high incidence of spontaneous leukemia, the virus could be demonstrated even in unborn embryonic animals and at all ages after birth; in strains with a very low incidence of leukemia, the virus could not be detected at any age under natural conditions. If the latter mice were irradiated or treated with cancer-causing chemicals, Type C virus could be readily detected well in advance of the tumors that developed. Mice of strains with moderate incidences of leukemia showed no detectable virus during the first third of their life spans, but Type C virus appeared spontaneously and could be detected with increasingly frequency as they became older and developed leukemia and other cancers. Irradiation or treatment with chemical carcinogens, however, resulted in detection of Type C virus early in life and in the development of cancers. These and other findings led the investigators to postulate that the genetic information of the Type-C viruses is transmitted "vertically" (from parent to offspring) in a covert form along with the genes bearing the normal genetic information of the animal. Like normal genes they can be repressed ("switched off") and show no action under some circumstances, but can become derepressed ("switched on") under other circumstances, such as during aging or under the influence of irradiation or carcinogenic chemicals. This theory has been supported by the demonstration of "indicators" of the presence within tumor cells of viral material even in the absence of detectable whole virus particles. These "indicators" are termed group-specific antiques (gs antigens) which are specific subunits of the internal structure of the Type C RNA tumor viruses. One type of group-specific antigen is common only to the viruses of a particular animal species (species specific) and has now been demonstrated in the embryonic tissues of most mammalian and avian species. This suggests the possible role of these viruses in normal cell growth and differentiation as well as in the induction of malignancy.

Projecting that Type C viruses will be found to be as ubiquitous in man and other vertebrates as in mice, chickens, and the cat, the hypothesis is proposed as a unifying theory consistent with the phenomena of radiation and chemically induced cancer as well as the predictable occurrence of spontaneous cancers that develop in various populations of animals, including man. An exciting consequence of this theory, even if it is found to hold only for a limited number of cancer types in man, is the prediction that a new approach may become available for the control of these cancers, namely the delineation of factors responsible for both derepression and repression of virus expression.

A somewhat different approach has been based on the premise that tumor cells containing a common antigen may indicate a similar viral causation. In examining the tissues from various human sarcomas, researchers found particles resembling known animal Type C viruses in at least one liposarcoma. With continued culture of the tumor, particle production ceased, but immunologic tests using the serums of sarcoma patients revealed that the cells still contained a substance (an antigen) which appears to be present only in sarcoma cells (sarcoma-specific). A high incidence of serum antibody to sarcoma antigen was found in patients with various types of sarcomas and their close associates; a significantly lower incidence was found in normal serums. The data suggest that a viral agent may be the causative factor in this disease, and, hopefully, continuing studies will establish a more definite relationship of the antigen to this disease.

Very recently, a second group antigen associated with Type C viruses has been demonstrated. Preliminary evidence would indicate that it may be an *interspecies-specific* group antigen in that it is present and common among the Type C tumor viruses of 3 mammalian species, the mouse, cat, and hamster, but not the chicken. Furthermore, this antigen has been detected in highly concentrated extracts of cells from two different human tumors, one of which has at times produced small amounts of a virus resembling animal Type C particles. Basic immunologic information on this antigen will most likely be forthcoming in the ensuing months. If confirmed, the implication of this finding is obvious—a formidable probe for the presence of virus or viral genetic material in human cells has been developed.

3. New approach to detection and possible control of viral carcinogenesis

Increasing evidence has accumulated to substantiate that the genetic material of Type C RNA viruses can become integrated into the host-cell DNA (mammalian genetic material). A dramatic breakthrough in the investigation of the biochemical pathways of tumor virus infection and replication has been the demonstration that RNA viruses contain enzymes called polymerases which can direct the synthesis of DNA by the host cell. In rapid succession many investigators found that one of these enzymes (RNA-dependent DNA polymerase) is associated with all of the known RNA Type C tumor viruses. Viruses that cause leukemias or sarcomas in chickens, mice, cats, and hamsters, as well as breast cancers in mice, rats, and monkeys, have been shown to contain polymerase activity. By contrast, well-characterized non-tumor producing viruses do not contain this activity. This research has resulted in the development of new, extremely sensitive methods for the detection of RNA tumor viruses in human cancer. Assays for the polymerase enzymes exceed by 100-fold the sensitivity of electron microscopy and are capable of detecting viruses which are present either in latent form or as whole virus particles.

Intensive investigations have now revealed polymerase activity in the cells of patients with acute lymphoblastic leukemia; more preliminary evidence has shown the enzyme is in cells of sarcomas, Burkitt's lymphoma, and breast cancer. Since the RNA-dependent DNA polymerase is apparently always present in the RNA tumor viruses of animals, its discovery in the human tumor cells offers good supportive evidence that viruses are associated with cancers in man. The RNA-dependent DNA polymerase of human leukemia cells is inhibited by a drug, n-demethyl rifampicin, which also inhibits the enzyme activity found in the Type C RNA tumor viruses of animals.

Studies are underway to explore the action of this drug and various modifications of it. These investigations could provide new approaches to the treatment of malignancies in man.

Another new approach to the control of virus-induced malignancies has been opened by the finding that treatment of virus-induced tumor cells with a bean extract called Concanavalin A causes reversion of these cells to a non-malignant state.

Type B Particles

"Type B" is the designation given the virus particles that cause breast cancer in mice. They possess certain properties in common with Type C viruses, such as having genetic material of the RNA type, and being transmitted from parent to offspring along with the normal genetic inheritance. But they also differ in certain respects, such as: (1) the manner in which the nucleoid or core is formed during virus reproduction; (2) the fine details of their structural appearance as viewed with the electron microscope; and (3) transmission in its infectious form, *under natural conditions*, is through the milk of mothers to their own or fostered suckling young. Such transmission has been demonstrated even in the milk of wild mice and the infectious form of some Type C viruses may be transmitted naturally in avian species.

The potential existence in humans of an infectious breast cancer virus similar to that of mice, together with epidemiological evidence of "clustering" of breast cancer in some human families similar to that observed in the earliest studies of cancer in mice, led to systematic viral studies on this human disease under the sponsorship of the NCI.

Particles resembling the B-type virus of mouse breast cancer have been observed in 40 percent or more of milk specimens from women with breast cancer, as well as from healthy women of high-risk populations (high-breast-cancer-families, inbred Parsi sect of Bombay, India), as compared with a frequency of only about 6 percent for specimens from healthy women of the general population. Similar particles have also been observed in two tissue culture lines of human breast cancer that have been successfully grown in the laboratory. More recent studies of one of these cell lines have revealed additional evidence consistent with presence in the cells of a RNA cancer virus, that is the presence of the RNA-dependent DNA polymerase and the interspecies antigen.

Breast cancer occurs in about 4 to 5% of American women. It is the most prevalent and responsible for more deaths than any other type of cancer, not only in American women but also among women of several other countries. Because breast cancer occurs 2 or 3 times more frequently in some families than in others. It is strikingly similar to observations made on breast cancer of different populations of mice. These animal studies led to unequivocal evidence of the association of a virus and the demonstration that an infectious form of it is transmitted through milk. One of the major objectives of the SVCP is now the determination whether an agent similar to that of mice is responsible for the unusually high incidence of breast cancer in certain human populations.

Herpes-Type Viruses

A type of virus associated with some forms of chronic leukemia, lymphoma, and postnasal carcinoma is the herpes-type virus (HTV), similar in size and shape but not identical to those herpes viruses known to cause fever sores or shingles. Unlike human Type C particles, HTV grows well in the laboratory and fairly large quantities of purified and concentrated HTV can be recovered for study. One of the most active areas of viral oncology is that concerned with definitive charcterization of the HTV.

Considerable interest has developed in the herpes group of viruses as cancer-causing agents in animals and man. Herpes-type viruses have been shown to induce kidney carcinomas of the frog and to be causally related to lymphoproliferative (uncontrolled multiplication of white cells) diseases in chickens, monkeys, marmosets and rabbits. Projects have focused on the significance of the Epstein-Barr virus (EBV) from Burkitt's lymphoma and postnasal carcinoma and Herpesvirus hominus type 2 (HSV–2) from cervical carcinoma.

Seroepidemiological studies on the relationship of EBV infection to nasopharyngeal cancer are being conducted through the International Agency for Research on Cancer. A study in the West Nile District of Uganda to determine the feasibility of further studies on EBV in relation to Burkitt's tumor is nearing completion.

Seroepidemiological data also suggest an association between infection by HSV–2 and cervical carcinoma. Results of a study made in Houston, Texas, showed the presence of serum antibodies to this virus in about 85% of cases of invasive cervical carcinoma in comparison to 22% in controls. Recent findings in Cali, Colombia, showed a much higher incidence of antibody in the control population selected, approximating the incidence in the tumor-bearing group. At present, insufficient data is available to conclude that this virus is implicated in this cancer.

EBV infection has been associated with the development of infectious mononucleosis in young adults, a disease with the attributes of a self-limiting leukemia. The generally high levels of antibodies to EBV in patients with Burkitt's tumor or with nasopharyngeal carcinoma also suggest that the virus might be causally-related to these diseases; high levels of antibody also occur in patients with the sarcomatous form of Hodgkin's disease, chronic lymphocytic leukemia, and sarcoidosis. Present methods show no significant differences between the EBV isolates from these different diseases.

Several facts make EBV suspect as a prime if not a sole factor in the induction of hematological disease in man. (1) The virus is ubiquitous; no human population has been found to be free of antibody to EBV. (2) The virus is consistently found in association with Burkitt's lymphoma. (3) Only lymphoid (white) cells appear to be susceptible to infection. (4) Lymphocytes from negative donors have not been capable of continuous cultivation unless they are infected by the virus. (5) Infected continuous cell lines which do not release

virus contain soluble antigens that react with serums containing antibodies to EBV. (6) EBV has been strongly associated with infectious mononucleosis, cell lines of which grew as tumors in immunosuppressed hamsters. (7) Other herpesvirus of animals have been casually related to lymphoproliferative diseases. (8) The genetic material of EBV is related to that of similar viruses known to induce malignancies in animals. Thus, EBV has several features characteristic of known tumor viruses. Current data suggest that: genetic material of EBV may be incorporated into lymphoid cells; mature virus production may be a rare event; infected cells acquire the capacity for unlimited growth and produce tumors in the immunologically deprived host; infection by the virus may be a factor in tumor development under certain unknown conditions affecting the immunity of the patients.

Chemotherapy Research

Even with the earliest diagnosis possible and treatment by surgery and radiation by the best doctors in the best medical centers, sufficient knowledge is not available to keep 335,000 Americans from dying of cancer this year. Lack of knowledge of the causes and lack of means for preventing cancer will result in development of the disease in hundreds of thousands more people; 635,000 new cases will be diagnosed for the first time during the year.

But, one by one, the number of different types of cancer successfully treated by drugs is steadily increasing. Under the stimulus of the National Cancer Institute's Chemotherapy program, new chemical agents are being discovered and developed into cancer drugs. New techniques of administering them are producing long remissions (absence of signs and symptoms of disease) and cures. In some instances, these results are being obtained with drugs previously found effective against some types of cancer but not against others when given by older, conventional methods.

One of the key factors in the new techniques is the use of combinations of drugs or therapies, such as drugs and surgery or radiotherapy. Use of drugs in combination takes advantage of the fact that different ones produce different types of toxic side effects, so that there is increased anticancer action without additive toxicities. Another important factor in the new treatment schedules is the timing of the administration of drugs. Increasing knowledge of the cancer cell and its behavior will permit giving a drug at a time in the life cycle of the cancer cell when it is most vulnerable to drug action.

1968 actual	$27,346,000
1969 actual	27,370,000
1970 actual	26,842,000
1971 estimate	31,406,000
1972 estimate	31,495,000

Note.—This Special Report excludes the proposed additional $100,000,000 for cancer research initiatives in 1972.

During the 1960's it became clear that a number of human cancers* were cured by the use of drugs (chemotherapy). In addition there are other tumors** previously fatal, that can be cured by X-irradiation plus chemotherapy. These drug susceptible cancers are those that are rapidly growing, highly malignant and occur usually in the young. Each year the list of susceptible and potentially curable tumors grows a little longer and now includes about 15% of all clinical cancer types. Analysis of the reasons for drug susceptibility of this 15% has led to new knowledge of the biology of tumor growth, which can be utilized in the study of the 85% of cancers which are drug resistant.

The major protagonist of this successful chemotherapy has been the National Cancer Institute. Increased appropriations beginning in 1954 permitted the NCI to build up the country's resources in all the elements essential to a drug development program. Usually in this country such drug development is left to industry, but because of the lack of commercial interest in cancer drugs, the chemotherapy program of the NCI was created. Since 1954, the NCI has developed a skilled scientific team that has welded together the disparate national resources into a unified national program, and has provided the leadership in their utilization. This team of physicians and scientists not only carries out its own research, but it has established and operated a complete drug development program. It has

*Choriocarcinoma, Burkitt's lymphoma, testicular cancer, acute lymphocytic leukemia.
**Ewing's tumor, Wilms's tumor.

analyzed every aspect of drug development, established and operated a detailed plan for all the steps leading from acquisition of chemicals to definitive clinical usage, and developed systems for monitoring and coordinating all its operations. In addition, the team has become the focal point for cooperation with other physicians and scientists and for contractural collaboration with the pharmaceutical and chemical industries. This central position of NCI permits a worldwide surveillance of every new lead that might speed up the drug control of cancer.

The growing success of drug control of cancer presents a new opportunity for the extension of current knowledge to a substantial proportion of the young with advanced cancer, and hope for the development of drugs to control the much more common cancers of later adult life. The object of this summary is to explain the elements of the chemotherapy program and to indicate the directions these opportunities should take.

Elements of the successful control of human cancer

Drug Development

The most important factor in the growing control of cancer by chemotherapy is the large number of active agents now available. Prior to the NCI program, there were less than a dozen agents, and little was known about their potentialities. Now there are over 35 active drugs and a great body of knowledge exists on their usage. The availability of a large number of active drugs permits the physician to kill tumor cells by being able to hit different biochemical pathways simultaneously when the drugs are used in combination. The large number of compounds arise from highly improved screening systems. The hard data collected by NCI in both animals and patients have permitted for the first time a full knowledge of the correlation of drug effects in animal and man with resultant improved confidence in predicting activity in man. Another reason for the increasing number of clinically active drugs has been the maintenance of the input of chemicals into the screen. First there is a continued search of new types of structures developed by chemists and of natural products from a worldwide collection of bacterial, plant and animal materials; secondly, the advancing knowledge of molecular biology, especially in relation to tumor producing viruses, has suggested a large number of compounds for testing.

In drug development, there have been important advances in predicting the safety of compounds that will be given to patients for the first time. These improvements have helped to speed up the flow of new drugs to clinical trial and increase the margin of safety for patients. From these data there has also been developed a general theory for explaining the differences in action among species that will have general application to the testing of all drugs in animals prior to use in man.

Clinical trials of antitumor drugs have been greatly improved. Some reduction in services at the Baltimore Public Health Service Hospital has been made up by expansion of activities at the NCI unit at the Washington VA Hospital. These units together with direct clinical studies at Bethesda and Uganda have permitted speedier work-up of new drugs in man. For the last several years an average of three new agents were studied per year, while in the present year at least eight new drugs will be completed for the first step (phase I) of trial. This speedup is due in part to methodological advances so that more information per patient is forthcoming. In addition there have been successful efforts at closer working relationships with the M. D. Anderson Hospital in Houston and the Sloan Kettering Institute in New York.

The second step in drug trials (phase II), wherein therapeutic efficacy is appraised, has also improved. This has been in part due to a fine contract with the Mayo Clinic and in part due to more effective communication with the national network of cooperative groups supported by NCI grants. Communication improvements have been achieved through fact sheets on drugs that get wide distribution and New Drug Seminars that are heavily attended. These successes in communication to the medical profession are heartening.

The NCI sponsors to the Food and Drug Administration and the Division of Biologics Standards most of the Investigational New Drugs in this country for antitumor drugs. In this role the NCI keeps a close surveillance on the safety and effectiveness of new drugs and reports these in a systematized way to the regulatory agencies. With the NCI team as the focal point, physicians throughout the country report by phone on any new development, and these findings can be communicated immediately both to the agency and to other physicians who are working with the drug.

One of the obstacles to precise clinical trials is the difficulty of assessing tumor regression. The physician cannot tell when a tumor has completely disappeared.

During the past year research leads have been uncovered concerning chemical products of tumors that appear in the body fluids and may permit practical application. The ideal situation is to be able to calculate the number of surviving tumor cells from a chemical determination of the urine or blood.

Best Ways of Using New Drugs

The improvements in drug control of cancer have resulted not only from the availability of large numbers of active agents, but also from an expansion in knowledge of the best ways to administer them. First of all there has been increasing proof that the schedule of drug administration can be vital to its efficient usage. For example, some drugs are useless when given once daily, but highly effective when given three times a day. Animal systems to study optimal dose scheduling have recently been developed, and provide part of the information requisite to efficient dose schedules in man. Even more recently it has been possible to relate dose schedules to the mechanism of action of some drugs and thus a general theory of dose scheduling is emerging.

A second important advance in the drug control of cancer derives from the growing knowledge in the use of drug combinations. The initial observations in acute lymphocytic leukemia has been followed by successful application of these principles to advanced Hodgkin's disease, acute myeloblastic leukemia and to a number of other fast growing tumors. Indeed, in the past year there has been a fresh attempt to reapply these principles, with different drugs, to cancers of the lung and breast. Preliminary good results indicate that these studies must proceed in depth, but since the tumors are slow growing, the studies will require considerable time.

There have been a number of advances in our knowledge of the best way to use drugs. Antitumor drugs have a number of peculiarities in terms of the most efficient and safest dose schedule. Activity can be lost or toxicity increased by the use of an inappropriate schedule. The newly discovered specific inhibitors of DNA synthesis have provided a tool for understanding the reasons for these dosage schedule vicissitudes. Work in the past year on arabinosyl cytosine has remitted in new insights into what must be done to understand the best usage of 35+ other drugs active in human cancer. There is then an opportunity to analyze existing data and to get new data in order to understand the best dosage schedule for each agent whether used singly or in combination. Certain principles have already become apparent, and a wholly new pharmacology is being built on these concepts.

Since some drug failures in the drug susceptible tumors occur because the tumor cells get into the brain and are thus protected by the blood-brain barrier from the drugs in the blood, compounds have been designed to get around this obstacle, and successful drug treatment of brain tumors may become feasible.

Supportive Therapy

Hemorrhage was once the commonest cause of death in leukemic patients. Because of observations on platelet replacement, routine prevention of hemorrhage is now possible. Death from infection has become the most common cause of death in leukemia as well as in other tumors. Research over the last several years has shown ways to treat or prevent many of these infections. Treatment of established infections has improved because of a new penicillin (carbenicillin) discovered in England. There is a great need for additional anti-bacterial agents for the bacteria not now susceptible and for anti-fungal and anti-viral agents. Since infection is due to lack of white blood cells, studies of treatment of established infections by transfusion of white cells has been examined and proved efficacious.

Improvement in typing of white blood cells has occurred in the past year, and this together with the continued evolution of the blood cell separator, makes such transfusions more widely applicable. Finally, patients get infections because they are transiently unable to handle infections during treatment, and keeping the patient's environment free of the disease-causing bacteria prevents these infections. The laminar flow room developed by NCI is now perfected, and has been installed in several clinics with excellent results. The next step will be to build entire nursing units around the concept of laminar air flow protection. With the use of the laminar flow rooms during the past year, a number of bone marrow transplantations have been successfully made in patients whose bone marrow was severely compromised, but more were done without the use of laminar flow.

The decision in 1966 to give a firmer scientific base to chemotherapy resulted in intense work on the relation of the kinetic state of cells (percentage of cells undergoing division) to susceptibility to drugs. There are enough data now to

say that this relationship is a key to rational chemotherapy, and more and more segments of the drug development program are based on this new knowledge. There are many opportunities to gather additional data in proving a more generalized theory for chemotherapy as related to cell division. New techniques for further application to man are required and some beginnings of this have been successful during the last year.

The recent discovery of an enzyme (RNA dependent DNA polymerase) that seems to characterize tumors produced by viruses provides additional opportunities to develop further rational chemotherapy. Since several chemicals have already been found to inhibit the enzymes, at the very least it will provide a number of new compounds with potential activity.

The role of the host in complementing the cure of drug susceptible tumors is under study. Non-specific stimulators of host resistance have received some study both at Bethesda and Uganda. This involves use of various fractions of the tubercle bacillus, an organism that is quite effective in inducing this type of non-specific host resistance.

CONCLUSIONS

The developments of past years have clearly confirmed the curability of some forms of advanced cancer. The drugs now available have allowed examinations of successes and failures and given insight and opportunities into extending curative chemotherapy to greater numbers of patients. The key scientific problems for the coming year are the development of a biochemical assay for the number of tumor cells in the body; improvement in the treatment of cancer within the brain; further evolution of an animal model for the small growth fraction tumors; and a continued flow of new agents to the clinic. The increaing knowledge of the biology of human tumors, and their correlation with animal models, give opportunities for rapid exploitation of present knowledge in the fast growing tumors and a conceptual framework for understanding the control of slow growing tumors.

GENETIC FACTORS IN CANCER

Dr. Baker. Part of the excitement among scientists with the advances in virus-cancer work relates to the accompanying enlargement of our understanding of heredity or genetics and of how the body cells' functioning is controlled. Such understanding offers hope of eventual correction of diseases produced by malfunctioning of the genes of the chromosomes.

We know that some diseases are due to alterations in the genes of the chromosomes. So further understanding of the cancer virology will help us develop new ways of cell control.

Closely related to this area is the first synthesis of a gene, accomplished by a Nobel laureate who had received 10 years of NCI grant support of his research, Dr. H. Gobind Khorana. This difficult achievement points the way to eventual synthesis of human genes, and perhaps correction of the chemical errors in human cells that are responsible for cancer and other diseases.

That is a long-range objective of research I might add.

AREAS OF GREATEST PROMISE IN CANCER RESEARCH

It is not possible within the limits of this statement to set forth the full state of the art or sum total of knowledge in cancer research, but the broad areas into which we should move with a large-scale endeavor are three: (1) viruses as probable human cancer causative agents; (2) chemical agents that induce cancer in man; and (3) treatment of cancer, particularly drug therapy. May I touch on some of the points emphasized by Dr. Steinfeld.

We know that viruses and chemicals produce cancers in many animal systems. We know how to detect these agents, and in many cases

we know how to prevent the induction of cancer. This knowledge and technology is ready for sizable expansion and for development leading to prevention of cancers in man. Numerous research leads are ready for extension to additional kinds of causative agents and types of cancers and for research development. There are over 100 viruses known to cause virtually all kinds of cancer in every major group of animals, including subhuman primates. In this field the efforts of highest relevance, priority, and need remain improved means of detection, propagation, and isolation of viruses from additional cancer patients; more efficient means of producing and purifying viruses on an industrial scale; required technology for producing and testing safe and potent vaccines when feasible; and surveys to determine which individuals and populations are at greatest risk to cancers of suspected viral origin. The major needs in the area of chemical causation and prevention of cancer are: better means for identification and removal of hazardous chemicals in the environment; enhancement of the body's ability to detoxify these agents; better understanding carcinogens such as radiation; and more rapid and sensitive means to detect and bioassay the cancer-inducing effects of chemicals for man. Plans for expanded efforts in these areas extend well beyond current investments of funding.

Of the 100 or more different kinds of cancer, about 10 have been shown to be curable by means of drugs. Knowledge gained through intensive research efforts in the decade of the sixties is making possible the extension of these gains to more and more patients; and, although there are obstacles to 100-percent success in the potentially drug-curable patients, the coming decade should see many of these obstacles overcome through research, permitting the cure of more than 15 percent of those with otherwise fatal cancer. A key problem is to predict from animal systems the delivery of a safe but tumor-destructive amount of drug to the tumor cell at a time in its division cycle when it is highly vulnerable to such treatment. New drugs and concepts cannot be tested rapidly, however, in the clinical resources available today. There is a need for quick expansion of these resources at the National Cancer Institute and in the cancer centers now in operation throughout the country. In addition, planning should be started immediately for the construction and staffing of multidisciplinary centers in several sections of the country where none now exists. As a backup for clinical research, the number of chemical compounds and natural products being screened through animal tumor systems for anti-cancer activity should be increased from the present rate of 15,000 to a new level of 50,000 a year to insure increased supply of new drugs entering clinical evaluation beyond the current level of six per year. Furthermore, the addition to the primary screen of new animal models that mimic the biology of the human tumor should certainly enhance our ability to control drug-resistant tumors with both new and known drugs. Much greater emphasis could then be given to studies of such drug non-responsive common tumors as cancers of the large intestine, breast, lung, pancreas, bladder, and prostate gland.

These kind of cancers constitute the major forms of cancer in man.

Underlying and supporting the major thrusts of research as described here must be, of course, a continuous effort in the many fields of fundamental scientific investigation to which all disciplines in biomedical science contribute. Special promise of rapid progress exists in immunology and molecular biology investigation.

MANAGEMENT AND PLANNING REQUIREMENTS

To undertake now a major expansion of cancer research with the intention of expansion to even higher levels as warranted throughout the present decade will require the development of a managerial capability for program planning, direction, and execution on a scale unprecedented in biomedical science. Although the nature of the cancer problem does not permit even an informed forecast of solutions within a definite time limit, it is altogether reasonable to expect that an intensified effort will move us toward the ultimate goal at an accelerated pace. Such accelerated progress will result both from the continuation of support of science required for uncovering new research leads and the energetic followup of them with adequate resources applied through carefully planned and systematically monitored programs designed to converge related pertinent lines of investigation upon end-points of accomplishment. In other words, a supplementation of the present activities with added systems coordination of scientific research will be required.

The mobilization and deployment of resources for such a major endeavor will be much more difficult in the biological and medical areas than was the experience in the physical sciences. The successful prosecution must involve the enlistment, participation, and commitment of several essential elements. We need the participation of the scientific community. We shall have to draw on the technical resources available in industry. There must be a good mix of planned and investigator-initiated research, and a proper relationship between short- and long-range goals. As planning proceeds, key problems must be better defined and priorities established for the solution of problems in the order of their promise and susceptibility. The entire endeavor must have unified, overall direction facilitated by a feedback system maintained through constant monitoring of the progress and difficulties in all areas of operation. We shall need to keep the public informed as the program proceeds. Most important, we shall need a continuing commitment to the program at all levels.

In closing, I should like to re-emphasize a key point. We should not look too soon for extraordinary results from a suddenly expanded major endeavor to conquer cancer. The time frame of accomplishment in the cancer field is quite different from that associated with the control of poliomyelitis, for instance. Significant research advances or cures in the cancer area cannot be predicted with accuracy, but what we can expect to see is a quickening of pace in the whole cancer area through a larger, carefully coordinated effort. This certainly will move the progress of cancer research more rapidly and effectively toward progressively better control of malignant diseases through prevention and cure.

Mr. Chairman, the request of the National Cancer Institue totals $334,338,000 for operations to be conducted in 1972. In comparison with the operating level of $334,338,000 for 1972, the 1971 operating level is $230,462,000. In addition to the $100 million increase for special cancer initiatives, the other changes in 1972 from 1971 are as follows: increase of $1,992,000 for research grants, increase of $2,334,000 for direct operations, and a decrease of $450,000 in fellowship grants. I shall be pleased to try to answer questions and supply any additional information desired for the record.

ORGANIZATIONAL FORM OF THE CANCER PROGRAM

Mr. FLOOD. It is still not exactly clear what is the organizational relationship between your Institute and the special $100 million program. Some of the testimony we have received so far gives us the idea it would be an organization separate from your Institute attached to Dr. Marston's office.

Testimony given last week made us wonder if the $100 million was to set up a new organization that will swallow the National Cancer Institute. What is the situation?

Dr. BAKER. The plans call for the establishment in Dr. Marston's office at the NIH level a Director of the new Cancer Conquest Program. This program includes the activities of the National Cancer Institute which will be maintained as the National Cancer Institute in that new program. The Director of the National Cancer Institue will be Deputy Director of the new Cancer Conquest Program.

So the NCI will be the major part of this new effort. We anticipate the actual operations then to consist of the NCI staff activities, plus two units which would be set up to assist the cancer conquest program director in planning and monitoring the program and carrying out the activities.

But it will be one program, it will not be two separate programs.

The head of the Cancer Conquest Program will also be a Deputy Director of the National Institutes of Health which is intended to give major thrust to this new special program.

Dr. MARSTON. Could I add emphasis on this point?

Mr. FLOOD. Yes, indeed.

Dr. MARSTON. We are talking about a program of $334 million, not of two programs, one of $234 million and one of $100 million. We are talking of one program, the Cancer Conquest Program.

BACKGROUND OF CANCER CONQUEST BUDGET

Mr. FLOOD. What knowledge did you not have concerning recent research findings, prospects for advances and breakthroughs, when you made up the regular 1972 budget that you did have when you decided to include the special $100 million request in the budget for 1972?

Here you were with all the years of experience and you worked hard during the summer and fall on the 1972 budget. What knowledge didn't you have then that all of a sudden you found out you had, and so you decided to include the $100 million request in the budget for 1972. What happened?

Dr. BAKER. I think what was going on was a series of discussions at different levels and in different parts of the Department all through that period; that is, discussions as to whether there was sufficient understanding and sufficient number of leads to warrant a special attack on cancer, and certainly taking into account in view of the fact that most of the public seems to place a high priority on additional cancer work if it can be effectively done.

These discussions went on at the same time the regular budget process was being developed. I think the discussions were not completed on such a major change until along toward the end of the calendar year and into the beginning of this year.

It was a matter I believe of getting all of the discussion completed in sufficient time rather than a sudden change in the information scientifically.

Mr. MEYER. If I may, I believe the decision to go forward with an initiative in cancer research, as Mr. Miller testified earlier last week, resulted from screening of a large number of health options that were before the Department, some of which were associated with the delivery of health care, and some of which were associated with research.

All of these received an intensive staff review in order to give the Department as much information as possible from which to make their final selection in the development of the 1972 budget.

Mr. FLOOD. The reason I ask that, your regular budget represents an increase of about 2 percent. Then just a few weeks after it was prepared you come up with this $100 million increase, over 40 percent. I wondered if something spectacular happened to prompt this, or whether the regular budget and this $100 million could have come up just as well as one item?

Dr. MARSTON. Mr. Flood, you remember that in the 1971 budget the largest increase was for the Cancer Institute—$25 million by the administration to which the Congress added $25 million which gave us a $50 million increase over the $181 million base in 1970.

We at NIH and the Cancer Institute in discussions with the Department about the 1972 budget did make the case that there was an opportunity for a substantial increase in investment in cancer research above that increase of $50 million last year. I don't think any of us know whether, if the increase due to the health options had not occurred, we would now be before you defending a $10, $20, $50 million increase in the 1972 budget.

When we made the case, from the standpoint of NCI and NIH, that a substantial increase was both justified and should get special consideration along with other opportunities in the research area and the health area, the decision was made that if there is this type of opportunity, let's not go up just $10 or $20 million in 1972, but let's really make a change and give it real emphasis.

It was in that context that we were involved in discussions on what one should do to make a special effort in this country in cancer—what would be a reasonable amount, a defensible amount in 1972? The $100 million was the figure that resulted from that discussion.

In view of our assessment that there were major opportunities, the real question was: If you really want to move rapidly and more energetically what should the new level be?

CHOOSING CANCER FOR A MAJOR INITIATIVE

Mr. FLOOD. But why cancer instead of something else?

Dr. MARSTON. As you recall that this committee, about 4 years ago, asked us to list a number of areas that should have greater emphasis. We came up with about 40 at that time.

We went through this exercise again, updated our assessments across the field of biomedical research, and laid out in some detail a number of areas that are exciting.

Our assessment of the scientific opportunity in cancer research, the fact that it is a major killer, the fact that the American people are

frightened of cancer as a disease, the fact that the Yarborough committee made its report early in December which attracted considerable attention, the fact that the President long ago, the previous year, had indicated his specific interest, all of these factors came together at this time.

It may happen in heart in another year, if one wants to take another large area that has some of the factors—a large number of people affected, large numbers concerned about the premature death of American males, the existence of scientific opportunity, and so forth.

It happened in cancer at this time, I think, for the reasons I have given.

FELLOWSHIPS AND TRAINING

Mr. FLOOD. You are budgeting for reduction from 242 to 216 fellowship and from 141 to 125 training programs. With this big expansion of the research program under the special $100 million add-on, isn't there a need obviously, to expand the fellowships and training programs instead of cutting them back? It would seem so to me.

Dr. BAKER. In the spread of the additional $100 million proposed, we would propose to at least put back part of that money in the fellowships area and put back a major part of the money in the training grants area because we will need additional manpower for this new conquest program, although we expect to utilize some industrial manpower that hasn't been previously tapped.

So we do reduce these reductions by putting $2 million of the $100 million into the fellowships and training grants.

Mr. FLOOD. The only thing wrong with that answer, Doctor, the justifications include the $100 million. How do you put that together?

Dr. BAKER. I think part of the problem with presenting this budget justification is that much of the text has the various conventional parts of the program listed in one part and the $100 million part listed under special cancer initiative in the back section of the budget justification. I admit it is rather difficult to read this budget justification.

Mr. FLOOD. We will agree with that. The $100 million is in the justification from which I quoted these figures on fellowships and training programs. That is pretty hard to put together.

Dr. BAKER. One has to take the spread of the $100 million and relate it to the various parts of the conventional budget to make sense of all of these various numbers in the justification here. So the best answer I can give is that we would restore the fellowships and training grants back.

Mr. FLOOD. How do you reconcile that with the reductions shown in the training programs and fellowships?

Dr. BAKER. Because we have to take the section on the additional $100 million for cancer initiatives on page 43 and relate the training and fellowship activities out of those special cancer initiatives back to the conventional sections on fellowships and training on pages 19, 20, 21, 22, and 23 to allow me to give you my answer that we will have essentially no cuts in the training and fellowships categories.

Mr. FLOOD. When are you going to do this?

Mr. MEYER. I can't answer that with any degree of preciseness.

Part of the reason for the apparently confused presentation relates to our request to have the $100 million available on July 1 by requesting necessary language in the 1971 supplemental.

As a result we prepared the justification in one kind of presentation for the 1971 supplemental and now have tried to go back and fit this into a revised 1972 justification so that you could also see the impact of it. It appears this attempt was not as helpful as we had intended.

Mr. FLOOD. We can't hate a guy for trying.

Dr. BAKER. I wonder if it would be helpful to put a table in?

Mr. FLOOD. Anything would be helpful.

Dr. BAKER. We testified to the spread of the $100 million at the hearings last week which allows us to present how we would propose to spend the $100 million. I think it would be easier to follow if the tabulations were made in a different format than they happen to be here.

I would like to ask if we could put that in the record to be more helpful.

Mr. FLOOD. I think you had better.

(The information follows:)

DISTRIBUTION OF THE $100,000,000 SUPPLEMENTAL

	1972 (excluding $100,000,000 supplemental)	$100,000,000 supplemental	1972 (including $100,000,000 supplemental)
GRANTS			
Regular program	$69,123	$10,389	$79,512
Cancer research centers	20,953	26,000	46,953
Leukemia research support centers	1,851		1,851
Scientific evaluation	201		201
General research support grants	5,275		5,275
Total, research grants	97,403	36,389	133,792
Fellowships	3,348	200	3,548
Training	8,358	1,800	10,158
Total grants	109,109	38,389	147,498
DIRECT OPERATIONS			
Laboratories and clinics	21,529	1,800	23,329
Collaborative research and development:			
Cancer therapy	31,881	19,000	50,881
Etiology	57,581	20,000	77,581
Task forces	4,079	10,311	14,390
Supporting services	4,260	1,000	5,260
Cancer research centers	500	8,000	8,500
Total, collaborative	98,301	58,311	156,612
Review and approval	3,636	200	3,836
Program direction	1,763	1,300	3,063
Total, direct operations	125,229	61,611	186,840
Total, NCI	234,338	100,000	334,338

Note: The $100,000,000 supplemental includes $16,000,000 within cancer research centers ($8,000,000 in grants and $8,000,000 in direct operations) for planning, renovation, and construction.

Dr. MARSTON. What Dr. Baker has said about the policy implication, and the thing that led to your question—that is, if you have a higher level of research activity in the country, will you not need to reflect that in the training and fellowship programs—is a very crucial policy point. It is one we discussed with the Department and with OMB.

As the only exception to the general agreement, which I described in my opening statement, that we would hold the training grant programs at these present dollar level until the study was completed, we do have, as a part of the cancer supplemental request, a $2 million increase for training.

We could perhaps be helpful by supplying a new table that shows the distribution of the $534 million rather than the mixture of things that are in this document.

Mr. FLOOD. Suppose you do that.

Mr. MARSTON. I think the principle, the point you have made, that you cannot carry out a markedly expanded program in research without providing for the training of the people to carry it out in the future is a point on which I am in complete agreement with you.

PROMISING LEADS IN CANCER RESEARCH

Mr. FLOOD. Would you like to expand on your comments concerning the promising leads you have regarding cancer cure. This is of tremendous interest.

Dr. BAKER. Yes, sir. I would like to first discuss the drug therapy and radiation therapy and elaborate a little on the causation and prevention side.

We have learned a lot over the past decade on how drugs should be selected for introducing them into man, how to evaluate them in man, how to develop new drugs, how to select which compounds will produce antitumor effects, and how we determine what kinds of undesirable side effects may be expected when these drugs are first taken into man.

Then we have progress made on the managerial side that has been built into the chemotherapy program over the past several years to tie this all together.

Our biggest successes to date in those disseminated cancers beyond help of surgery, that is in cancer that has spread, is with radiation and more recently with drugs. We will have to find additional drugs or other means such as immunotherapy to knock out cancer cells without undue harm to normal cells to make future progress.

The drug successes have been in what we call rapidly growing tumors constituting about 15 percent of cancers, the most dramatic being acute leukemia of childhood where we believe we are probably curing some of these patients now. They have long-term disease-free remissions. Some 200 children we know have gone 5 years or more without recurrence. Yet before the advent of drugs, they would be dead 3 months after the diagnosis. We understand now how these drugs work, and we have animal screens that can select these active compounds.

Our drug selection apparatus so far has been set up with animal screens utilizing rapidly growing tumors. If we had had more resources, we would have probably developed additional screens to include the slow-growing tumors in the animal screens (the slow-growing tumors are the more common tumors).

So we see great potentiality now of extending the success with these rapidly growing tumors to the more common, slow-growing tumors by enlarging the animal screens we have been using.

Secondly, we can proceed with reasonable certainty now with studies in four species of animal to predict what the undesirable side effects of a new drug on man will be. When we take drugs into man, we do not know exactly how severe they will be, but we are now able to correlate results quite well and make predictions of what kind of undesirable side effects we must look for when we first introduce a drug into man.

CANCER VACCINATION POSSIBILITIES

Mr. FLOOD. What about prevention? What are the possibilities of a vaccine against cancer in the foreseeable future?

Dr. BAKER. The question of vaccines still looks quite hopeful as I reported last year. In certain kinds of cancer caused by so-called herpes type viruses (these viruses are somewhat similar to fever blister causing viruses), the evidence is still strong that viruses are transmitted in ways that permit help from vaccines.

The leads are still holding up on uterine cervical cancer as regards the evidence pointing to it being transmitted by virus. The new developments in breast cancer, just beginning when I appeared here last year, have been moving well, and the evidence is still holding up quite strong that the B-type viruses found in breast cancer patients and women who have high risk to breast cancer compared to control patients who do not have the high risks, all point to the idea that vaccines may be usable as they have been in animal studies.

On Burkitt's lymphoma in Africa I have an interesting thing to report because I predicted that we might have enough information to make a decision this year on whether a vaccine might be a good thing to use in the Burkitt's lymphoma, a kind of cancer common in African children. Because of successes in chemotherapy treatment for Burkitt's lymphoma in children, we don't have enough cases showing up in that population to get enough numbers to complete a study this year. The success results from treatment with a drug called cyclophosphamide. We are producing 90 percent remission in these children.

I think most of these patients are likely to be cured with this one drug; therefore, we don't have as many cases of lymphoma this time as we had before we had the successful cure, so we can't get enough numbers of Burkitt's lymphoma patients to get all the data we were expecting to get within the year. So we will have to extend the time period.

Another area where we are hoping to get requisite information is in nasopharyngeal carcinoma—cancer in the back part of the mouth and the upper part of the throat—which has the same kind of association as Burkitt's lymphoma. So the evidence is still building very well in the direction of vaccines for some kinds of cancer.

On the other hand the interesting developments I touched on last year, like Dr. Huebner's work in particular and others with type C viruses, make it look like a conventional vaccine is not going to do the job because the genetic information of the virus is being transmitted to offspring from parents, not as a full-blown virus but only as a piece of genetic information of that virus.

Vaccines are not likely to work on this. We will have to find drugs to do that or immunological means. And these drugs I mentioned in the opening statement are very important for the possibiilty of controlling this kind of cancer.

INCREASE IN KNOWLEDGE OF CAUSES

Mr. FLOOD. What more do we know about the causes of cancer than we did last year?

Dr. BAKER. We have increased again some additional viruses that

have been shown to produce cancer. I don't think that is worth getting too excited about in itself. The main developments are the improved means of detecting these viruses so we can apply this knowledge to man. They are being applied and the progress is detailed in the special reports.

PROGRESS IN EARLY CANCER DETECTION

Mr. FLOOD. Let me put two questions together. Have we made any advances in earlier detection of cancer since you were here last year?

Dr. BAKER. In preliminary results there are some suggestions that we are picking up a few more cancers earlier in lung cancer. In a major study we are supporting at Johns Hopkins University, we are applying the kind of approaches we used in the Pap smear test against lung cancer. We are able to pick up some lung cancers before they would be picked up in the conventional X-rays. Other techniques, such as use of tantalum powder to outline the cancer changes on X-ray in suspected lung cancer cases are also being developed. We are looking at the groups with the greatest risks here, which is allowing us to identify a few tumors earlier than before.

In the area of breast cancer, we now have good evidence that the soft X-ray mammography technique allows us to pick up more cancers than we could pick up in breast by conventional examination.

So there are leads and progress is being made and there is concrete evidence in patients.

MARY HITCHCOCK CANCER RESEARCH CENTER

Mr. FLOOD. What about the Mary Hitchcock Cancer Research Center. How much is budgeted for 1971 and 1972 for the center?

Dr. BAKER. In 1971 we have $3 million budgeted for that, because it includes partial costs for special construction. This area of the country has among the highest rate of cancer per 100,000 population.

Mr. FLOOD. Where is it?

Dr. BAKER. It is at Hanover, N.H., in conjunction with the Dartmouth Medical School, and a distinguished clinic of long standing. The people in that whole upper Northeast region have not had available to them a very active cancer research program.

Mr. FLOOD. What percentage of the operating costs will this appropriation bear when it is fully developed and who will pay the rest of the expenses?

Dr. BAKER. We expect to have about $500,000 operating costs as a continuing contract operated for the center during 1972. Their main thrust here is radiotherapy with special skills in computer know-how. They have special expertise in radiation both researchwise and secondarily from the care standpoint.

We don't pay for straight care costs, of course, in any of our activities. There are a number of research projects that are being developed in conjunction with this center which will be funded in the usual way. Our budgeted operating level for 1972 is $500,000. Other funds will come from operating income, grants, and other gifts from various sources.

A CANCER RESEARCH CENTER IN THE SOUTHEAST

Mr. FLOODS. Is there a major cancer treatment, training and research center in the Southeast United States?

Dr. BAKER. At the present time there is no large scale, major cancer treatment, training and research center in the Southeast United States. There are some specialized centers in existence, one at Memphis, St. Jude's Hospital, dealing with childhood cancer, and another general center in New Orleans at the Tulane University Medical School.

Mr. FLOOD. Is there a demonstrated need for one in the Southeast?

Dr. BAKER. Yes.

Mr. FLOOD. Has anyone made an effort to plan such a center in the Southeast?

Dr. BAKER. Such a center has been planned at the University of Alabama Medical School in Birmingham, Ala.

Mr. FLOOD. How much money would it take to build such a center?

Dr. BAKER. As planned at the present time it is estimated by the university that approximately $15 to $20 million would be required to construct such a center. This would comprise approximately 200 beds of which 50 would be devoted to intensive cancer research activities under control of the coordinated center program. The remainder of the beds would be allocated under the traditional departmental jurisdiction.

Mr. FLOOD. Has anyone raised any money on their own to build such a center? Where did that money come from?

Dr. BAKER. Approximately $5 million has been raised by private contributions to assist in this effort. Of this $5 million, almost $400,000 came from individual donations from the faculty and staff of the University of Alabama. In addition, the State plans to fund approximately $1 million of the total costs.

Mr. FLOOD. What are the advantages of putting such a center in Birmingham in addition to plans which have already been made?

Dr. BAKER. Birmingham, Ala., is an excellent location for this center. It is centrally located and is an important air and rail transportation center. It has an excellent medical school and within Birmingham there exists a southern research institute which provides a tremendous research base for smooth coordination with the activities. I would anticipate effective interactions with cooperating institutions in Alabama and in other areas in the Southeastern United States.

Mr. FLOOD. Have any definite plans been made for the facilities?

Dr. BAKER. A long period of planning has preceded the present state of development. The University of Alabama was awarded an exploratory grant by the National Cancer Institute to aid in the planning of the cancer center. A program facility development report has been prepared through the activities of the center staff and through a contract with a private firm of consultants. These plans are now in a state where they are ready for operational implementation.

Mr. FLOOD. How much will it cost to get this facility started?

Dr. BAKER. Additional startup costs for this center will amount to about $7.5 million. This includes construction costs and equipment and supplies. Operational costs will amount to approximately $2 million per year.

Mr. FLOOD. How will the operation of the center be financed if it is built?

Dr. BAKER. Direct patient services of the center will be mainly self-supporting. Support for training and research will be sought from various agencies in the Department of Health, Education, and Welfare such as regional medical programs and the National Cancer Institute. Other sources of support will be expected to come from foundations and private donations.

Mr. FLOOD. Have any plans been made so that this facility will serve the people of the Southeast?

Dr. BAKER. It is planned that the facility will be involved in the treatment of over one-fourth the patients now being treated for cancer in Alabama, plus about 650 new patients per year from out of State. In addition to this, a network of computers will coordinate the treatment patterns of cancer patients throughout the southeastern region.

Mr. FLOOD. Have funds been granted from the National Cancer Institute to plan or operate such a facility?

Dr. BAKER. As I indicated, the National Cancer Institute has awarded a 2-year grant for planning purposes so that a cancer center may be developed in Birmingham, Ala. The first year award was in the amount of over $100,000 and the second year award for fiscal year 1971 was over $130,000.

Mr. FLOOD. Mr. Michel.

COMPREHENSIVE CANCER INSTITUTE ADMINISTRATIVE PLAN

Mr. MICHEL. In your testimony you speak of developing a comprehensive plan. Is this a condition precedent to getting an infusion of an extra $100 million, or was that a comprehensive plan that would have been put into effect whether or not you had this extra $100 million or had $200 or $300 million added by the committee or somebody on the floor?

How did that come about? You make mention in your testimony something about S. 34. That hasn't even come out of committee yet. What are we talking about here anyway?

Dr. BAKER. As you know, we testified last year to the developments of research planning in the Cancer Institute over the past 8 years, and two of our major programs areas utilize this kind of research programing with heavy planning.

This is the chemotherapy program and the etiology program, which includes the cancer virus and chemical causation studies of cancer.

I think we have reached the stage where we now know how one goes about setting forth the program in a total overall, coordinated way which we didn't know how to do in earlier years. In reviewing the program we have reached the stage where we feel it is timely to lay this out for a total NCI effort.

Frankly, we didn't think we were ready to do that in the past. So we have reached a stage of development where this kind of planning can now be done. I don't think we can implement anything like that without additional funds. It does tie in in that sense with the $100 million that we are now ready with such planning capability.

What we see needed in the coming year is really a more detailing of the specifics of this plan. In it we want to engage many scientists throughout this country in this process, not only to get their inputs but to make sure that they are part of this and hopefully that they will become motivated and interested and make the necessary commitment to this national interest.

PROFESSIONAL SUPPORT FOR THE CONQUEST PROGRAM BEING IN NIH

Mr. MICHEL. The article I read in yesterday's paper with respect to the number of distinguished medical scientists around the country representing medical schools, indicated that they are in accord generally with our making this big push and effort through the established Institutes of Health rather than setting up some independent autonomous unit that would itself take this on.

Dr. BAKER. Yes, sir. I think most of the medical schools and professional societies have gone on record to that effect. Dr. Marston has been in communication with these people.

Dr. MARSTON. The only exception I know of is the American Cancer Society, although there was some confusion about the American Heart Association's testimony on this. Groups ranging from the representatives of the practicing professions, such as the AMA, to the representatives of the administration of medical schools such as AAMC, to the chairmen of the departments of medicine, which I think you were talking about here, the federated professional societies, the basic scientists, have all backed the need for serious and accelerated research in the cancer area and, in many instances, have come out quite strongly against separating the support and administration of cancer research from the support and administration of other areas of research.

What is happening in Atlantic City right now is that two groups are meeting there. These meetings for the exchange of scientific information attract more people working in clinical research than any other meeting at any other time. That is the reason 77 of the chairmen of the departments of medicine throughout this country were avilable at that meeting to sign this resolution which will be a part of the record.

In addition to that, the senior organization, the Association of American Physicians, which is having its meetings now and its scientific dinner tonight, which I am going to attend, there is an intermediate group which represents the best of the clinical investigators, called the Society for Clinical Investigation.

Their council also passed a resolution this past week calling for the maintenance of the cancer research effort within NIH. This group includes not only individuals in medical schools but also individuals who are not in medical schools.

Mr. FLOOD. You will have that for the record, too?

Dr. MARSTON. Yes, sir; we will.

What I want to make clear about the importance of these meetings is the fact that whatever we are going to accomplish in the area of cancer research, or any other research, particularly as it involves patients, is going to have the wholehearted support of this group of scientists who are the people in this country who will be doing the research in cancer and in other fields.

Dr. BAKER. I might add the American Cancer Society is not in disagreement on any issue about moving ahead with the enlarged effort, only how.

PROGRAMING THE $100 MILLION FOR CONQUEST OF CANCER

Mr. MICHEL. Tell me about any new planning or restructuring of your research as a result of this additional $100 million you are pro-

posing. What I am getting at now, with this infusion of an extra $100 million plus the other increases, is it just an expansion of those same general areas and approaches or are there some new general categories?

Dr. BAKER. Let me see if I can summarize how we see the new planning and structure. We must continue to insure the supply of new leads. Here looser coordination is ideal for insuring the diversity one wants. So we would see a continuation certainly and expansion of the typical grant supported, investigator initiated type of program.

Second, we would see expanding along the same programatic coordinated effort in therapy that we have been doing with one exception. We have not developed as far in combination therapies between drugs and surgery, and drugs and radiation as we would like to go. Nor have we been able to develop in the various kind of common cancers as far as we would want to go.

I would see expansion and more attention to some of the more common forms of cancer as well as the qualitative expansion of drugs, therapy, and combination therapy.

In the virology area we wouldn't see much change. That areas is well laid out and moderately well funded and moving well, so it would continue pretty much as is with some enlargement.

We hope to expand some diagnostic work. The leads are not plentiful here so we will not be able to develop that very far, but by getting more people interested in that program and laying plans in further detail than we now have we would expect to expand that further.

We would expand task forces where we take a particular important form of cancer like colon cancer or cancer of the large bowel, and lay out full plans involving causation, prevention, diagnosis, and treatment aspects. We have these preliminary plans laid now and they need more work. These multiple approaches—that is, both the coordinated, and the less tightly structured programs—we think constitute proper balance here.

Last, the cancer centers. The grants we have had we think are important both in terms of the larger institutes that have the various disciplines tied together around cancer, like the M. D. Anderson Hospital & Tumor Institute in Houston—Mr. Casey is well familiar with that wonderful cancer organization—and in terms of specialized centers, including departments of radiation where we hope to strengthen radiotherapy research and add around them additional disciplines and specialties. We expect to expand center activities appreciably and in more geographic areas. We have already been successful in some areas of starting out in a radiation therapy program and then strengthening other aspects of cancer around that theme.

We would hope to do all of these things as main thrust. So in one sense it is more of the same but quite different in quantity and emphasis. We would see more coordinated efforts in much of the addition.

Therefore, it is important to have what I call a "nervous system" tying together all of the parts and getting information on all of these activities, putting them together and redistributing derived information. We have made some progress in communicating to practicing physicians the latest results in drug therapy, but it is not adequate. I would see additional efforts on disseminating information.

OPTIMAL LEVEL OF $100,000,000

Mr. MICHEL. There will probably be some attempt, if not in our full committee, then on the floor of the House, for Members to make all kinds of hay. They will say regardless of what this subcommittee might do, they want to do more. They think they can get more points back home by raising our $100 million to $200 or $300 or $400 million. We have gone over this hurdle a number of times before.

What arguments do we use against those who would band together and say "Let's add another few hundred million dollars to get this done. What you fellows are talking about is chicken feed."

I am not saying that from my point of view, but we will get that kind of argument, I am sure.

What do we use to combat those arguments to keep this program, hopefully expanding as fast as we can, but as wisely as we can also?

Dr. BAKER. Certainly there will be different judgments on the rate of expansion by knowledgeable people here.

We picked a round figure in the $100 million increase. We thought this was proper in view of the aspects of the scientific leads, constraint in manpower, space and so on.

One of our most critical factors is manpower in expansion. We think the $100 million addition is a prudent level of addition that can be effectively carried out.

A lot of discussion went into this not only by our own staff but with many of our advisers. So in our best judgment that is the best figure.

We have made some projections of resource needs. The question of whether you are going on up to higher levels, of course, is not definitely answerable, but we studied the possibilities of different rates of expansion to higher levels. We did get into manpower constraints as we tried to look at some of these larger levels. Frankly, we have studied the possibilities of $1 billion a year. But we don't think it would be feasible to hit that level before about 5 years from now.

Again, if you look at it from that point of view, the $100 million seems to be about the right kind of level of expansion even if you want to go to those higher levels. So these kinds of answers I think are perhaps the best to give.

Is it possible to go to another level? Perhaps. I think we picked the best figure we could.

BUDGET AND TIME CONSTRAINTS

Dr. MARSTON. The manpower constraints and the construction constraints and the time constraints that Dr. Baker has just pointed out are things that one has to take into consideration.

There often is a confusion about different types of research. We are probably going to get a high payoff in the chemical causation screening programs up to a certain level, but there is still some advantage in going beyond that level though the payoff will probably not be as great when you screen either less likely candidates, as carcinogens, or screen compounds that are not released into the environment in as large quantities.

Dr. Baker and others in the Cancer Institute have tried to look at all of these factors. Something that is released in ton quantities becomes more important to study than something that is released in 10-pound quantities.

There is no real answer to how much money can be spent in cancer research. We have maintained a rather clear distinction between the cost of patient care for research purposes and the cost of patient care per se. If you ever get into paying more and more of the costs of the care of cancer patients, you expand by many fold the number of dollars needed.

ESTIMATED OBLIGATIONS IN FISCAL YEAR 1972

Mr. MICHEL. Of the $334 million budgeted for the fiscal year 1972, about what proportion or percentage of that would you consider to be a kind of a contingency fund? Is there anything?

Dr. BAKER. I don't really approach programing that way. We try to have our plans made pretty thoroughly and beyond current resources, and programing with adjustments that are continually made as new information becomes available, so we don't set aside contingency funds.

There have been occasions where we set aside an amount of money in my office, let's say 10 percent, to have the program leaders recompete for it along toward the end of the calendar year which we find useful to keep everybody on their toes and make sure they are updated. We really have it all planned and well laid out and we readjust implementation continually as required.

NCI FUNDS FOR EVALUATION

Mr. MICHEL. What amount of these funds would you say would go for evaluation of what you are doing, what you are finding? Is it possible to put a handle on that?

Dr. BAKER. Yes, sir. Part of the expansion of the item called "program direction"—you may have noticed it has a larger than usual increase—is to develop information systems much more fully than we now have for two kinds of things—first, program monitoring on how well we are doing. Are the programs doing what our plans call for and do we need improvement there? Second, to develop information systems gleaning information from all over the world and feeding it back out not only to our investigators but to practicing physicians.

Mr. MICHEL. Expand on that for the record, if you will. I think that is a very important part of it, knowing where we are going, keeping tab on what we have done.

(The information follows:)

A MANAGEMENT AND RESEARCH INFORMATION SYSTEM FOR CANCER

Regardless of how well the cancer research programs are planned and implemented, their optimum effectiveness as the instruments for achieving the desired objectives in cancer cannot be realized unless the work being performed is continuously evaluated with respect to how well it is progressing toward the achievement of program objectives, and the further assessment of this achievement in terms of future directions and courses of action. Program monitoring provides the information which forms the basis for the decisionmaking required to operate and modify ongoing programs so as to maintain the condition of performance as optimal as possible.

Thus, one of the major tasks ahead in planning for the cancer research is the design and operation of a management information system, national in scope, which will be responsive to program needs. In the course of planning the research to be conducted for the achievement of defined objectives, the specific types of data needed to satisfy critical decision criteria will be specified. The management information system for the program must be the instrument whereby these critical data are collected, processed, put in the appropriate format, and dis-

seminated to the appropriate program managerial control points for evaluation and action. Special attention will need to be given to obtaining cooperation of the scientific community for generation of the information in the requisite form.

As research programs are conducted, the management information system, through the process of monitoring, provides program management with information on four important elements of the ongoing work:

(a) Fidelity (or relevance): is the work being performed, the work that was specified, and are associated activities necessary and directly related to the achievement of established objectives.

(b) Quality: is the work being performed at a level or caliber commensurate with generally accepted criteria requisite to the successful accomplishment of given activities; or in accordance with quality standards specifically established for a particular activity.

(c) Rate of performance: is the specific work being performed at a satisfactory and acceptable pace when compared to a realistic, anticipated rate of accomplishment.

(d) Prospectiveness: what do the results of the work mean in terms of future courses of action and activities.

Although program monitoring is performed usually on an intermittent basis (i.e., usually scheduled—every week, every month, three times per year, etc.), the management information system should be designed so as to allow for continuous monitoring (i.e., provide a more-or-less uninterrupted flow of data) for critical situations or projects when this is warranted.

The system should efficiently process three basic kinds of data important for monitoring purposes:

(a) Direct data: all the data which are a direct result (output) of the accomplishment of an activity or activities.

(b) Representative data: The selection from all data generated, particular bits of direct data on the basis that the selected bits will provide an acceptable and valid representation of all the data generated.

(c) Derived data: the utilization of certain selected bits of data from the total data generated in an adapted, manipulated, or devised form to produce a type of data which is not found in this form in the total direct data generated.

The NCI has formulated the principles of monitoring technical progress in research and development contracts, and has applied these principles in its current research programs funded by contract. However, there does not exist one management information system with a network of loci functionally integrated for the purpose of monitoring the operation of a single national program effort—this will have to be developed.

In addition to a system for management information, it has been proposed that the NCI also have the responsibility to develop a system for providing research information from the world's biomedical literature to investigators in cancer and to practicing physicians. There is considerable question whether the value of such a function is worth the cost, but it appears that such activities are expected from many quarters. This clearinghouse function, or cancer data bank, will perform a variety of functions: provide information on demand, possibly preparing and selectively disseminating specific information to individual scientists based on profiles of interest; compile and disseminate periodic reports, abstracts, indexes, and so forth; and generally serve as the research communication link between investigators within the program, and between the program and investigators and practicing physicians who are not directly participating in cancer research programs.

The establishment of an international data bank for cancer research represents an extremely difficult undertaking because of the great diversity of informational needs of cancer researchers around the world, and the large number of diverse information systems which already exist in many countries, cancer research organizations, and professional areas. An effort to consolidate, synthesize, and integrate all informational needs and existing information systems into a single international cancer data bank would include, as a minimum, the following steps:

(a) All countries interested in participating in, contributing to, and supporting the data bank would be identified, and each country would assign one professional to the planning group for the data bank.

(b) Since a data bank that would provide all desired functions to all users would be impractical to operate, the first function of the planning group would be to clearly define the performance objectives of the data bank, that is, information on demand, periodic selective dissemination, etc.

(c) Once the ingredients of the target system are established, then a comprehensive survey and analysis of existing systems throughout the world would have to be made to determine the extent to which the desired objectives of the overall data bank are already being met by existing systems, and also to establish the discrepancies between existing systems and the data bank.

(d) The actual design of the international system would then take place with specific operating plans (software) for each of the key system functions (data collection, storage, retrieval, dissemination, etc.). Selection of the hardware for the system (on-line and off-line) would have to be based on the consideration of existing systems and methods for making maximum use of existing equipment.

(e) The last phase would be a carefully worked out implementation plan in which the major participants in the international data bank would each carry out a particular segment of the effort until the network of control centers was established in each participating country. As with all information systems, a central processing and operating headquarters would have to be established responsible for the overall surveillance of the international system in addition to providing the informational services for the participating country in which it would be located.

Currently, there is no one data system for cancer research information in the sense of a specifically planned operation with common characteristics formulated before hand. Rather, the "system" consists of the traditional communication accomplished through the publication of research papers in scientific journals, the reporting of prepublication data in documents specifically for this purpose, the publication of abstracts, summaries, indexes, and special reports by areas in cancer research, and the publication of the proceedings of the major symposia and meetings held in various disciplines and areas in cancer research. Most investigators consider the need to selectively identify those sources of data most pertinent to their research as part of the research process. In addition, there do exist information systems in many cancer research institutions tailored for both general and specific needs of the cancer researcher, and some national systems (e.g. Medlars, see below) which can be used for both general and specific requirements.

Medlars (Medical Literature Analysis and Retrieval System) is essentially a large-scale, computer-based operation for biomedical reference storage and retrieval. The system whose input depends on a detailed surveillance of 2,300 biomedical journals is designed to provide ready and rapid access to the biomedical literature for scientists and physicians. Besides the Medlars at the NIH there are several regional Medlars centers in the United States and a number of Medlars centers in Europe as well as in Japan and Australia. The chief output of Medlars is index medicus, current catalog, recurring bibliographies, and demand bibliographies, as well as a host of special publications, which are issued periodically. Since it became operational in 1964, new generations of the system have been developed and have enhanced the speed and effectiveness of Medlars. A recently inaugurated experimental service, AIM–TWX, will add versatility and flexibility to the basic type of service performed by Medlars.

The limitations of Medlars are essentially those of the medical literature. There is in many instances a great lag between the completion of a research project and the publication of the definitive article describing and analyzing the study. While Medlars can provide rapid access to the printed words, it cannot shorten the period required for publishing the words. Thus in terms of certain research fields there may be a considerable lag in time and relevance between what has been reported and what is now ongoing. Some important work may be also reported in journals not covered by Medlars and thus may be overlooked. This would be particularly true from the viewpoints of many foreign scientists whose main biomedical interests and problems would not be reflected adequately in the journals now surveyed for Medlars. Moreover, the information is not generally stored and cannot always be retrieved in forms required to influence certain program and research decisions. Conversely, there is a great deal of information that is collected, stored, and used little or if retrieved does not provide useful information. Furthermore, the scientists in many research fields rely on sources other than Medlar searches or even the recent literature to provide information influencing their research activities or updating them on the state of the art.

Thus, as a means for storing and providing rapid entree to a vast body of biomedical information, Medlars could constitute a valuable although limited constituent of any comprehensive international data bank. It would be neces-

sary to develop other techniques for generating, collecting, analyzing, organizing, and disseminating information that would be truly useful to the investigator in the course of his research, and to the physician in the course of his practice.

A very careful analysis should be made of the investment versus expected return from an international data bank for cancer research before an effort of this scope is undertaken.

FUNDS FOR ST. JUDE'S HOSPITAL

Mr. MICHEL. I have had some complaints from parents of the young people going to St. Jude's Hospital down in Tennessee from time to time. I think I have 12 or 14 from the Peoria area there. They have been told because of a reduction in funds from NIH or a lack of funds, they are having to curtail some of the things they have done before, and then those persons in turn have been getting in touch with me.

If you can't off the top of your head at this point, could you for the record give me an idea what the problem is there? How much support do we give to that particular hospital from NIH?

Dr. BAKER. One of our largest grants is to Dr. Pinkel and his group at St. Jude's. They have as good a record as any in treating child leukemia. I might say they have added to the combination drug treatment the use of radiation to make an important advance in treating some kinds of leukemia children. We testified here in the past that one of the problems of treatment failure of leukemia results from leukemic cells lodging in the brain and many drugs don't get into that area of the body because of the so-called blood-brain barrier.

There are two approaches here: One, to find drugs that will cross that barrier. We have some drugs doing that now. Two, to irradiate the brain with radiation to kill those cancer cells. Dr. Pinkel has had some outstanding success by combining radiation and drug therapy.

At the time the complaints were made, I think it was in that period when we were not able to let Dr. Pinkel and his group know whether we would be able to fund because of the timing. We did not yet have our apportionment. In the past month and a half Dr. Pinkel was here and at that point we did learn what our budget levels were. We were then able to fund a number of projects that were being held up. So the situation is much improved.

CEILINGS ON GRANTS TO COOPERATING GROUPS FOR CHEMOTHERAPEUTIC DRUGS

There is one other item on the cost of drugs. We have had to put some ceilings on the availability of drugs used in chemotherapy.

Mr. MICHEL. What do you mean by ceilings?

Dr. BAKER. The amount of drugs or dollars for drugs available to the cooperating chemotherapy groups of which Dr. Pinkel is one. The cost of drugs has been skyrocketing in chemotherapy as in other areas. We have two kinds of these drugs: those commercially available and those not.

We supply the drugs to these research groups from our own chemotherapy program if they are not commercially available. For those that are commercially available, dollars are supplied in two ways. We supplied some through the cooperative group funding and some money was put into the grants for this purpose.

This was getting a bit out of hand for the money available and also because the degree of flexibility available to these cooperative groups allowed them to order drugs we think beyond the research needs. So we put a ceiling on the amount of money and drugs that were made available. This led to some cutbacks which pinched in some areas and led to a few objections.

We will ease the problem a little bit if the budget is increased to make up for some of it. I think it was prudent to put some constraints on it. There was an indication it was getting beyond research needs. I don't mean in that particular place but in general.

Mr. MICHEL. The reasons this gets so much visibility at home is that this particular hospital has raised a considerable amount of money locally, and I think the figures show Peoria does better than any other community in the country, probably because we have a large Lebanese community. With all of that attendant publicity, the children and their families are more inclined to be tuned into that.

Dr. BAKER. This is something to be proud of.

Mr. MICHEL. It is.

INCREASED STAFF IN FISCAL YEAR 1972

With this expanded effort, how many additional personnel are you requesting in your new budget?

Dr. BAKER. We are requesting 250 positions.

Mr. MICHEL. And those will be in what categories of employees?

Dr. BAKER. The only difference from adding staff in the conventional sense would be to add more people in systems planning, analysis, and the tying together of the information I was talking about. We will give heavier weight to that than would be customary in the past. We hope to be able to use perhaps some systems engineers but the number will not be great.

We are also urging some of the centers to begin to think about utilizing the systems specialists in helping operate the larger cancer centers and some places are agreeing with us and looking for some people now.

Mr. MICHEL. You are aware of the attitude with which our committee usually looks upon increases in personnel in any Government agency, and that generally speaking the subcommittee want real good hard justification for increased personnel. It is not unknown for those personnel requests to be cut in half or cut by 25 percent or cut out altogether.

What would be the effect if the committee did not see fit to go along with the entire 250 people you are requesting?

Dr. BAKER. First, I would like to comment that we are down 83 positions since 1968 during which time our program magnitude went up nearly $55 million, and in some areas frankly it is beginning to pinch a little.

So we would hope we would get help here. Whether 250 is the right number, this was again our best judgment. We have in the record available if you would like it, the kinds of positions and we did touch on this at the hearings last week. We can elaborate for the record if you wish.

(The information follows:)

POSITIONS REQUESTED FOR EXPANDED CANCER RESEARCH EFFORT

The 250 positions would be utilized in three broad categories: Program planning and staff management; program managers to run large segments of the program; and expanded and additional in-house laboratory and clinical research. Some of the positions will be used to establish the new organizational structure called for by the President; that is, to appoint a director of the cancer conquest program, provide him a supporting management staff, and advisory council.

More specifically, the 250 positions will be utilized as follows:

(A) LABORATORY AND CLINICAL RESEARCH (NUMBER OF POSITIONS, 35)

Emphasis would be placed on the areas of (1) immunology, tissue responses to infections, and cell membrane changes; (2) mechanisms of genetics control and differentiation of cells from normal and abnormal conditions; (3) alterations of structure and functions of tissue in diseased states; and (4) enlarging our concepts of how disease conditions develop, such as gaining further understanding from nutrition, molecular biology, biochemical, metabolic, and other studies.

(B) CAUSATION AND PREVENTION (NUMBER OF POSITIONS, 97)

This would consist of etiology activities pertaining to viral oncology, chemical carcinogenesis and demography. Methods for prevention and control of virus-related human cancers are being developed, and the relation of these viruses to human cancers must be precisely elucidated. In the area of chemical carcinogenesis, emphasis will be given to developing more rapid and more sensitive means to detect and bioassay the cancer-inducing effects of chemicals on man, and to develop better means for the removal of hazardous chemicals from the environment.

(C) TREATMENT (NUMBER OF POSITIONS, 68)

Research on treatment of cancer will be expanded, with emphasis on chemotherapy. Major effort will be placed on the development of cures (and improved palliation) for patients through the development of drugs that will selectively control the cancer tissues. Principles learned over the past several years can now be extended to screening of drugs for treatment of the more common tumors, and clinical evaluations of new drugs and treatment combinations can be profitably extended to more types of cancer patients.

(D) TASK FORCES (NUMBER OF POSITIONS, 13)

Research on lung and breast cancer will be expanded. Preliminary planning efforts are just getting underway for bladder and prostate cancer. We will be making plans for establishing task forces for brain and pancreas.

(E) SCIENTIFIC AND ADMINISTRATIVE SUPPORT TO GRANT ACTIVITIES (NUMBER OF POSITIONS, 12)

These personnel will be used in the expansion and addition of new cancer research centers.

(F) PGOGRAM PLANNING AND MANAGEMENT (NUMBER OF POSITIONS, 25)

The program planning function cannot be over-emphasized. Program approaches will be set up to attain the goal of prevention of all human cancers. We will organize a series of program objectives formulated in terms of key problems to be solved. After the key problem definitions are selected, optional R. & D. program approaches aimed at solving each problem will be formulated. Also it will be necessary to develop operational and managerial objectives, as well as accountability for results in the conduct of the program. Plans will be initiated for a "nervous system," a central information means for data analysis, decisionmaking and program implementation. The establishment of the cancer conquest program will require additional staffing. In addition, positions will be needed to take care of the increased workload of public inquiry information activities.

Dr. MARSTON. As a general thing, Mr. Michel, I think Dr. Baker was using the right figure of speech when he said it was beginning to pinch a little bit. Throughout NIH we are having serious problems

in carrying out programs in effective fashion because of the pinch. It is a lack of men. It is one of our major problems and I am sure you will hear this from the other institutes.

ASSOCIATION OF SUGAR CONSUMPTION AND CANCER

Mr. MICHEL. I have been reading articles recently that raise a question about possible association of heart disease and certain cancers, and sugar consumption. Can you tell us anything about this, particularly what studies you might presently be funding and if you have any specific plans for this?

Put that in the record.

(The information follows:)

ASSOCIATION OF HEART DISEASE, CERTAIN CANCERS AND SUGAR CONSUMPTION

There are no data to show that sugar directly causes either cancer or heart disease. It is now generally acknowledged that development of coronary heart disease is influenced by a variety of factors which may include exercise, diet (particularly fat intake), high blood pressure, weight, smoking, and so forth. There are some scientists who suggest on the basis of certain data that high sugar intake may play a very important role, by influencing body metabolism, in the causation of atherosclerosis and coronary heart disease in certain susceptible people. There is also disagreement with this point of view based on other studies. It is reasonable to believe that sugar intake along with many other factors is involved in the development of coronary heart disease, but the exact weight that can be given these factors—alone or in combination—will be determined only from continued research.

In the case of cancer there are no data at all to suggest that ingested sugar serves directly as a carcinogenic (cancer-causing) agent. It has, however, recently been suggested that the nature of the diet in Western countries (with a high content of refined carbohydrates, including sugar) may play an important role in the high incidence of cancer of the large bowel in the United States, Canada and a number of Western European countries. The idea is that such diets, which contain less roughage than the diets of other countries with a low incidence of colon cancer, tend to promote slow passage of materials through the intestine. Thus, it is suggested that carcinogenic substances that may be in the stool will remain in contact with the colon for considerable periods of time, resulting in a high incidence of colon cancer. Although it appears likely, on the basis of studies of different populations, that diet does play a role in the causation of colon cancer, there are insufficient data to support the theory that high carbohydrate and low ronghage content is the determining dietary factor. There is certainly no information to suggest that ingested sugar as such is a cause of cancer of the colon or any other body site.

NCI ADVISORY COUNCILS

Mr. MICHEL. Dr. Baker, you have various advisory committees and councils. There are a number of them are there not?

Dr. BAKER. Yes, there are.

Mr. MICHEL. Could we have those spread out in the record here?

Dr. BAKER. We can supply that.

(The information follows:)

NCI ADVISORY COMMITTEES

The National Advisory Cancer Council is established under section 217 of the Public Health Service Act. A listing is provided below of those committees established under section 222 of the Public Health Service Act. In addition, many working groups and subcommittees are utilized which carry out specific segments of the research engaged in causation, treatment, and diagnosis of cancer.

Board of Scientific Counselors.

Cancer Clinical Investigation Review Committee.

Cancer Research Center Review Committee.

Cancer Special Program Advisory Committee.
Chemotherapy Advisory Committee.
Clinical Cancer Training Committee (Dental).
Clinical Cancer Training Committee (General).
Etiology Program Advisory Committee.
Cancer Research Training Committee.
Medical Care and Medical Economics Advisory Committee.
Carcinogenesis Advisory Committee.
Epidemiology Advisory Committee.

Mr. MICHEL. That is all, Mr. Chairman.

CAUSES OF RISING CANCER INCIDENCE RATES

Mrs. REID. How do you account for the fact noted in your statement on page 2, that new cancer cases are appearing at an even greater rate than the improved rate of cures?

Dr. BAKER. The cancer incidence rate of new cancer cases is increasing faster than is the survival rate for some sites. This is particularly true of lung cancer incidence which has increased more than threefold in the past 25 years. Survival is particularly poor for lung cancer—the 5-year relative survival rate showed only a twofold increase from 4 percent in 1940–49 to 9 percent in 1960–64. This is the most common site of cancer among men, and while it is not as common in women as in men, it is increasing at the same rate. I will be pleased to submit other examples for the record.

INCIDENCE RATE OF SELECTED CANCERS

The incidence of bladder cancer has increased from 14 to 23 per 100,000 in the past 25 years (64-percent increase), while the 5-year relative survival rate increased from 41 percent to 57 percent (40-percent increase).

The incidence of pancreatic cancer has increased among men from 6 to 10 per 100,000 (a 67-percent increase), while survival has shown little or no increase remaining at between 1 to 2 percent 5-year survival.

The incidence of colon cancer has increased from 22 to 31 per 100,000 (a 40-percent increase), while survival has increased from 39 to 41 (a 10-percent increase).

The incidence of prostatic cancer has increased from 27 to 39 per 100,000 (45 percent), while survival has shown a 5-year rate from 37 to 53 percent (a 43-percent increase).

IMPORTANT FOREIGN RESEARCH

Mrs. REID. What research of importance in the cancer field is being done by scientists in other countries?

Dr. BAKER. Mrs. Reid, we have a little over $1 million in contracts outside the United States, about $135,000 in research grants, and about three-quarters of a million dollars paid from Public Law 480 foreign currency funds. All of these projects have special characteristics which provide a uniqueness that cannot be matched within the United States. For example, in conjunction with our viruses breast cancer studies, we have a project in India in which we are determining whether the type B viruses occur more frequently in Parsi women in India who are known to have a much higher risk to breast cancer than other groups of women. Preliminary results indicate that virus particles are found in the milk at a much higher frequency than is the case in normal women. Several important epidemiologic studies involving different population groups are funded as projects outside the United States; several of these are essential for comparisons of

cancer incidence in similar population groups that have migrated to other countries, including the United States.

To save time, I will submit as an insert for the record, with your permission, a list of projects important in the cancer field conducted outside the United States.

(The information follows:)

RESEARCH OF IMPORTANCE IN THE CANCER FIELD OUTSIDE THE U.S.

Country and principal investigator	*Title*
India: Dr. M. L. Dhar, Central Drug Research Institute.	Development of Therapeutic Agents Against Cancer.
India: Dr. D. J. Jussawalla, Secretary ICS.	Study of Distribution of Cancer Cases in Greater Bombay Hospitals and Generally Throughout the State of Maharasthtra.
India: Dr. M. B. Sahasrabudhe, Cancer Research Institute.	Development of a Cancer Chemotherapy Laboratory at the Cancer Research Institute in Bombay.
India: Dr. L. B. M. Joseph, Christian Medical College Hospital.	Cancer Chemotherapy Radiation Trials.
India: Dr. J. C. Paymaster, Tata Memorial Center.	Study of Breast Cancer in Parsi Women.
Israel: Prof. Ephraim Katchalski Weizmann Institute.	Study of the Pharmacological Properties of Synthetic Oligo and Macromolecules.
Israel Prof. Michael Feldman, Weizmann Institute.	Immunogenetic studies on Tumors and Radiation Chimeras.
Israel: Prof. Isaac Berenblum, Weizmann Institute.	A Possible Two-stage Mechanism in Leukemogenesis.
Israel: Dr. Baruch Modan, Tel Hashomer Government Hospital.	An Epidemiological Study of Gastrointestinal Cancer in Israel.
Israel: Dr. Leo Sachs, Weizmann Institute.	Investigating aspects of enzyme induction and chemical carcinogenesis relative to lung cancer incidence; also investigating virus induced specific transplantation antigens.
Poland: Dr. Tadeusz Koszarowski and Dr. Jerzy Staszweski, Instytut Onkologii im. Marrii.	Epidemiology of Cancer in Poland and the Influence of Environmental Factors on Some Selected Forms of Cancer.
Poland: Dr. Karol Taylor, Institute of Medicine.	Identification and Control of Viral mRNA.
Japan: Dr. Toju Hata, Kitasato Institute Kitasato University.	Screening of Anticancer Antibiotic from Streptomyces.
Japan: Dr. Tosihide H. Yosida, National Institute of Genetics.	Chromosome Alteration and Tumor Development.
Japan: Dr. Iwao Hirono, Gifu University, School of Medicine.	Studies in Carcinogenicity of Cycasin.
Japan: Prof. Osamu Hayaishi, Kyoto University Faculty of Medicine.	The Mechanism and Function of Oxygenases.
Japan: Dr. Yohei Ito, Aichi Cancer Center Research Institute.	In vitro Virological Studies of Human Tumor Specimens.
Japan: Dr. Mitsuo Segi, Tohoku University.	Studies in the shifts in cancer risk among Japanese migrants.
South Africa: Dr. E. F. Rose, Rhodes University.	Evaluation of Transkeian Cancer Survey.
East Africa: Dr. D. Burkitt, Makerere College Medical School.	Studies on distribution and etiology of African lymphoma.
East Africa: Dr. Ian McAdam, Makerere University College.	Treatment of lymphoma using chemotherapy and immunotherapy; also epidemiology of the various lymphoma diseases.
Switzerland: Dr. H. J. Tagnon, EORTC.	EORTC cooperative clinical groups.

Germany: Dr. Gerhard F. Schramm, Max-Planck-Institut fur Virusforschung.	Function of nucleic acid in virus synthesis.
Denmark: Dr. Johannes Clemmesen, The Danish Cancer Registry.	Danish and International Cancer Review.
Sweden: Dr. George Klein, Department of Tumor Biology, Royal Karolinska Institutet Medical School.	Viral Tumorigenesis and Cellular Phenotype.
Sweden: Dr. George Klein, Royal Karolinska Institutet Medical School.	Cytogenetics of Variability in Cancer Cell Populations.
Sweden: Dr. A. Holmgren, Royal Karolinska Institutet.	Control of Enzymic Synthesis of Deoxy-Ribonucleotides.
Peru: Dr. Pablo Mori-Chavez, Facultad de Medicina.	The Effect of High Altitude on Neoplastic Growth.
Canada: Dr. Gold and Dr. Freedman__	Developed the carcinoembryonic antigen (CEA) testing method; potential diagnostic procedure for gastrointestinal tract malignancies.
Norway: Dr. Einar Pedersen, Norwegian Public Health Service.	Studies of Shifts in Cancer Risks Among Norwegian Migrants.
France: Dr. J. Dausset, Institut de Recherches sur les Leucemies.	Surface Leukocyte Antigens and Skingrafts.
France: Dr. Francoise Haguenau, College de France.	Role of Viruses in Entiology of Cancer.
Colombia: Dr. Pelayo Correa, University of Valle.	Epidemiology of Indian Populations in Colombia. Correlation with pathology data.
England: Professor Sir Alexander Haddow, Chester Beatty Research Institute of the Institute of Cancer Research.	Experimental Chemotherapy and Immunotherapy and Carcinogenesis.
England: Dr. A. M. Stewart, Oxford University.	The Survey Approach to the Problems of Cancer Prevalence.
England: Dr. Roger Berry, Churchill Hospital.	Radiation biology studies using high energy accelerated particles.

CONTAGIOUSNESS OF VIRAL CANCERS

Mrs. Reid. Has there been any further information developed concerning the possibility that virus-caused cancer may be contagious?

Dr. Baker. To date, there is no evidence that virus-caused cancer in animals is contagious to humans. Indeed, there is much evidence to the contrary. For example, extensive studies conducted by the National Cancer Institute have resulted in data which show no correlation between incidence of cancer in domestic animals and similar neoplasms as they occur in man.

It is only under special conditions that certain known animal tumor viruses can be made to infect human cell cultures. It must be understood that this is the exception rather than the rule. These are considered model systems and are excellent for the development of information which may lead to an understanding of a possible viral etiology of certain human tumors.

On the other hand, based on virologic, epidemiologic, and genetic studies, there appears to be some evidence that there is a predisposition to the development of tumors in certain human populations. This would indicate noninfectious transmission of information from parent to offspring. It could result in the later development of certain tumors. These studies have been confirmed in the model animal tumor virus systems where, again there is no evidence of horizontal transfer, but clear-cut data on the transmission of tumor-inducing agents.

ATTRACTIVENESS OF CANCER FIELD TO NEW RESEARCHERS

Mrs. Reid. Of those scientists and medical people who would be motivated to go into research, are they more inclined to come into the picture with respect to cancer as distinguished from heart disease or some other disease?

Dr. Baker. Mrs. Reid, in the past several other areas of medicine and research probably were more popular for investigators than the cancer area. I believe this has been changing and with the exciting developments in viruses and cancer, we have had more and more really outstanding scientists coming into the cancer field. Also, successes in drug treatment of some forms of cancer are attracting more clinical investigators into cancer. We believe that our programs have done much to interest additional investigators in cancer and have been able to develop and provide important resources which were not available prior to the development of our Etiology and Chemotherapy Programs. Some areas of cancer research are still not very popular, to a large extent, I believe, because of the slowness of the generation of results; these areas are: studies of chemical causation of certain types of cancer; cancer epidemiology, particularly on the chemical causation of cancer; and chronic toxicology and pharmacology studies. Since the leads are plentiful and the pace of several areas of cancer research is moving well, I believe we will attract sufficient manpower into the Cancer Conquest Program, but will not produce serious shortages in other areas. We will certainly try to be mindful of possible dangers should we seriously deplete other areas of biomedicine.

INFECTIOUSNESS OF CHICKEN TUMORS

Mrs. Reid. Last year there was some publicity concerning the fact that infected chickens may carry leukemia—has there been any further research in this area?

Dr. Baker. This publicity was unwarranted and not based on scientific fact. Over the past year, extensive studies in avian tumor research have been sponsored by the National Cancer Institute.

Results of these studies have shown that no virus of the avian leukosis complex nor their specific antibodies can be found in human patients with cancer. Further, the avian tumor viruses, which include the leukemia agents, do not infect or induce diseases in other animals tested, including human cells grown in tissue culture.

In addition, extensive epidemiological studies on large human populations have shown no evidence of increased cancer incidence among individuals with unusually high exposure rate to chickens or chicken products.

INCIDENCE AND TREATMENT OF SKIN CANCERS

Mrs. Reid. According to most reports skin cancer is the most prevalent among Americans, what research is being done in this field?

Dr. Baker. Malignant melanoma is one of the seven signal tumors employed in the chemotherapy program. Studies of three drug therapies, DCIT, BCNU, and BCNU plus Vincristine are currently being investigated against this form of cancer.

In addition, topically administered nitrogen mustard has been used successfully against mycosis fungoides. It has also been shown that

topically administered 5FU and some of the vitamin A compounds can cause regression of skin cancer in animals and these will soon be in clinical trial in man.

Some antitumor agents when topically administered, evoke a strong immunologic response against skin cancer as shown by Dr. Kline at Buffalo.

There are studies concerning the production of skin cancer by ultraviolet light and means to prevent this.

Several animal models for chemotherapy of skin cancer have been developed and new agents in the chemotherapy program are being studied in these models.

It should be pointed out that while skin cancer is the most prevalent form of cancer, it is lethal only in a small percentage of the cases.

I will provide for the record a report on the current status of skin cancer.

Report on Skin Cancer

INCIDENCE

Skin cancer is the most prevalent cancer among Americans, with approximately 200,000 new cases occurring each year in the United States. Although it is the most prevalent cancer only 2 percent of all cancer deaths are related to skin cancer—about 5,000 per year in the United States. The low mortality rate results from early recognition of the easily visible tumors. There are three major forms of skin cancer, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. The most common type—basal cell carcinoma, has a 5-year survival rate which approaches 100 percent primarily because it does not metastasize. The 5-year survival rate of squamous cell carcinoma patients is only 85 percent. This cancer can metastasize. The same is true for malignant melanoma, which has a 5-year survival rate of from 20 to 60 percent depending on the size of lesions when first diagnosed. *Mycosis fungoides*, a lymphoma of the skin, it is not as common a cancer as the three above, but does produce hundreds of new cases per year in the United States and has a 5-year survival of about 35 percent.

RESEARCH AS TO CAUSE AND PREVENTION

It has been long known that prolonged exposure to sunlight leads to skin cancer. In fact, ultraviolet (from sunlight) is considered to be the main predisposing factor to the initiation of skin cancer. The incidence seems to depend upon skin pigmentation and the amount of exposure to the sun. The trend toward suntanning in our population has resulted in an increase in the frequency of skin cancer. The reeducation of the public as to the dangers of chronic sun exposure, and the development of chemicals which could screen out ultraviolet from the sun, are two important areas of endeavor which should lead to reduced incidence of skin cancer.

Currently, important work is being done on the genetic skin disease, *Xeroderma Pigmentosum*, which is relevant to sun-induced cancers. As a result of inheriting a defective gene, patients with *Xeroderma Pigmentosum* cannot repair sunlight damaged DNA (the cell's genetic map or code) and die at an early age from skin cancer. Whereas normal people have an enzyme system which repairs this damaged DNA, patients with the *Xeroderma* gene defect cannot repair this damage. The role of DNA-repair system in preventing sun-induced skin cancer will likely provide information important to the prevention of cancer in people.

There are environmental factors other than sunlight, which serve as skin carcinogens. In fact, the first example of cancer causation with an environmental carcinogen in man was hydrocarbon chemical causation of cancer on the skin of the scrotum of chimney sweeps (Pott's tumor). It is important to identify these kinds of carcinogens and to eliminate them.

The main function of the skin is to serve as a barrier to the environment; that is, keeping the outside out, and the inside in. The skin cell divides and manufactures a tough protein known as keratin. This impervious keratinized cell serves as the chief barrier to the environment. The mechanism by which the balance of cell division and cell maturation is regulated, is one that is under study. Under-

standing this mechanism of control should lead to new insight into the mechanism of skin cancer, since cancer is a state in which ordinary normal cells become savage or cancer cells.

The other major cell of the skin is the pigment cell. When this cell goes out of control it leads to the malignant melanoma, one of the most vicious of all cancers known to man. Early diagnosis of metastases have been made easier by development of a radioactive chemical which specifically absorbs to melanin-containing cells and can be detected by a body-scanning device. Melanomas may sometimes arise from pigment cells in normal skin or from pigmented moles or birthmarks. Little is known as to how these cells become cancerous. Research is being done on the biology of the pigment cell and how the growth of these cells is controlled.

Viruses have been shown to be causative in many animal cancers. Now, evidence is accumulating to show that viruses are probably important in inducing some human cancers. One of the most frequent skin diseases in man is the common wart and warts are caused by viruses. The skin reacts to the virus by dividing at a rapid rate. In almost all instances the wart disappears as host defenses bring the wart under control. However, in patients with the genetic diseases, *Epidermal Dysplasia Verruciformis*, multiple warts containing the wart virus develop and these patients are unable to mount defenses against the wart and in many cases develop squamous cell cancers. Research into the mechanism of wart virus-induced cancers is potentially valuable research. Efforts are now underway.

TREATMENT

Surgery.—Since by its very nature, skin cancers are visible, they are diagnosed early. The most common form of treatment is surgical. This is feasible when there are limited number of lesions, which is usually the case. However, when there are multiple lesions or when there is metastases to internal organs, other forms of therapy must be sought.

Chemotherapy.—Many drugs have been developed for the treatment of cancer in man. Some of these when given systematically have been found to be therapeutic for skin cancer. In fact, some of the drugs when applied directly to the cancers from the outside have been found to be effective. This is true of 5-fluorouracil and nitrogen mustard. The latter has been used to treat lesions of mycosis fungoides and the former has been successful in the treatment of multiple keratoses which are premalignant. Specific drugs are being tailored for treatment for melanomas. Chemicals active against cancer cells are complexed with specific chemicals which preferentially absorb to melanin, concentration high doses at the tumor cell. New chemicals which absorb in high concentration within keratin-containing skin cells are also being developed.

Immunotherapy.—There is much research being done in the field of immunotherapy. It has been observed that if one produced an allergic reaction around a skin tumor, that in many cases the tumor disappears. It probably is not merely an inflammatory reaction which reverses the tumor, but some specific immunological phenomenon, perhaps a hyperreactive immune response. Also, antigens have been prepared from tumor cells. These antigens when injected into animals have been shown in some instances to be able to marshal a reaction against cancer in these animals. This kind of immunotherapy in man is proving to be successful in some forms of cancers.

OTHER GOVERNMENT RESEARCH ON CANCER

Mrs. REID. What other Government agencies besides the National Cancer Institute are supporting research on cancer?

How do you cooperate with these agencies?

Dr. BAKER. There are several Government agencies supporting limited research on cancer. The principal agencies involved are: the Atomic Energy Commission; Regional Medical Program, Health Services and Mental Health Administration; the Armed Forces Institute of Pathology; and the Veterans' Administration. In addition to the research supported by each agency, the NCI also provides additional research funds for collaborative studies, except the RMP. The staff of these agencies from time to time also participate as members

of our review groups. There is a constant exchange of information between the NCI staff and the staff at the various agencies.

PRIVATE SUPPORT OF CANCER RESEARCH

Mrs. REID. I believe in the past we have heard that cancer research has been supported by the private sector to the extent of $60 million or more.

What are the latest figures available and where does this money go? Does it complement or duplicate the research of NIH?

Dr. BAKER. The single largest contributor to cancer research from the private sector is the American Cancer Society. This past year it supported research projects totaling about $22 million. The Damon Runyon Fund and the Leukemia Society of America each funded research projects totaling about $1 million. There are many more private organizations devoting their energies and money to the local support of cancer research. Total support from the private sector certainly exceeds $60 million, but it is impossible to get an exact figure. These funds supplement and complement research support from Government and institutional sources.

Mrs. REID. That is all, Mr. Chairman.

Mr. FLOOD. Mr. Hull.

THE ADVISABILITY OF LIMITING NITRITE PRESERVATIVE

Mr. HULL. Dr. Baker, I noticed in an article which appeared in the Washington Evening Star on March 16 of this year that Dr. Lijinsky, a professor at the University of Nebraska in testimony before the House Intergovernmental Relations Subcommittee stated that the Food and Drug Administration should allow barely one-tenth the amount of nitrite preservative now permitted in cured meat and fish.

He went on to comment that high concentrations of these preservatives in certain foods might be as responsible for the prevalence of lung cancer as elements in tobacco smoke.

Would you agree that this is a possibility?

Dr. BAKER. This is a possibility. Dr. Lijinsky bases his statement on what ought to happen chemically when nitrites are in the stomach in the acid fluids. There is a possibility that nitrosamines could be formed. I don't believe he has showed they are in fact formed there.

The reason he mentioned lungs is that nitrosamines in animal experiments do produce lung tumors. It is a possibility, sir.

CARCINOGENS IN CIGARETTE SMOKE

Mr. HULL. Dr. Lijinsky was also quoted as stating that in spite of 20 years of work on tobacco smoke, no one has been able to identify enough carcinogens in it alone to account for the high incidence of lung cancer.

Do you agree with that statement, Dr. Baker?

Dr. BAKER. I agree if one adds up the respective effects of the individual components it is so, but we also know there are promoting agents in cigarette smoke which are not in themselves cancer causing, but enhance the activity of other materials that are and therefore the

combinations are more potent than the additions of the individual components.

DR. LIJINSKY'S RESEARCH GRANTS

Mr. HULL. Doctor, I also read in the Washington Post that Dr. Lijinsky has a National Cancer Institute grant for his studies at Nebraska's Eppley Institute.

Could you supply for the record how much was budgeted for this project in the past year and how much is projected for future years?

Dr. BAKER. Yes, sir.

(The information follows:)

SUPPORT OF DR. WILLIAM LIJINSKY

The National Cancer Institute currently supports a research contract with the University of Nebraska, Eppley Institute for Cancer Research. Dr. Phillippe Shubik is the principal investigator of the contract with Dr. William Lijinsky as a co-principal investigator. The level of funding for the contract for fiscal year 1970 was $1,201,600 and for fiscal year 1971 is $1,335,508. Continued support of the contract is planned, however, future levels of funding have not as yet been firmly established.

Mr. HULL. Isn't it possible, Doctor, that a significant part of lung cancer may have in fact been caused by nitrites?

Dr. BAKER. I think it is possible that some have. I don't think we have enough data today to even guess at what quantitative proportion it would be.

Mr. HULL. Wouldn't you agree, Doctor, that it would be foolish to say if he could eliminate any one of the suggested causative factors for lung cancer, we could eliminate all lung cancer?

Dr. BAKER. There are 18 materials in cigarette smoke that have been shown to produce cancer in animals. There are about 900 known compounds in cigarette smoke already identified. There are many more that have not yet been identified.

So removing one component I doubt would do the trick. I think we will have to modify the smoke or remove many of them before we will see a significant reduction.

OPPOSITION TO A SEPARATE CANCER PROGRAM

Mr. HULL. I understand that you recently appeared before a Senate Health Subcommittee and gave your opinion that you favored keeping the proposed increased cancer research program under the National Institutes of Health and that you opposed setting up a separate and independent agency for cancer research.

Why are you opposed to setting up a separate program for cancer research?

Dr. BAKER. I think the connection we have built in the National Institutes of Health in the operating aspects both at our end and from the rapport developed with the scientific units throughout the community will work best if the expanded activities are made within the National Institutes of Health.

I think the problem of pulling out, let's say, the Cancer Institute from NIH certainly offers some possible dangers to this excellent institution, NIH. I think the connections scientifically between the pro-

grams at NIH and the cancer work indicate that it is best making the decisions within that framework.

Perhaps Dr. Marston would like to elaborate.

Dr. MARSTON. We have made a number of statements on this, Mr. Hull. It comes down to the point that we do not believe that either cancer research or research generally will go forward as rapidly with the separate authority for cancer as it would by keeping it a part of NIH.

I think that is the most important question. On the negative side is the point Dr. Baker has mentioned, to try to have a national program that has one administrative channel for cancer, another for heart, another for arthritis, for infectious diseases, and soon would actually set back all of these programs significantly.

Mr. HULL. An editorial which appeared in the New York Times on Monday, March 29, said:

> Any expanded cancer research program should be organized in a way that it will assure it the closest possible links with all other basic biological research, and that will minimize bureaucratic barriers between researchers and research organizations. On that basis better funding for fundamental biological research through the National Institutes of Health would seem a sounder procedure than creation of a new separate cancer organization that could waste scarce resources on needless duplication.

I take it that you agree with this editorial?

Dr. BAKER. In principle, yes, sir. I think what we have tried to present here is a combination of the very fundamental research and applied developmental research, and this constitutes a continuum. Therefore, we see it best done together. In principle, then, I agree with the statement.

POSITION OF FORMER NIH DIRECTOR

Mr. HULL. Dr. James Shannon, the former Director of the NIH, has, I understand, expressed his opposition to the separate agency proposal by calling it "dangerously destructive." Instead of balanced biomedical research. Dr. Shannon warned, "emphasis would be entirely determined by uncritical zealots, experts in advertising and public relations and rapacious 'empire builders.'"

Do you agree with Dr. Shannon's appraisal?

Dr. BAKER. I don't believe I would go that far.

Mr. HULL. So you don't agree with Dr. Shannon's appraisal?

Dr. BAKER. I wouldn't say it quite that strongly, no, sir.

POSITION OF AMERICAN CANCER AND HEART ASSOCIATIONS

Mr. HULL. I have noted that both the American Cancer Society and the American Heart Association have publicly stated their support for the separate cancer research agency outside of the NIH. Interestingly enough, Dr. Campbell Moses, medical director of the American Heart Association, even went so far as to say—

> If we are successful in getting this major cancer emphasis implemented, those of us working in heart disease control particularly will certainly be calling for a similar program.

Now, Doctor, the fears expressed by you and your associates in your testimony before the Senate subcommittee and those expressed by Dr.

Shannon appear to be fully justified in view of the positions taken by the American Cancer Society and the American Heart Association.

Could it be that these are the "uncritical zealots, experts in advertising and public relations" that Dr. Shannon was referring to?

ADMINISTRATIVE FAULTS OF A SEPARATE PROGRAM

Dr. Baker. Certainly as I indicated before, one of the objections to creating a separate agency would suggest the next step might be the pulling out of the National Heart and Lung Institute which I don't think would be a helpful thing for either NIH or the heart field.

I might add we can't have every agency head reporting to the President. I think it would be a bad step to continue in this direction.

Mr. Hull. Then, if I understand your testimony altogether, Doctor, your position is that cancer research should remain under the National Cancer Institute and that you strongly oppose the recommendations by the American Cancer Society and the American Heart Association for a separate agency. Am I correct?

Dr. Baker. I oppose that recommendation for a separate agency; yes, sir.

Dr. Marston. Mr. Hull, in the recent conversations with the American Heart Association they have clarified their position as far as what they advise for heart.

I believe I can supply to you a statement of that position which is essentially the elevation of the Heart and Lung Institute to bureau status, but it would remain a part of the National Institutes of Health. I will see if I can make that available to you, Mr. Hull.

Mr. Hull. Thank you, Doctor.

Mr. Flood. Mr. Shriver?

CONQUEST OF CANCER ADVISORY GROUPS

Mr. Shriver. Dr. Baker, would you explain the difference between the functions of the Cancer Conquest Advisory Council and the Executive Task Force on the Conquest of Cancer?

Dr. Baker. The Cancer Conquest Advisory Council will have responsibility for the guidance and advice on the direction and accomplishments of the Cancer Conquest program. The functions of the Council are to provide: guidance in policy and program formulation, management overview of the programs and specific review of grants. The Council will be comprised of both outstanding scientists and top management experts. Appointments to the Council are to be made by the President. The Cancer Conquest Advisory Council will absorb the functions, responsibilities, and membership of the present National Advisory Cancer Council.

The Executive Task Force will be established to assure that DHEW and other Federal top management officials will give increased time and attention to the cancer research program and to guarantee frequent access of the Director of the Bureau of Cancer Research to the Secretary and senior health officials in DHEW. The task force will review program performance and problems. The membership will include: the Secretary of Health, Education, and Welfare; the Assistant Secretary for Health and Scientific Affairs; the Director, National Institutes of Health; the Director, Bureau of Cancer Research; and

the President's Science Advisor or his delegate. The task force will meet periodically to review plans, progress and problems. The group will meet with the President to present an annual report on the program and to discuss future plans.

DRUG CURABLE CANCERS

Mr. SHRIVER. On page 6 you say that of the 100 or more different kinds of cancer, about 10 have been shown to be curable by means of drugs. Would you identify those 10 types for the record?

Would it be possible to list the 100 different types of cancer and give some indication as to the state of the art regarding prevention and therapy for each as of this time? Such a list might be helpful to the committee and the public in the future in understanding whatever progress is accomplished by the Cancer Conquest Program.

Dr. BAKER. The 10 forms of cancer that respond favorably to drug therapy are: acute lymphatic leukemia, Choriocarcinoma, Wilm's tumor, Ewings sarcoma, Hodgkin's disease, Embryonal Rhabdomeyosarcoma, squamous cell carcinoma skin, Burkitt's tumor, Retinoblastoma, and some testicular tumors.

The term cancer is applied to a large group of diseases that have in common generally a high growth rate of abnormal cells which invade and destroy the surrounding tissues and usually continue to grow beyond the controls of the body that keep most cells in a normal state. Usually sooner or later if not treated, cancer cells break loose from the original body site of origin of the cancer and spread to other locations in the body through the bloodstream and lymphatic vessels, often reestablishing new growths called metastases. When these metastases are growing, the structure as seen through the microscope usually resembles the structure of the parent cancer which in turn usually bears some resemblance to the tissues of the organ in which the cancer originated. Occasionally, the changes occurring when the normal cells change into cancerous cells are sufficiently great that the structure does not resemble the tissues of origin. Most cancers also contain a mixture of cell types, and many tumors progress as they get older, sometimes changing the degree of malignancy, rate of growth, sensitivity to radiation and anticancer drugs, hormonal responsiveness, et cetera. The hundred diseases really refer to the different kinds of diseases resulting from the various kinds of cancers; these are generally grouped according to the organs in the body where the tumor originated. For example, we have cancer of the liver, cancer of the lung, cancer of the breast, and so on. However, within each organ there are often different kinds of cancer depending upon the precise kind of changes that occur when the normal cells are transformed into cancer cells. Moreover, even normal organs have different kinds of cells and cancers can arise from these different types of cells. Thus, we may have liver cancer which originates in the cells that make up the bile ducts in the liver or we may have liver cancer which originates from the main functioning cells of the liver (hepatic cells). The kinds of cancers thus resulting in the two cases, though both would be called liver cancers, are different and may produce different diseases in the clinic. Also, for reasons not understood, some organs rarely have any cancer originating in them at all. Cancers of the heart are extremely rare. Most kinds of cancer in the small intestine are essentially unknown. Cancers of the muscles are relatively rare. Cancers of lung,

breast, uterus, large intestine, prostate, pancreas and the blood forming tissues are relatively high.

The state of the art regarding research on prevention and therapy for each of these varies greatly. As regards treatment, one in three cancer cases are cured by surgery and/or radiation. Over 95 percent of skin cancer cases are being cured today. Less than 10 percent of lung cancer cases are cured, though some recent developments suggest we may be able to improve the results over the next few years. In the so-called rapidly growing tumors which include leukemias, chroiocarcinoma, Burkitt's and other lymphomas, testicular tumors, Ewing's bone sarcoma, Wilms' kidney tumor and possibly oat-cell lung cancer, long-term, disease-free remissions are occurring with the use of drugs, most commonly given in combinations. Some of these patients are being cured with drugs alone and we are probably beginning to cure childhood leukemic patients. Results with drug treatment of advanced, disseminated slow growing cancers of the more common types have not yet been as good as those with rapidly growing tumors which constitute 15 percent of the total. Important palliation has been achieved with many of these common tumors, and we may be beginning to see lengthening of remission in some cases. It is important to extend studies on determining optimal use of existing active drugs and develop new drugs selected against slow growing tumor animal screen systems mimicking the common human cancers. From developments of the past decade and one-half the state of the art is ready for expansions along these lines as has been detailed in other parts of this testimony.

CAUSATION AND PREVENTION OF CANCERS

Studies on causation and prevention of cancer have shown that about 1,000 chemicals can produce cancers in animals and 20 or 30 materials are known to produce cancers in man. Many cancers have been prevented by reducing or avoiding exposure to chemicals. I will include for the record a list of those materials that are cancer causing in man.

Chemical Agents Shown To Produce Cancer in Man[1]

The following list of agents consists of materials for which the evidence is very strong that they lead to increases in cancers in people exposed to the dangers. The weight of the evidence varies to some extent with different materials and is somewhat weaker for those compounds toward the end of the list.

1. β-naphthylamine.
2. Radium.
3. Thorotrast.
4. Uranium ores.
5. Other radioactive materials (radiophosphorous, fluorspar ores, thorium).
6. Soots.
7. Coal tars.
8. Pitches.
9. Tobacco.
10. Tobacco smoke.
11. Asbestos.
12. Chromates.
13. Arsenicals.
14. Mustard gas.
15. Nickel compounds.
16. Chlornaphazine.
17. Auramine.
18. Magenta.
19. Benzidine.
20. High boiling petroleum oils.
21. Isopropyl oil.
22. Various combustion products.
23. Cutting oils.
24. Shale oils.
25. Asphalts.
26. 4-aminobiphenyl.
27. 4-nitrobiphenyl.
28. Betel nut.
29. Creosote.

[1] In addition ultraviolet light and other forms of radiation are known to be cancer causing in man.

Additional prevention could be effected if exposure to these materials were further reduced; for example, if cigarette smoking were further reduced or eliminated. In the food additives, drug and cosmetic areas, materials shown to be cancer causing in well designed experiments in animal species have not been allowed on the market and have very probably prevented many additional human cancers. Further assays for cancer-causing activity, with improvement in assay techniques, are needed and further actions based on these results are called for. It is also possible to block the action of cancer-causing chemicals at different steps in the process leading to cancer formation and opportunities for further research exist here. Plans were presented before the committee last year on how an expanded effort in these directions could be implemented.

The virus causation and prevention aspects of cancer have been detailed at length in the testimony before this committee. We have identified over 110 cancer-causing viruses which produce cancers in many species of animals. We have prevented cancer formation by vaccines in several examples. Major efforts are attempting to determine whether a similar situation holds in man and it is anticipated that some human cancers will be shown to be caused by viruses though at present no human cancer has been absolutely proven to be caused by a virus. Many leads in the area are being actively pursued. Further details have been given in testimony regarding the additional $100 million as well as ongoing efforts.

NEW CANCER RESEARCH CENTERS

Mr. SHRIVER. Dr. Steinfeld mentioned earlier that the new cancer research centers would go to the Southeastern region, the North Central region and the Far West. Can you be more specific as to where these centers will be built?

Dr. BAKER. New cancer research centers in the Southeastern region are planned at the University of Miami, University of Alabama and the Bowman-Gray Medical College in North Carolina. With regard to the Far West, cancer research centers are planned for development at the University of Southern California and the University of New Mexico and preliminary inquiries have been made from the University of California at Los Angeles and the University of California at San Diego, possibly in conjunction with the Salk Institute. I should also mention that the regional medical program has been considering the award of $5 million for the construction of a cancer center in Seattle. The National Cancer Institute anticipates providing operational funds if recommended by the National Advisory Cancer Council as a followup to the planning grant we have had with them following construction. In the North Central region a cancer center will be funded at the Mayo Clinic at Rochester, Minn. I will put in the record a listing of current cancer centers by type and geographical location.

(The listing follows:)

LIST OF NCI CANCER RESEARCH CENTERS

Institution	State	Principal investigator	Type of center
Duke University Medical Center	North Carolina	W. G. Anlyan	Multidisciplinary.
Tulane University	Louisiana	E. Krementz	Do.
Children's Cancer Research Foundation	Massachusetts	S. Farber	Do.
University of Wisconsin	Wisconsin	Johnson	Do.
Cancer Research Center	Missouri	J. S. Spratt	Do.
St. Jude Children's Research Hospital	Tennessee	D. P. Pinkel	Do.
Mayo Foundation	Minnesota	Silverstein	Do.
Memorial Hospital for Cancer	New York	J. Burchenal	Do.
Oklahoma Medical Research Foundation	Oklahoma	P. T. Condit	Do.
M. D. Anderson	Texas	R. L. Clark	Do.
Health Research, Inc	New York	J. F. Holland	Do.
Johns Hopkins	Maryland	A. H. Owens	Do.
Yale University	Connecticut	J. R. Bertino	Do.
University of Minnesota	Minnesota	B. J. Kennedy	Do.
University of Washington	Washington	E. D. Thomas	Do.
University of California	California	D. A. Wood	Do.
University of Rochester	New York	T. Hall	Do.
Michigan Cancer Foundation	Michigan	Brennan	Do.
Mount Zion Hospital	California	J. M. Vaeth	Radiation.
Jefferson Medical Center	Pennsylvania	S. Kramer	Do.
Stanford University	California	H. S. Kaplan	Do.
M. D. Anderson	Texas	G. H. Fletcher	Do.
University of Wisconsin	Wisconsin	M. Boone	Do.
University of Maryland	Maryland	M. J. Wizenberg	Do.
Yale University	Connecticut	M. M. Kligerman	Do.
Case-Western Reserve	Ohio	H. L. Friedell	Do.
M. D. Anderson	Texas	G. H. Fletcher	Do.
Allegheny General Hospital	Pennsylvania	J. P. Concannon	Do.
University of Rochester	New York	P. Rubin	Do.
Tufts University	Massachusetts	F. G. Bloedon	Do.
Washington University	Washington	W. E. Powers	Do.
Institute for Cancer Research	Pennsylvania	T. R. Talbot	Immunology.
Baylor University	Texas	H. Busch	Carcinogenesis.

POSSIBLE USE OF AEROSPACE PERSONNEL IN NCI MANAGEMENT

Mr. SHRIVER. On page 8 of your statement you discuss the need for a managerial capability for program planning, direction and execution on a scale unprecedented in biomedical science. When I discussed the use of aerospace technical personnel with you and Dr. Steinfeld during the hearings on the supplemental request, both of you stated it was your intention to use such personnel for this expanded program. Wouldn't this managerial capability category be an ideal area in which to use some of these people?

Dr. BAKER. Yes; I had in mind the use of systems analysts, some of whom could come from the aerospace fields which we would hope could contribute significantly to program planning, direction and execution on the managerial side. It was such type of personnel that I was referring to when I said that some of the larger cancer institutes were also considering adding this type of planning and analytical staffs to their own organizations. I must reiterate, however, that we will not be able to utilize more than a few such individuals and we may need some time to have them learn enough about the complex biological and medical aspects before their full use can be at hand.

NCI PUBLIC INFORMATION EFFORTS

Mr. SHRIVER. On page 9 you say you will keep the public informed as the program proceeds. What do you have in mind for this? How much is in this budget for this purpose?

Dr. BAKER. In review of the major technical programs, the importance of seeing that the public is well informed was especially evident. It seems appropriate, if we are to further enlarge the attack on cancer, that the public should have more information than perhaps has been the case in the past. Therefore, I would visualize making special efforts to inform the public of the state of the art, the complexities, and the opportunities, but done in a perspective which will not produce overexpectation. As we have so often mentioned here and elsewhere, the time frame in cancer research is long and results are not likely to come all at once, particularly since we are dealing with many different diseases and the most likely course evident is that we will make progress in one type of cancer, then another, then another, rather than a penicillin type drug which will cure all forms.

Currently in our public information activities we have only 19 people and the amount budgeted for fiscal year 1971 is $403,000, one quarter of which will be for a film which we discussed before this committee last year. It will be essential that additional investments of resources be made in this area as the total program goes above the current $230 million level.

MAKARI INTRADERMAL SKIN TEST

Mr. SHRIVER. Are you familiar with the Makari intradermal skin test, which would be used for the detection of cancer? Are any NIH funds being used for these experiments?

Dr. BAKER. Dr. Makari has reported on his work for the past 20 years. Dr. Makari claims to have developed a test for the detection of cancer. Briefly, this test requires the intradermal inoculation of extracts of cancer cells mixed with the patient's serum. A review of information has revealed:

(*a*) Methods used by Dr. Makari for preparing extracts from cancer cells have not been standardized.

(*b*) Chemical analyses of the products do not confirm Makari's claim for their content.

(*c*) A properly designed double blind study of Makari's test has never been carried out.

(*d*) Many of Dr. Makari's statements do not appear to be supported by the facts or current knowledge.

(*e*) There exists an extensive file in DBS on Dr. Makari's tests; it contains information insufficiently useful for the detection of cancer.

Dr. Makari was supported by a grant in 1955 for 1 year. At that time he was employed at M. D. Anderson Hospital. An application for grant support was disapproved in December 1958. At that time, Dr. Makari was on the staff of Muehlenberg Hospital. He then sought contract support. Dr. Makari's work was judged not to merit contract support.

Mr. SHRIVER. Your total budget request is for about $334 million. Would you describe this as a "full speed ahead" budget?

Dr. BAKER. I would describe the $334 million budget as a "high speed ahead" budget, based on the resources currently available and the time required to build the capacities. As I discussed in answer to Mr. Michel's question, the $100 million increase this year seemed in our judgment as an appropriate type of increase. If all stops were pulled in exempting these efforts from all kinds of constraints which are present in customary real life situations, I suppose it would be possible to

enlarge the level somewhat which then might be called a "full speed ahead" budget.

LEUKEMIA CHEMOTHERAPY

Mr. SHRIVER. Dr. Sidney Farber at Harvard has stated that acute leukemia will be cured by chemicals alone in the not too distant future. Do you agree with that statement? How much are you requesting for this purpose?

Dr. BAKER. I certainly agree with Dr. Farber's statement that acute leukemia will be cured by chemicals alone in the not too distant future. I think it very likely we are curing some acute leukemic children now, but we have not had sufficient lapse of time to follow the course of such patients long enough to be absolutely sure. In studies involving combination therapy with different drugs, a comparison of the death rates of the group of patients in comparison with a group of children matched for age, sex and so on without the disease shows that the two rates have become indistinguishable for a period of a few years. It is therefore probable that some of these children are cured.

I estimate that of the $334 million requested, approximately $8 million is requested for chemotherapy of acute leukemia in the several program areas. Obviously this is a very rough figure since we do not separate out the chemotherapy research on acute leukemia from many other efforts in chemotherapy, both in the laboratory and in the clinic.

BREAKDOWN OF TOTAL BUDGET BY AREA OF RESEARCH

Mr. SHRIVER. Would you break down this total request in terms of (1) prevention and (2) therapy or cures?

Dr. BAKER. As a rough estimate I would say that about a little over $100 million would be for prevention studies and about $115 million for treatment studies. The remainder would be for studies on diagnosis; detection; basic biology of cancer and fundamental studies aimed at the nature of cancer; development of resources, including centers; training; program management; and the cost of reviewing the research project and program proposals.

Mr. SHRIVER. How much is in this budget request for the chemical carcinogenesis program?

Dr. BAKER. There is approximately $21.6 million in the 1972 budget request for this program (including the $100 million).

NITRITE AS A POSSIBLE CARCINOGEN

Mr. SHRIVER. I have read that two University of Nebraska scientists have produced lung cancers in up to 90 percent of mice which were fed large amounts of nitrite. Are you familiar with this study?

What are the possible sources for nitrite which the public might be exposed to?

Is lung cancer, like cancer in general, many diseases with many causes including air pollution, cigarette smoking, viruses, occupational hazards, nitrites and other substances?

Dr. BAKER. Work performed at the University of Nebraska under contract from NCI has shown that an increased frequency of lung tumors can be induced in mice fed sodium nitrite in conjunction with a secondary amine type of nitrogen compound. The amine combines in the organism with nitrite giving rise to a nitrosamine which is a carcinogenic chemical. The tumors induced in mice in these tests were mostly benign adenomas and therefore not cancerous. These results confirm others previously obtained by different investigators. However, they represent a still preliminary investigation in a field of study where it is very critical to consider all the conditions of exposure and the chemical reactivity of the test compounds before the results of the tests can be properly interpreted. It is not possible on the basis of these results alone to indict nitrites as cancer producing agents, however, it is important to define the conditions under which they may interact with other food products as contaminants to give rise to carcinogenic chemicals. An extensive effort is presently underway to define the problem. Nitrites are used mostly as food additives, particularly in preserved meats.

Lung cancer is a general term which includes several types of cancers found in the respiratory tract. By far, the most frequent type in man is bronchogenic carcinoma or cancer arising from smaller air tubes in the lung (bronchi). The most important causative factor for this type of tumor is cigarette smoking. Other causative factors have been identified and include asbestos, chromates and other occupational hazards. Air pollution is also being found associated with lung cancer hazards. particularly through the inhalation of radioactive materials. Nitrites are not recognized as being carcinogens. There is no present evidence that viruses alone cause lung cancer.

Mr. SHRIVER. That is all, Mr. Chairman.

Mr. FLOOD. Mr. Patten.

RATIONALE AGAINST A "CRASH" CANCER PROGRAM

Mr. PATTEN. Doctor, you lead off by saying we split the atom and sent a man to the moon and we are going to make a like effort in total national commitment to achieve this goal.

I was on the NASA committee in 1963 after President Kennedy said we will go to the moon this decade. That first appropriation for NASA was over $5 billion, 50 times your $100 million.

My question is suppose we gave you 10 times as much? How about if we gave you $1 billion this year in the appropriation. This would be closer to appropriations that resulted in splitting the atom and going to the moon—or should I forget about it?

I introduced a bill for $1 billion.

Dr. BAKER. I don't believe we could effectively spend that much this year.

Mr. PATTEN. Would you compare it to splitting the atom or going to the moon, the same crash program as far as dollars go? I don't think the comparison stands up. There is a lot of politics here especially when we use a term like "Cancer Cures."

Dr. BAKER. I think it is a matter of timing. The time frame in cancer is peculiarly lengthened. The evaluation of a new drug, for example. It takes a matter of years to pinpoint whether it is effective or not compared to another drug unlike pneumonia, and penicillin where in a matter of hours you had the data.

The causation and prevention side is even worse. We have evidence that some agents are acting over a 15- or 20- year period before they show up. The whole time frame is quite different as one point of difference.

The state of the art is not as far along as in the biomedical field generally and in the cancer field as the state of the art was in the moon shot. So we don't think the same kind of pacing to higher magnitudes is in order. We don't think of this as a crash program. We think of it as a program proposal that can be developed soundly at as fast a pace as possible.

As to the moon shot and Manhattan project kind of effort, I think the kind of commitment that was called for and was made there, and secondly certain managerial aspects of those programs had great merit. We would like that kind of commitment and we hope to be able to learn and apply some of their managerial techniques, but the situation in biology with the living material changing while you are working on it is much more complicated problem than the hardware one.

So I don't think we can think of it in the same terms dollarwise as we could with the aerospace industry all ready to expand there.

Mr. PATTEN. Even though you expect 10 million people to be hit with cancer in the next decade, I shouldn't tell my people this $100 million is a crash program comparable to the successful effort of splitting the atom, the effort we had in 1940, 1941 and 1942 in the Manhattan project. Certainly not in dollars and cents?

Dr. BAKER. No.

Mr. PATTEN. Do you recall how much we spent?

Dr. BAKER. I know it got up to $5.4 billion in the peak year.

Mr. PATTEN. We readily admit the first appropriation for 1963 for the moon shot was $5 billion and 500,000 people were involved in the program in a year or 2. So I shouldn't tell my people this $100 million is going to put us at the same level, and the difference in the program does not permit us to have a crash program like we had in the space program or in splitting the atom where I think we had results and achieved a sense of victory. We are not anywhere near them dollarwise. We are not going to put one-fiftieth of the effort next year on cancer research.

Dr. BAKER. I don't think it is feasible to do that kind of funding right away, no, sir.

Mr. PATTEN. Mr. Chairman, I have no further questions.

Mr. FLOOD. Mr. Conte?

SUITABILITY OF HEW PROGRAM MANAGEMENT FOR CANCER CONQUEST PROGRAM

Mr. CONTE. A 26-member bipartisan panel convened last spring to study U.S. cancer research programs concluded in part, "there is real doubt whether the kind of organization that is required for this pro-

gram can be achieved within the National Institutes of Health or within the Department of Health, Education, and Welfare." What is your response to this conclusion?

Dr. BAKER. In discussions within the DHEW that took place over the last 6 months, assurances were given that necessary actions, including organizational changes and delegations of authorities, will be taken to insure that the cancer conquest program will move ahead in a way appropriate for the kind of national commitment called for by the President in his state of the Union message.

MOON LANDING-CANCER CONQUEST ANALOGY

Mr. CONTE. Finding a cure for cancer has been likened to landing a man on the moon and producing the atom bomb. Is this really a helpful analogy? Isn't more than just technology and money needed to discover a cancer cure?

Dr. BAKER. Mr. Conte, the kind of concentrated efforts in the managerial, coordination, and drive aspects of the programs for landing a man on the moon and producing the atom bomb are, I believe, useful analogies as regards a national commitment to launch a major attack on cancer. It is not a sound analogy scientifically and in terms of the state of the art because cancer research, like other biomedical research, is much more complicated and is not likely to be as mature in terms of the state of the art as was the case with the producing of the atom bomb and placing a man on the moon within the decade. We have presented testimony indicating the likelihood of a longer time frame in cancer research than was the case in these two technological programs. For example, it takes a few years to establish whether a corrective measure for the prevention of cancer is in fact producing the desired result, and it takes many months to evaluate a new drug even after it is introduced into man. Moreover, since cancer consists of a collection of many diseases, it is more likely that progress will be made in different forms of cancer at different rates. Most do not believe we are likely to have anything like a pencillin for all forms of cancer. Nevertheless, the leads available give us great confidence that the rate of progress can be appreciably speeded up with the investment of more resources as leads are developed into practical results.

ALLEGATION THAT CANCER RESEARCH FUNDS WERE FROZEN

Mr. CONTE. In view of the administration's professed interest in increasing its commitment for discovering a cure for cancer, why has the administration reportedly frozen more than $15 million appropriated to the National Cancer Institute this year?

Dr. BAKER. The administration did not freeze any of the NCI funds for fiscal year 1971.

ADMINISTRATIVE ORGANIZATION OF THE CANCER CONQUEST PROGRAM

Mr. CONTE. Dr. Roger Egeberg recently declared in an interview that a small staff of four or five to pull together the research in various parts of NIH and open lines of communication is the major admin-

istrative change in the Nixon plan. Is this all that is really needed to launch a major attack on the disease of cancer?

Dr. BAKER. I do not believe that Dr. Egeberg meant that it was the only thing that would happen and that it was all that would be needed to launch a major attack. The plans already laid by the National Cancer Institute call for major expansion and implementation of many program areas beyond resources available. We therefore believe we are in a position to extend this planning into a total national plan worthy of a national commitment and a major attack on cancer. Such a plan was described at the hearings on the supplemental request before this committee last week. We intend to enrich the details of the plan by asking many outstanding scientists to participate in further planning or detailing of this plan.

In order to give special attenion to the program and to elevate cancer research within the National Institutes of Health, a Director and small staff will be placed organizationally in the Office of the Director, NIH, to direct these efforts and coordinate activities relating to cancer in other Institutes and other organizations. We believe moving ahead on these fronts broadly will provide the means for launching a major attack.

EVALUATION OF NCI GRANT PROCEDURES

Mr. CONTE. A recent GAO study concluded that the present system of administering and funding NCI research causes delays in approval and funding of contracts and grants and that these delays make initiation of some research uncertain and could cause problems for institutions in attracting and retaining qualified researchers. What have you done to rectify this situation?

Dr. BAKER. HEW is currently taking action to extend research-contracting authority to the Cancer Institute. HEW also plans to evaluate the grant review system with a view toward strengthening and expediting the review process. The evalutaion is to include consideration of granting authority to NCI to award grants up to a specified dollar limit without review by study sections.

POSSIBLE REQUEST FOR FUNDS BEYOND $100 MILLION

Mr. CONTE. Is it anticipated that additional funds besides the initial $100 million request for cancer control will be sought in the near future?

Dr. BAKER. In his State of the Union message and his health message, the President said that he would ask for additional moneys beyond the $100 million if they can be effectively used. As we have outlined in the testimony, we expect to extend the planning done over the past 8 years in the National Cancer Institute into a full-scale national plan involving participation of large numbers of scientists. Part of this planning at the detailed level will be the definition of projects required to carry out the plan and will provide better estimation of resources required for the carrying out of such a full-scale attack. It would be my guess that this plan will in fact set forth ways to effectively use moneys beyond $334 million. Therefore, I anticipate that additional moneys will be sought in the future.

PROFESSIONAL PARTICIPATION IN NCI PLANNING

Mr. CONTE. You state that large numbers of scientists will be asked to participate in preparation of a comprehensive national plan during 1972. Approximately how many do you expect to participate?

Dr. BAKER. In our plans for developing the national plan we anticipate having some 50 or so sessions with groups of scientists, expert in different areas of cancer research. It is reasonable to assume that each group would number about five. Therefore, something in the neighborhood of 250 scientists would be participating in the planning.

Mr. CONTE. How many additional multidisciplinary centers are needed in the country and what are the locations of existing facilities of this type?

Dr. BAKER. In response to Mr. Shriver's question pertaining to cancer centers, we will include for the record a listing of cancer centers by type and geographical locations.

DEVELOPMENTS IN IMMUNOLOGY AND MOLECULAR BIOLOGY

Mr. CONTE. What developments in the immunology and molecular biology fields have given you cause for optimism?

Dr. BAKER. A number of exciting advances in the field of immunology have made us optimistic about the usefulness of immunology in the diagonosis, treatment, and ultimately, the prevntion of cancer.

Th fundamental observations which form the cornerstone of cancer immunology are that under some conditions: (1) tumor cells contain on their surfaces chemicals that are different from those found on the surfaces of normal cells, and (2) the immune system of a patient can recognize these differences, and that it can respond to them in such a way as to kill cancer cells, without killing normal cells. This chemical difference between cancer cells and normal cells which has repeatedly been demonstrated by immunologic tests, may provide an important "handle" that chemists and biologists have sought in vain as a means for discriminating malignant from normal cells. The unequivocal demonstration of this chemical difference on the cancer cell surface opens many possibilities for exploitation in terms of selectively killing tumor cells.

The importance of these cancer cell surface chemicals, or antigens, which can be detected in the laboratory by the tools of the immunologist, is magnified by the demonstration that these cancer cell antigens can also be detected by the immune system in the body of a patient with cancer. Not only is there evidence that the immune system can recognize the cancer cell, but, more importantly, it has been shown that under the appropriate conditions, the immune system can destroy cancer cells. It is quite clear, however, that although the immune system can destroy cancer cells, unfortunately, in most patients, the immune system does not destroy them, at least not efficiently enough to eradicate the tumor. Based on this information, it seems that we may have a problem in biologic engineering. We have an immune system which consists of a number of interrelated components that operate in concert to give an immune response. In the cancer patient there is a system failure. Fortunately, immunologists have acquired sufficient in-

formation concerning the basic way in which the immune system functions to allow us to apply this information toward solving the problem of the cause of the apparent malfunction in cancer patients. The work of the next few years will be concerned, in part, with unraveling the nature of this malfunction and with finding ways to manipulate the immune system for the "immunotherapy" of established tumors.

It appears that the immune system alone has the capacity to completely destroy human tumors. With certain types of cancers that occur in the skin or just under the skin, it has been possible to create a local immune reaction which completely kills the tumor at that site. In addition, some patients have inadvertently had cancer transplanted into their bodies with a kidney graft. To permit acceptance of the kidney graft, the patients were treated with drugs to depress their immune system. The transplanted cancers spread from the kidney to other organs. When the drugs were stopped and the immune system was again allowed to function normally, the cancer was killed by the immune system and the patient appeared to be "cured" of the tumor. The great importance of these observations are that they indicate that immune reactions can be sufficiently strong to kill tumor cells in a patient, and that a tumor that has spread through the body may be destroyed by a properly functioning immune system.

The identification of cancer cell antigens also has important implications for immunodiagnostic tests of cancer. The antigens present on cell surfaces can "break" off the cell membrane and may circulate in the blood of the patient. Sensitive immunologic tests are able to detect tiny quantities of these materials in a patient's blood, and this may form the basis for a diagnostic cancer test. Such a test for cancers of the large bowel is under study currently at the National Cancer Institute and at other institutions, to determine whether the test becomes positive early enough in the course of the disease to make possible increased cure rates by surgery or other types of therapy. The availability of tests suitable for screening large segments of the population for the presence of at least some cancers, seems a realistic possibility in the near future.

Finally, it is clear from animal experiments that it is possible to use the immune system to prevent cancer. Animals immunized with tumor cells can subsequently be shown to be completely resistent to the injection of amounts of the tumor that normally would kill the animal. It is a long way from the animal model to human cancer, but the results of these experiments make us optimistic about the possibilities of devising methods for immunizing people against cancer cell antigens. When a cancer develops in such an immunized patient, the immune system should be better able to recognize it and destroy it. Thus, we may be able to protect people against the development of cancer even before we know the true cause or causes of this disease.

Molecular biology investigations are concerned with structure and functions of cells described by considerations at the molecular level, that is what chemical molecules in the cell are doing, how they are structured, how they relate to each other and what chemical reactions are involved in the complex activities of the cell. Special attention is being given to the genetics or hereditary aspects of cells and organisms

when considered at the molecular level and the way the cells' functioning is controlled. When this control is orderly, normal cells result; when abnormal, diseased cells result, sometimes as cancer. Because of the rapid developments in this field, particularly in conjunction with cancer virology investigations, several segments of the scientific community expect to gain considerably more understanding of cancer causation and possibly of treatment. The discussion of the enzymes polymerase and ligase in conjunction with tumor-causing viruses and cancer cells alluded to in the opening statement represents an example of major developments in molecular biology and cancer.

A major part of molecular biology investigates how gene activity is controlled in living cells. Many of the genes in such cells are quiet and only a fraction of them are at work. Cells, therefore, must have some means of making decisions as to which genes to turn on and which genes to turn off. It seems likely that in many types of cancer. genes which ordinarily would be quiet have been activated and that the result of this inflow of new information is the abnormal growth characteristic of cancer cells. Studies have been initiated to examine how cells make decisions as to which genes to use and which genes to allow to remain quiet. In order to understand how human cells work, we also study simpler systems such as the bacterium *E. coli* which contains only about 3,000 genes, thus serving as a useful model for animal cells. A chemical substance which activates or turns on many *E. coli* genes has been identified. This compound, cyclic AMP, acts as a chemical switch or trigger and we have been able to reproduce in a test tube with purified genes and purified proteins how this chemical switch, cyclic AMP, acts in the living cell. This is the first time that the activity of a gene prepared from a living cell has been studied in a test tube in this manner. Studies are now underway in investigating the exact chemical events that occur in this process. It is also planned to isolate other genes and investigate the manner in which their information is switched off and on.

Animal cells also contain this chemical switch, cyclic AMP, and we were led to investigate whether cyclic AMP metabolism was altered in cancer cells. When studied in tissue culture it is found that treatment of certain types of cancer cells (sarcoma cells) with cyclic AMP made the sarcoma cells look more like normal cells and grow more like normal cells. It is also found that the enzyme that makes cyclic AMP is altered in cancer cells. Thus there appears to be an abnormality of cyclic AMP metabolism in certain types of cancer, and these findings may serve as a rational basis for use in the chemotherapy of cancer. In the coming year it is planned to measure the level of cyclic AMP in various normal and cancer cells to sort out which types of cancer may be associated with low cyclic AMP levels. Plans are being developed to study in more detail how cyclic AMP is metabolized in cancer cells and investigate how cells make their decision as to how much cyclic AMP they synthesize.

It has been established that various types of cancer can be produced by viruses which bring new information into the cell. In order to learn how this new information (DNA) is incorporated into cancer cells, we have been investigating how the genes from a bacterial virus com-

bine with the genes of the bacterial cell and change the properties of that cell. We have isolated mutants which are unable to combine with the genes of bacterial cells, have devised a simple cell-free system in which studies can be conducted on how the viral genes combine with the bacterial genes, and are initiating studies in this area.

These and other studies are expected to greatly enhance our understanding of cancer and hopefully will provide additional insight useful for improving the treatment and providing additional clues to causation and prevention in cancer.

Mr. CONTE. That is all, Mr. Chairman.

Mr. FLOOD. Thank you, Dr. Baker.

Dr. BAKER. Thank you, Mr. Chairman and members of the committee.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation

	1971	1972
Appropriation:		
Contained in 1971 Bill	$230,383,000	$100,000,000 1/
Requested in 1972 Bill	---	234,338,000
Real transfer to:		
"Departmental Management"	-28,000	---
Real transfers from:		
"National Institute of Neurological Diseases and Stroke"	+1,879,000	---
"National Institute of General Medical Science"	+898,000	---
(Proposed transfer for increased pay costs)		
Comparative transfers to:		
"Office of the Director"	-151,000	---
"John E. Fogarty International Center for Advanced Study in the Health Sciences"	-22,000	---
"Research Resources"	-27,000	---
"Health Manpower"	-2,470,000	---
Total, obligations	230,462,000	334,338,000

1/ Included in 1971 Supplemental bill (H. Doc. 92-92).

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
15	Research.....		$95,411,000		$97,403,000		+$1,992,000
	General research support grants		(5,901,000)		(5,275,000)		(-626,000)
	Scientific evaluation grants..		(201,000)		(201,000)		---
	Specialized research centers		(19,453,000)		(20,953,000)		(+1,500,000)
	Leukemia research support centers		(1,851,000)		(1,851,000)		---
19	Fellowships.....		3,798,000		3,348,000		-450,000
22	Training.....		8,358,000		8,358,000		---
	Direct operations:						
24	Laboratory and clinical research	473	20,518,000	476	21,529,000	+3	+1,011,000
26	Collaborative research and development.....	771	97,419,000	778	98,301,000	+7	+882,000
41	Review and approval of grants.....	110	3,321,000	110	3,636,000	--	+315,000
42	Program direction..	56	1,637,000	56	1,763,000	--	+126,000
	Cancer research initiatives:						
43	Cancer research initiatives....	250	---	250	100,000,000	---	+100,000,000
	Total obligations	1660	230,462,000	1670	334,338,000	+10	+103,876,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	1,660	1,670	+10
Full-time equivalent of all other positions	66	66	---
Average number of all employees	1,441	1,646	+205
Personnel compensation:			
Permanent positions	$19,013,000	$23,350,000	+$4,337,000
Positions other than permanent	464,000	567,000	+103,000
Other personnel compensation	229,000	275,000	+46,000
Subtotal, personnel compensation	19,706,000	24,192,000	+4,486,000
Personnel benefits	2,000,000	2,430,000	+430,000
Travel and transportation of persons	995,000	1,144,000	+149,000
Transportation of things	140,000	202,000	+62,000
Rent, communications and utilities	595,000	700,000	+105,000
Printing and reproduction	473,000	548,000	+75,000
Other services:			
Project contracts	79,235,000	135,013,000	+55,778,000
Payment to NIH Management Fund	10,672,000	11,659,000	+987,000
Other	3,279,000	4,089,000	+810,000
Supplies and materials	4,150,000	4,863,000	+713,000
Equipment	1,650,000	2,000,000	+350,000
Grants, subsidies and contributions	107,567,000	147,498,000	+39,931,000
Total obligations by objects	230,462,000	334,338,000	+103,876,000

Summary of Changes

1971 estimated obligations	$230,462,000
1972 estimated obligations	334,338,000
Net change	+103,876,000

	Base Pos.	Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of new positions in 1971	---	---	---	+$319,000
2. Annualization of 1971 pay increase costs	---	---	---	+946,000
3. Within-grade increases	---	---	---	+384,000
4. Extra day of pay	---	---	---	+66,000
5. FTS rate increase	---	---	---	+18,000
6. Non-competing continuation grants	---	---	---	+2,643,000
B. Program:				
1. Research grants	---	$95,411,000	---	+2,000,000
2. Laboratory and clinical research	473	13,097,000	+3	+408,000
3. Collaborative research and development	771	95,468,000	+7	+2,281,000
4. Review and approval	110	2,164,000	---	+50,000
5. Program direction	56	1,494,000	---	+50,000
6. Cancer research initiatives	250	---	---	+100,000,000
C. Payment to "National Institutes of Health Management Fund" for centrally furnished services	---	10,672,000	---	+487,000
Total, increases	---	---	+10	+109,652,000
Decreases:				
A. Program:				
1. Research grants	---	95,411,000	---	-2,651,000
2. Fellowships	---	3,798,000	---	-450,000
3. Laboratory and clinical research	473	13,097,000	---	-175,000
4. Collaborative research and development	771	95,468,000	---	-2,500,000
Total, decreases	---	---	---	-5,776,000
Total, net change	---	---	+10	+103,876,000

Justification of the Budget Estimates

Explanation of Changes

Built-in Increases--These increases will provide: $319,000 for annualization of new positions in 1971; $946,000 for annualization of 1971 pay increase costs; $384,000 for within-grade pay increases in 1972; $66,000 for extra day of pay in 1972; $18,000 for increased costs in 1972 of using the Federal Telecommunications System; and $2,643,000 for the continuation costs in 1972 of those grants funded in 1971.

Research grants--The program increase of $2,000,000 represents an increase of $500,000 in the regular research grant program for an expanded research effort concerning viruses as cause of cancer and an increase of $1,500,000 in specialized research centers for the establishment of one or two new centers in geographical areas where none now exists. The program decrease of $2,651,000 represents a decrease of $2,025,000 in the regular research grant program which will result in an overall reduction in on-going programs and a decrease of $626,000 in general research support grants, a program included in each NIH appropriation containing research grant projects, but administered separately by the Division of Research Resources.

Fellowships--The program decrease of $450,000 will still allow for support of 142 postdoctoral and special fellowships and 74 career award and career development fellowships.

Laboratory and clinical research--The program increase of $408,000 and three new positions will provide for a modest expansion in immunology research related to virus and is directed towards applying recent advances to the treatment and prevention of cancer in man. The program decrease of $175,000 will result in an overall reduction of on-going programs.

Collaborative research and development--The program increase of $2,281,000 and seven new positions will provide for a modest expansion of effort in the Special Virus Cancer Program to identify viruses directly involved in the causation of cancers in man and to develop effective vaccines or other means for the prevention and control of human cancers. The program decrease of $2,500,000 is in the radiation therapy area, however, this is not a decrease of effort since the 1971 obligations of $3,000,000 were for initial development of the Mary Hitchcock Cancer Research Center. An amount of $500,000 is included in this budget which will cover the operational cost of the center for 1972.

Review and approval--The program increase of $50,000 will provide funds for program management in connection with the additional funds provided for regular research grants and specialized research centers.

Program direction--The program increase of $50,000 will provide funds for the support of contracts to assist in the further development of program planning and computer applications to the research programs of the Institute.

Cancer research initiatives--The obligation of an additional $100,000,000 will provide funds for the launching of an intensive campaign towards the ultimate goal of prevention of all human cancers. In order to work towards this goal, the expanded research and development efforts will be undertaken in all major components of cancer research.

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action Taken or to be Taken
1971 House Report	
1. The Committee again heard convincing testimony on the need for expanded work on cancers caused by chemicals. The Committee has received from the Institute plans for an expanded effort in research on causation of cancers by chemicals and hopes that these plans will be promptly put into effect along with the planned studies on causation involving both viruses and chemicals.	1. Plans furnished to the Committee relative to a Chemical Carcinogenesis Program are being followed to the extent that resources are available.
2. The Committee was much encouraged by the continuing improvement in treatment for many forms of cancers. Much of this success is directly attributable to the Institute's Cancer Chemotherapy program. The Committee looks forward to the extension of the chemotherapy program into research on the more common, slow growing cancers.	2. With additional funds included in the 1971 appropriation for the National Cancer Institute, the Chemotherapy program can be extended into more research on the common, slow growing cancer. Special report requested on this subject by the Committee has been furnished.
1971 Senate Report	
1. The Committee was advised that progress continues to be made in exploring the role played by viruses in causing various forms of cancer. The Committee was pleased to note that the 1971 President's Budget and the increase allowed by the House included additional funds for this important activity.	1. The 1971 appropriation included an increase of $22 million to exploit the exciting leads and opportunities in the virus area. With the passage of the appropriation, expansion of this field can now be effected. Special report requested on this subject by the Committee has been furnished.
2. While the improvements of treatment are gratifying, the Committee was quite concerned about the rising mortality rate and an even faster rise in new cancer cases. The Institute has plans for an expanded program aimed at prevention of cancers and has launched initial activities under this plan. The Committee feels that these efforts aimed at preventing cancer should be accelerated as much as practicable as a means of halting the rising incidence.	2. Causes of cancer are related to chemicals and possibly viruses. Plans have been developed and furnished to the Committee relative to expansion of the Chemical Carcinogenesis Program. These plans are being followed to the extent that resources are available.

Item	Action Taken or to be Taken
1971 Senate Report--continued	
3. The Committee felt that steps should be taken to establish cancer centers in parts of the country that do not yet have ready access to such a facility so that advances in cancer research can be most quickly and effectively brought to bear on the treatment and care of patients.	3. Increases provided in the 1971 appropriation will allow for the initiation of additional cancer research centers. The 1972 budget also includes $1.5 million for this purpose, as explained in the written justification portion of this budget.
4. The Committee was informed that an additional $3 million would be needed for the development of a center at the Mary Hitchcock Memorial Hospital in Hanover, New Hampshire.	4. The House-Senate Conferees agreed that $3 million of the 1971 NCI appropriation shall be for the development of a cancer center at the Mary Hitchcock Memorial Hospital at Hanover, New Hampshire. Negotiations are now underway to award a contract for this purpose.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation requested
Public Health Service Act Section 301-Research and Investigation, in general.....	Indefinite	$234,338,000
Title IV, Part A--National Cancer Institute.....	Indefinite	234,338,000

PUBLIC HEALTH SERVICE ACT

The legislative authority which provides for the award of grants for research, research training, and fellowships is included in Section 301 of the Public Health Service Act.

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 Advisory Cancer 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

	1971 Estimate	Purpose
Real transfer to:		
Departmental Management	-$28,000	To establish the Facilities Engineering and Construction Agency.
Real transfers from:		
National Institute of Neurological Diseases and Stroke	+1,879,000	Proposed transfer for increased pay costs.
National Institute of General Medical Science	+898,000	Proposed transfer for increased pay costs.
Comparative transfers to:		
Office of the Director	-151,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director.
John E. Fogarty International Center for Advanced Study in the Health Sciences	-22,000	To provide an equitable distribution of the NIH Management Fund in 1972.
Research Resources	-27,000	To provide an equitable distribution of the NIH Management Fund in 1972.
Health Manpower	-54,000	To provide an equitable distribution of the NIH Management Fund in 1972.
Health Manpower	-2,416,000	Transfer of institutional support funds to Health Manpower.

National Cancer Institute

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$117,167,000	$125,672,000	$160,000,000	$142,836,000
1963	139,109,000	150,409,000	158,409,000	155,742,000
1964	145,114,000	144,340,000	145,114,000	144,340,000
1965	139,714,000	138,970,000	148,970,000	148,970,000
1966	153,968,000	157,618,000	163,768,000	163,768,000
1967	163,957,000	170,656,000	175,656,000	175,656,000
1968	183,356,000	183,356,000	192,356,000	183,356,000
1969	187,707,000	182,592,000	191,592,000	185,149,000
1970	180,725,000	180,725,000	200,000,000	190,486,063
1971	202,383,000	227,383,000	235,383,000	230,383,000
1972	334,338,000 1/			

1/ Includes $100,000,000 for cancer research initiatives.

Justification

National Cancer Institute

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	1,660	$21,706,000	1,670	$26,622,000	+10	+$4,916,000
Other expenses.....	---	208,756,000	---	307,716,000	---	+98,960,000
Total.....	1,660	230,462,000	1,670	334,338,000	+10	+103,876,000

General Statement

The National Cancer Institute conducts, fosters and assists research and training directed toward preventing, diagnosing, treating and controlling cancer in man. These objectives are pursued directly within government laboratory and clinical facilities and through universities, non-profit research organizations and commercial concerns supported with grants and contracts and include both laboratory and clinical studies.

Despite continuing improvements in the results of therapy, cancer mortality is increasing at a rate that cannot be explained entirely by population increase or increasing average age. About one in four persons will get cancer and two-thirds of those afflicted will die with the disease. Approximately 335,000 Americans will die of cancer in 1972; this is one death every 1 1/2 minutes. Clearly the burden of cancer causing factors still outweighs our present capabilities for curing cancer.

Cancer is no respecter of age, color, or economic status. Yet, the disease's most severe toll is levied on the urban poor. This is a harsh circumstance caused by a number of factors including exposure to environmental and occupational pollutants, financial status, and quality of available medical care. Provision of care of cancer patients constitutes an enormous drain on medical care resources, and the best treatment, which is not universally available, can only be provided by a system that includes highly trained specialists, extensive paramedical support, and modern and expensive facilities.

However, continuing progress against cancer and the reversal of the trends of increasing incidence and mortality depend not only on more effective and comprehensive delivery of care but also on the nature of the measures applied. The first line of defense against cancer lies in prevention. It is becoming abundantly clear that cancer initiation in man depends on a complex interrelation of external factors, including viruses and chemicals, and internal factors such as genetic makeup. Organization of the information flowing from the intensive research of past years now permits us to visualize more clearly specific measures by which certain forms of cancer may be prevented. The link between certain chemicals and the genesis of human cancers has been established. Additional opportunities for more rapid identification of carcinogenic chemicals, for characterizing the nature of human exposure to such materials and for diminishing the hazard of such substances have been identified.

Although the causative link between viruses and human cancers has not been definitely established, the nature of the interrelation between viruses and hosts is becoming progressively clearer as is the nature of the preventive measures that may be developed. Success in answering the questions that still exist depend to a large extent on vigorous prosecution of a carefully-planned, integrated, targeted effort now underway.

The second line of defense lies in the effective treatment of human cancer. In terms of the time required for many cancers to develop and evolve in the host, cancer is a chronic process. Moreover development, administration and evaluation of cancer preventive measures is a lengthy process. Even with development and use of a broad spectrum of effective preventive techniques, heavy reliance must be placed on therapy for many years. The use of drugs in the treatment of certain forms of cancer has been increasingly successful, and now points the way for more effective treatment of other cancer forms. Opportunities for progress in this field can be visualized and await vigorous exploitation.

The network of cancer centers supported by the National Cancer Institute constitutes a resource for the conduct of many important clinical and fundamental research activities. Centers represent a further potential not only for generation of new knowledge but also, by standing at the interface of research and practice, have a great potential for benefiting large numbers of actual and potential cancer patients. The Institute continues to seek and realize opportunities for strengthening this system.

A separate section entitled "Cancer Research Initiatives" reflects the requirement for 250 positions and $100,000,000 to launch an intensive campaign towards the ultimate goal of prevention of all human cancers. In order to work towards this goal, the expanded research and development efforts will be undertaken in all major components of cancer research consisting of the following: (1) causation and prevention; (2) diagnosis and detection; (3) treatment; (4) programs (extended task forces) on each kind of cancer that represents a major form of human cancer defined by organ sites (lung, large bowel, breast, leukemias and lymphomas, bladder and prostate, brain and pancreas); (5) cancer centers; (6) grant-supported activities; and (7) management and coordination of the total program, including a "nervous system" with incoming sensing data inputs, central analyses and decision-making for action, and implementing communication links to the decentralized activities.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Research Projects.....	$68,005,000	$69,123,000	+$1,118,000
Special Programs.....	27,406,000	28,280,000	+874,000
Total Research Grants.....	95,411,000	97,403,000	+1,992,000

Introduction

The research grant program of the National Cancer Institute, stimulates and supports a basic and applied research effort in the broad areas of causation, diagnosis, treatment, prevention and control of cancer. These programs cover a full spectrum of activity, ranging from single objective research projects to broadly based multidisciplinary program centers.

Program Plans in 1971 and 1972

In basic research, emphasis is being placed on projects of known or potential relevance to cancer, including radiation, chemical carcinogenesis, the nature of cancers and their interactions with host organisms, immunology, drug development, and epidemiology. Studies involving a variety of cancers in laboratory animals, human patients, and in selected populations will be continued as well as those projects attempting to identify cancer-producing agents in air, water, food, tobacco, drugs, and other related aspects of mankind's total environment.

To elucidate the causes of cancer along with achieving control of the many manifestations of this disease, a concerted effort will be made to capitalize on new concepts, leads, and approaches involving the interactions between cancer viruses and their natural hosts, and between viruses and chemicals.

There will be further studies on the techniques of therapy, such as the effect of drugs and radiation in controlling the growth and spread of cancerous cells in living organisms. Clinical investigations of new and complex anticancer therapies will continue to be carried out in approximately 250 institutions across the nation. The investigators at these institutions are presently organized in 23 cooperating groups on the basis of the therapy under study, e.g., pediatrics, urology, etc.

In conjunction with the cooperative therapeutic research program, the Institute will continue to support investigations into the control and treatment of the two major causes of death in cancer--hemorrhage and infection. The control of hemorrhage is being studied by approximately 28 investigators receiving Leukemia Research Support Center funds. The control of infection is being actively pursued at three institutions where the complicated "life island" and even more complex "laminar flow" techniques are under investigation. These procedures attempt, by physical and chemical means, to produce a germ-free environment for the patient during the periods of greatest susceptibility to infection. Although the "Protected Environment" program is beginning to demonstrate beneficial effects, further elucidation of these benefits will be sought during the coming year. In addition, plans have been made to alter the direction of this program to provide more clear-cut answers to the problem of infection.

In 1972, the program decrease of $2,651,000 includes $626,000 for general research support grants and $2,025,000 in the regular research grant program. The decrease in the regular research grant program will result in an overall reduction in on-going programs with the exception of the efforts in virus research. The Program increase of $500,000 requested in the virology program will be used to support new research in virology where indications are that transformation, at least on the part of small DNA tumor viruses, results from the attachment of one or more viral genes to cellular genes. Activities relating to the identification of these genes, their mode of attachment and how this results in transformation will be pursued.

In the area of cooperative clinical cancer research, development will continue at about the same total dollar level in the following programs: (1) brain tumor studies, (2) the fast neutron source now under development, (3) a pion beam study, (4) the immunotherapy of malignant diseases, (5) the intensive combined therapy of breast cancer, (6) radical versus simple mastectomy in breast cancer, and (7) the development of a biostatistical and data processing and coordinating center for the program.

The Institute currently supports 33 Specialized Research Centers which are performing intensive, highly specialized clinical research on cancer in man. The role which man's environment plays, as related to his susceptibility to malignant disease from viral and chemical carcinogenesis agents, will continue to be studied, with the ultimate goal being prevention. Studies on radiation biology, physics, and nuclear medicine will expand. Prime emphasis will continue to be given to determining the optimum methods of employing chemotherapeutic drugs, and other forms of therapy and to the use of radiation as an adjuvant to surgery and chemotherapy. The currently active centers are predominantly located in the northeastern part of the United States, with few or none at all in many parts of the south, midwest and far west. The program increase of $1,500,000 in special programs will be used to initiate one or two new cancer research centers in geographical areas where centers do not exist at this time.

The leukemia research support centers will continue at the same dollar level in 1972 as 1971. It has been demonstrated that the use of platelet transfusions is efficacious in the treatment of bleeding due to an imbalance of platelets within the body. Emphasis is now being placed on delineating the best conditions of platelet isolation and processing for maximum yield, and to elucidate those situations in which platelet transfusions will be most effective in achieving the desired therapeutic goal.

Research Grants Program Analysis

	1971 Estimate	1972 Estimate	Increase or Decrease
Fields			
Carcinogenesis	$16,680,000	$17,059,000	+$379,000
Cancer biology	15,504,000	15,947,000	+443,000
Pharmacology	8,153,000	8,190,000	+37,000
Epidemiology	1,061,000	1,066,000	+5,000
Radiation	3,557,000	3,573,000	+16,000
Surgery	1,817,000	1,826,000	+9,000
Immunology	4,897,000	5,053,000	+156,000
Chemotherapy	6,326,000	6,354,000	+28,000
Basic research and other 1/	10,010,000	10,055,000	+45,000
Subtotal regular program	68,005,000	69,123,000	+1,118,000
General research support grants	5,901,000	5,275,000	-626,000
Scientific evaluation grants	201,000	201,000	---
Specialized research centers	19,453,000	20,953,000	+1,500,000
Leukemia research support centers	1,851,000	1,851,000	---
Total research grants	95,411,000	97,403,000	+1,992,000

1/ Includes Sloan-Kettering Single Instrument grant.

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Noncompeting continuations.....	648	$45,316,000	655	$47,959,000	+7	+$2,643,000
Competing projects.....	354	20,589,000	299	19,064,000	-55	-1,525,000
Supplementals.....	(153)	2,100,000	(139)	2,100,000	(-14)	---
Subtotal regular program.....	1,002	68,005,000	954	69,123,000	-48	+1,118,000
General research support.....		5,901,000		5,275,000		-626,000
Scientific evaluation.....		201,000		201,000		---
Specialized research centers.....		19,453,000		20,953,000		+1,500,000
Leukemia research support centers.....		1,851,000		1,851,000		---
Total research grants.....		95,411,000		97,403,000		+1,992,000

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Total fellowships.....	$3,798,000	$3,348,000	-$450,000

Introduction

Several kinds of awards designed to meet particular objectives are granted under this program. The program provides research training to individuals whose career development extends from the immediate postdoctoral period through the advanced stages of scientific attainment. Postdoctoral awards are made to qualified individuals with doctoral degrees and up to three years of relevant research experience. Special fellowships are for those who have had at least three years of postdoctoral research or professional experience, or who have completed at least three years of residency training in a clinical specialty. Special fellowships may also be awarded to senior investigators who wish to undertake additional training e.g., that during sabbatical leave periods.

This program also supports two other types of awards made to institutions - research career development awards and research career awards. Research career development awards support investigators who require five to eight years of experience to improve their research skills and develop a capability for independent investigation. Research career awards have been made to established investigators of high quality for a protracted period of their research careers.

Program Plans in 1971 and 1972

The Fellowship program will continue to provide training to promising young investigators in cancer research. As in past years emphasis in 1972 will continue to be given to the shortage areas of medicinal and organic chemistry, epidemiology, radiation therapy, surgery, hematology, and clinical pharmacology.

Funds requested for 1972 will provide for 216 awards, compared to 242 in 1971, a decrease of 26.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Continuations:						
Noncompeting.....	110	$2,144,000	106	$2,100,000	-4	-$44,000
Competing.....	39	415,000	22	323,000	-17	-92,000
Supplementals.....	--	---	--	---	--	---
New awards.....	93	1,239,000	88	925,000	-5	-314,000
Total fellowships....	242	3,798,000	216	3,348,000	-26	-450,000

Fellowships (By Type of Program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Postdoctoral.....	98	$796,000	95	$796,000	-3	---
Special.....	50	701,000	47	701,000	-3	---
Development awards.....	83	1,970,000	63	1,520,000	-20	-$450,000
Career awards.....	11	331,000	11	331,000	--	---
Total fellowships....	242	3,798,000	216	3,348,000	-26	-450,000

Fellowship Program Analysis

	1971 Estimate	1972 Estimate	Increase or Decrease
Fields			
Carcinogenesis.....	$841,000	$742,000	-$99,000
Cancer biology.....	1,612,000	1,421,000	-191,000
Pharmacology.....	434,000	382,000	-52,000
Epidemiology.....	57,000	50,000	-7,000
Radiation.....	160,000	142,000	-18,000
Surgery.....	25,000	25,000	---
Immunology.....	483,000	423,000	-60,000
Chemotherapy.....	186,000	163,000	-23,000
Total fellowship program..	3,798,000	3,348,000	-450,000

Training Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Total training grants.....	$8,358,000	$8,358,000	---

Introduction

Graduate research training grants provide support for trainees in the various fields related to cancer research and underwrite expenses for equipment, supplies, and training staff. Clinical cancer training grants are awarded to qualified institutions to provide training in the prevention, diagnosis, treatment, rehabilitation, and public health aspects of cancer.

Program Plans in 1971 and 1972

Approximately 587 full-time equivalent trainees will be supported in 1971 through 141 training grants. Emphasis will be placed on continuing training programs in disciplines where cancer researchers are in short supply, such as radiation therapy, clinical pharmacology, chemical carcinogenesis, epidemiology and training related to regional medical programs.

The estimate for 1972 will provide for 125 training grants which is 16 below the 1971 level of 141. This relates to a decrease of 61 full-time equivalent trainees.

Distribution of Training Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Continuations:						
Noncompeting.....	118	$7,321,000	96	$6,420,000	-22	-$901,000
Competing.....	23	1,037,000	29	1,938,000	+6	+901,000
Supplementals.....	--	---	--	---	--	---
Total training grants.....	141	8,358,000	125	8,358,000	-16	---

Training Grants (By Type of Program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Graduate.....	74	$4,906,000	66	$4,906,000	-8	---
Cancer clinical training.....	67	3,452,000	59	3,452,000	-8	---
Total training grants.....	141	8,358,000	125	8,358,000	-16	---

Laboratory and Clinical Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	473	$7,261,000	476	$7,753,000	+3	+$492,000
Other expenses.....	---	13,257,000	---	13,776,000	---	+519,000
Total.....	473	20,518,000	476	21,529,000	+3	+1,011,000

Introduction

The mission of the General Laboratories and Clinics area of the Institute is to obtain information and knowledge for the understanding of the fundamental biological processes underlying cancer in man through the conduct of research in the biomedical sciences. The research of the General Laboratories and Clinics is carried out in 11 units. Five are in the basic sciences; namely Biology, Cell Biology, Molecular Biology, Biochemistry, and Physiology. Six are engaged in clinical research programs of Surgery, Immunology, Radiation, Dermatology, Pathology, and Metabolism and have 68 hospital beds to complement these clinical programs. The scientists and physicians of these 11 units are conducting studies broadly described by the title of their unit. Their research is designed to add to our knowledge about the changes caused by cancer, whether they be in the biochemistry of the cell or the effect of cancer upon the patient. They include studies of the treatment of cancer by surgery, chemical and radiological means.

Program Plans in 1971 and 1972

Malignant (cancer) cells differ from their normal counterparts - they can grow locally beyond the bounds limiting the normal counterparts; they can be transported and grow in distant sites. The shape of the cancer cell and size and shape of its nucleus are often sufficiently different so that cancer cells can be recognized by structural criteria; they can also be readily recognized by when they grow in remote sites. The properties of the malignant cells that permit them to grow locally out of control and to spread to distant sites are not known. The mechanisms by which a cancer drains resources from the rest of the body are also not known.

These large gaps in our understanding of the whole cancer problem require a broad attack upon the disease. This attack ranges from a study of the processes involved in translating information in the cell nucleus in the form of DNA to operations within the cell by enzymes. This is a facet of molecular biology, and how the cell functions is biochemistry. The Laboratories of Molecular Biology and Biochemistry are engaged in research involving normal cells and cancer cells. The Laboratory of Biology's Tissue Culture Section has played a leading role in developing the techniques of tissue culture. A number of General Laboratories and Clinics units are studying the antigens of tumor cells, and attempting to develop methods of utilizing them properly to create new therapeutic tools. These therapeutic studies are at an early developmental stage. This area of research is growing rapidly, its ultimate role is to be determined. At present, GL&C is engaged in pursuing several lines of research in immunology and immunotherapeutics, both in man and the experimental animal.

Studies in patients range from those designed to improve radiation therapy and surgery as therapeutic tools together with those designed to determine how a cancer affects the patient, how anemia is produced, and why host defenses to bacteria are reduced. Of particular significance is the possibility that immunological techniques may offer new ways of making an earlier diagnosis of cancer of the bowel.

This broadly based program to study cancer in man and experimental animals by a team comprised of physicians and scientists in a variety of specialties and disciplines has led to the development of newer methods of treatment and has provided new knowledge about cancer, that will permit better care of patients and an increased understanding of the fundamental aberration that results in cancer.

The program decrease in 1972 of $175,000 will result in an overall reduction of on-going programs with the exception of research in the virus program. The program increase of 3 positions and $408,000 will permit a modest expansion in immunology research as related to virus. This is needed to apply advances in immunology to the treatment and prevention of cancer in man. Research in tumor immunology has arrived at a level that warrants an intensive effort in this direction. Immunologic defects contribute to the development of some tumors, while in other circumstances immunologic factors may play an important role in controlling cancer. It has been demonstrated that tumors in animals can be prevented by immunization or by bolstering the immune system.

In addition to the program change, there is an increase of $778,000 which includes $57,000 for annualization of new positions in 1971, $312,000 for annualization of 1971 pay increase costs, $135,000 for cost of within-grade pay increases, $22,000 for extra day of pay in 1972. and $252,000 for payment to the National Institutes of Health Management Fund for centrally furnished services.

Collaborative Research and Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	771	$11,971,000	778	$12,909,000	+7	+$938,000
Other expenses.....	--	85,448,000	--	85,392,000	--	-56,000
Total.....	771	97,419,000	778	98,301,000	+7	+882,000

Introduction

The programs under Collaborative Research and Development include national efforts utilizing the research contract mechanism as well as investigations carried on directly in Government laboratories and clinical facilities, to concentrate on major cancer problems. The interrelated research projects under this activity are coordinated within programs involving integration of multi-discipline research attacks. They are continually critically assessed and modified as research findings accumulate in these targeted programs conducted by the Institute.

The 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 cancers and their occurrence patterns and prevention. The Therapy programs are concerned with finding the best methods of treating cancer through the screening, testing and clinical evaluation of drugs.

The Breast Cancer and Lung Cancer Task Forces comprise the Cancer Task Forces area. Planned programs initiated from these activities tend to cut across organizational lines and are dependent on a variety of on-going activities within the Institute.

The following table indicates level of support by major program areas:

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Etiology.....	408	$54,731,000	415	$57,581,000	+7	+$2,850,000
Cancer Therapy.....	294	31,582,000	294	31,881,000	--	+299,000
Task Forces.....	15	4,068,000	15	4,079,000	--	+11,000
Cancer Research Center...	--	3,000,000	--	500,000	--	-2,500,000
Supporting Services.....	54	2,087,000	54	2,153,000	--	+66,000
National Institutes of Health Management Fund	--	1,951,000	--	2,107,000	--	+156,000
Total Collaborative Research and Development.....	771	97,419,000	778	98,301,000	+7	+882,000

Etiology

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Total.....	408	$54,731,000	415	$57,581,000	+7	+$2,850,000
Office of the Scientific Director.	25	1,056,000	25	1,084,000	--	+28,000
Special Virus Cancer..	187	4,416,000	194	5,002,000	+7	+586,000
Contracts.....	--	34,091,000	--	36,101,000	--	+2,010,000
Carcinogenesis.....	105	2,373,000	105	2,548,000	--	+175,000
Contracts.....	--	8,081,000	--	8,031,000	--	-50,000
Demography.....	91	1,680,000	91	1,794,000	--	+114,000
Contracts.....	--	3,034,000	--	3,021,000	--	-13,000

Introduction

The Etiology Area is charged with responsibility for the major share of the Institute's programmed research on cancer causation and prevention. In order to develop methods of prevention and treatment of human cancers, research is directed toward identification of causative agents (viruses and/or chemicals) in defined human and animal populations which are at different risks to cancer. These investigations include fundamental studies on the mechanisms by which these agents produce abnormal alterations in living systems. Scientists are responsible not only for their individual research but also for provision of strong central leadership and management of a broad, multidisciplinary and integrated programmatic attack upon these problems. The overall goal of the Etiology Area is prevention and control of cancer in man. Specific studies toward this goal are conducted by contract with investigators throughout this country and abroad and through the in-house laboratories of the Sections and Branches of the three major areas of Etiology—Carcinogenesis, Demography, and Viral Oncology.

Program Plans in 1971 and 1972

Special Virus Cancer Program (SVCP)

The Viral Oncology area of the National Cancer Institute has responsibility for planning, implementing, and managing all programmed research on viruses in relation to cancer. The Special Virus Cancer Program's primary objectives are: (1) To determine whether viruses comparable to those known to induce cancers of laboratory and domestic animals are causative agents of human cancers, and (2) to develop therapeutic and preventive measures (including vaccines) for control of human cancers when such causative agents are found. Since the beginning of the Program in 1964, the Institute has developed an effective science management program which has made substantial progress toward determining the virus causation

of such human cancers as leukemia, lymphomas, sarcomas, and carcinomas. Despite this progress, the overall death rate from cancer continues to rise. The probability is very high that a virus or viruses are responsible for many of these new cases and that these viruses will be identified in the very near future, thus making it possible to take measures for the prevention or control of these cancers in man. These predictions are based largely on recent findings through work conducted within and in collaboration with the SVCP of the National Cancer Institute.

Because many scientists are convinced that an effort to identify viruses or to detect virus expression in human tumors is one of the best approaches to the solution of this aspect of the cancer problem, the SVCP has developed a targeted research and management apparatus which effectively musters the scientific talent available worldwide in a highly effective pursuit of research leads.

The administrative mechanisms and scientific operations of the SVCP provide a flexible program which can respond to changing research needs and exploit new leads that emerge through the efforts of the SVCP and other laboratories throughout the world. Recently, new biochemical and immunological approaches aimed at understanding cancer induction by viruses at the subcellular (or genetic) level have provided basic information which may aid the physician in detecting and treating cancers earlier than would otherwise have been possible. These new areas will be expanded and refined during the coming years as part of the continuing effort in the overall program to pursue important new scientific findings and to modify the program as research progresses.

Cancer is the second leading cause of death in the United States. The outlook for the prevention or control of some of these diseases is very bright. The following areas represent promising leads, new hypotheses, and/or new techniques with unusual significance for determining the role of viruses in human cancer:

(1) Herpes-type viruses (one of which is the EB virus) have been implicated in cervical cancer, post-nasal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and perhaps chronic myeloid leukemia.

(2) Virus particles resembling the RNA agents (Type B), which cause breast cancers of mice, have been observed in milk specimens from women with breast cancers, and healthy women of high risk populations (e.g., inbred Parsi sect of India).

(3) Certain cancer-causing viruses are unable to produce malignancies unless a second "helper" virus is present, thus suggesting that under certain conditions tumor induction may involve the interaction of more than one viral agent.

(4) Certain tumor-inducing chemicals as well as irradiation may act as co-factors in activating latent cancer-causing viruses within cells.

(5) New evidence strongly suggests that sarcomas of children are produced by viruses resembling Type C of the RNA animal tumor viruses. These diseases of bone and muscle together with leukemia constitute the most important cause of death from cancer in the young.

(6) A dramatic breakthrough in the investigation of biochemical pathways of tumor virus infection and replication has been the demonstration that RNA viruses contain enzymes called polymerases which direct the synthesis of genetic material in the host cell. This discovery not only opens the way to a total understanding of the subcellular (molecular) events which occur as a cell becomes malignant but also may provide effective new approaches to cancer treatment.

Very recently a naturally occurring herpes virus which causes Marek's disease in large numbers of chickens has been isolated. Two vaccines have already been developed which provide virtually 100 percent protection to the flocks. When one relates this to the finding of herpes-type viruses in certain cancers in man and non-human primates, we can understand the excitement that has been generated. Successful prevention of virus-induced cancers may be one of the single most important findings with relevance to cause and prevention of cancer in man since the recognition of cancer viruses in the early 1900's. The relationships are so clear that NCI and the scientific community believe plans should be developed to produce and test vaccines, conventional or otherwise, for use in man. It is anticipated that the virus program will soon have sufficient information to decide on whether production of a vaccine is feasible. Additional time would probably be required before actual field testing. It would take four to seven years to determine the effectiveness of a vaccine because of the probable latent period of the disease.

It appears that a number of tumors are induced by hereditary information (RNA) derived from a virus which in its fully expressed form appears on electron microscopy as a virus particle. Yet, under many conditions the virus is covert and cannot be detected directly as a complete virus. Nevertheless, the hereditary information which carries with it the potential to produce cancers is transmitted from one generation to the next, apparently through the germ cells. Under certain laboratory conditions or with treatment by certain chemicals or radiation, this genetic information is expressed, sometimes producing virus or other characteristics detectable in the laboratory, and sometimes producing cancer itself. It is extremely important to find as soon as possible whether this route of cancer causation occurs in man and the extent to which this mechanism applies to the more than one hundred different types of human cancer. This is particularly important, since the means for controlling and preventing such cancers will be determined from this information. This may be accomplished not only by vaccination, but also by developing inhibitory agents (drugs, anti-enzymes, etc.) which block any or all of the various steps required in the sequence of events within the cell, beginning with infection by a tumor virus or activation of latent virus and culminating in malignant transformation.

To explore fully all new leads and approaches in investigating the role of viruses in human cancer, it is necessary to develop a capability for conducting field studies in populations on the natural ecology and for expanding related laboratory capabilities. These studies require highly skilled manpower to perform and correlate massive testing programs with epidemiological findings, and to provide the logistics to acquire large amounts of carefully produced and monitored sources of susceptible cells, tissues, sera, and viral diagnostic reagents. Successful production and purification of several different isolates of the herpes-type virus, the Type C and Type B viruses, from human cancers make it possible to

determine the amount of virus or antibody to the virus in selected human populations. Following these studies we will know whether the virus, virus antigen, or specific antibody are consistently and predominantly associated with leukemia, lymphoma, and solid tumors, and/or whether the amount of these factors is significantly different from that of normal and diseased controls. Other basic studies in animals will be required for meaningful research on viruses and interactions of viruses with chemical carcinogens. This necessitates controlled environmental facilities for rearing animals and protecting them from extraneous infections during experiments. The complexities and the cost of these studies and logistics are substantial.

The program increase of seven positions and $2,281,000 in 1972 will permit the Special Virus Cancer Program to undertake and exploit the many promising and exciting research leads currently recognized by the scientific community. The principal areas of emphasis and major opportunity for advancing the program in 1972 are:

(1) The determination of cancer-causing activity in animals by viruses already isolated from human cancers.

(2) Relating this activity, and other characteristics of the candidate viruses, to cancer in man.

(3) The determination of the entire sequence of molecular events, including specific enzymatic activities (e.g., polymerases) in viral replication and tumor induction.

(4) Relating this information to the control of cancer in man.

Carcinogenesis

The Carcinogenesis Area is responsible for planning, implementing, and managing the Institute's coordinated research program on the occurrence of cancer in man following exposure to chemical and physical agents in the environment, and on the prevention of these cancers. The program accomplishes its objectives through three main approaches: (a) identification of cancer hazards for the human population, which includes selection, animal testing and evaluation of types of tobacco smoke, pesticides, air pollutants, industrial chemicals, food additives, drugs, natural products, and other agents; (b) development and definition of animal and cellular models for bioassay and for the study of the controlling factors in the genesis of specific tumor types (e.g., lung cancer, colon cancer, bladder cancer, endocrine cancers); selected animal models are standardized for use in screening bioassays of environmental chemicals; and (c) research aimed at identifying key processes in the host tissues and cells required for the development of cancers, and exploitable as a basis for inhibitory or preventive measures capable of minimizing the occurrence of cancers in man.

Plans to accomplish the objectives outlined above and recognized as national needs, have been formulated by the Carcinogenesis Area, and the highest priority activities in this plan are being implemented through an integrated intramural and contract-supported program.

Long-term animal testing will be continued to screen potential environmental cancer-causing agents (carcinogens) at a rate of at least 150 materials per year, or a greater number if additional resources become available. Even this increased

screening effort, however, covers only a small portion of the thousands of chemicals now in the environment and awaiting testing as well as the thousands newly introduced into the environment every year. The first systematic approach to select the top priorities for such testing is being developed.

The development of biologic models for carcinogenicity studies will continue at an increased rate, as will efforts to document the degree of human relevance characteristic of these systems. The progress obtained in the Lung Cancer Program recommends extending a similar program orientation to other organ-specific types of cancer. It is planned that this organ-related approach will be extended to develop extensive program segments on colon cancer and on other organ systems such as the bladder, the pancreas, and the endocrine-related organs. The resulting definition of organ-specific animal cancer models will provide an essential resource for specialized bioassay of suspected causative agents for those cancer types in man, and the means for identifying and developing preventive measures at the host's level. Continued efforts will be made toward the establishment of data collection and retrieval systems to improve efficiency in coordinating information generated by the program and disseminating it to the scientific community. A newly developed Bioassay Data System for storage and retrieval of bioassay data will be given an extensive field trial.

Studies will continue on molecular processes, cellular responses, and immunological and biochemical mechanisms related to the control of neoplastic transformation and tumor growth. The recognition of enzyme mechanisms, controlling the activation of environmental carcinogens at the target-cell level, will be further defined. Immune control of carcinogenesis is going to be further exploited in the direct context of chemical carcinogenesis models. Other basic research leads, considered to have a high potential for the development of protective measures against cancer induction, will also be pursued. They include mechanisms for control of nucleic acids metabolism, for repair of genetic damage induced by carcinogens in target cells, and for selective control of protein synthesis. The identification of chemical-viral interaction mechanisms is given a high priority. Besides their basic value in the understanding of the genesis of cancer, these studies will also be essential for identifying the susceptible individuals in a population, most likely to develop certain forms of cancer.

A Special Lung Cancer Program in the Carcinogenesis Area is providing a definition of factors responsible for the pathogenesis of this most important type of cancer in man. The role of various chemicals and dusts in the induction of lung cancer is being tested. New biologic models are used to correlate tissue reactions in animals to those observed in the respiratory tract of man. Biological tests for the evaluation of the potential carcinogenic effects of marijuana smoke have begun and will be continued. Studies of the role of tobacco smoke components in lung cancer induction (which may lead to formulation of a less hazardous cigarette) represent a significant segment of the Carcinogenesis Program: these activities are funded mostly by the Lung Cancer Task Force and are described under the heading "Cancer Task Forces".

The Carcinogenesis Program will be continued at the same dollar level as 1971.

Demography

The Demography area has three major functions: (a) Research into the etiology of cancer in free-living populations, largely but not exclusively human; (b) development of the basic data of cancer incidence, prevalence, and mortality in the United States; (c) consultation and support in mathematics, statistics (including experiment design and analysis), and system analysis in problems of cancer research. The two branches and one special unit within the Demography area supplement and support each other in these activities.

Cancers not of genetic and familial concentration likely derive from the environment. There is growing evidence that the great majority of cancers have strong environmental components. These cancers fall into two groups: those related to a way of life (diet, habits, environment), and those related to occupations. In the studies of the Japanese, English, Norwegian and Polish migrants to the United States, a strong trend has been set for the migrants and their children to move toward patterns of cancer similar to those in the new country. For example, colon cancer is rare in Japan. Among the Japanese in Hawaii the rates are 4-5 times higher than in Japan, and compare closely to the rates for the white population. Whether this pattern is related to adoption of diet of the new country or to the new environment and its pollutants is not known. Diet is also being studied. One study, for example, is the role of dietary contributions to changing breast cancer patterns and to determine reasons for the increase in breast cancer incidence among women under the age of 55.

Cancers not preventable through manipulation of environment require the identification of high-risk persons and their early diagnosis. One early-diagnosis project, the use of mammography for the detection of breast cancer, has resulted in a 40 percent reduction in mortality from breast cancer in women screened by this technique. Other possible high-risk groups include persons having above average exposure to pesticides, chemicals, or radiation.

Because childhood cancer offers a field of investigation not clouded by smoking habits, certain diseases (not yet contracted), or occupational hazards, analyses of the 30,000 death certificates in the National Registry of Childhood Cancer Deaths will be pursued, to clarify the observed concurrence between specific congenital defects and cancer. The Register also helps identify familial clusters of cancer that could denote a hereditary tendency.

There is a strong indication that cells of people from "cancer families" have an increased susceptibility to malignant transformation that can be measured in the laboratory. If this implies increased personal susceptibility and if cancer derives from an interaction of environmental risk and personal susceptibility, identifying susceptibles and then protecting them from exposure could prevent much disease.

These genetics or hereditary studies are augmented and complemented by similar studies of domestic animals. Analysis of animal disease data will continue in expectation that the more than 50,000 case records (all diseases) now reviewed annually will yield information on the origin of cancer in animals and thereby speed the identification of factors responsible for cancer in man. The animal disease register also permits testing hypotheses that relate to the possible transmissibility of cancer from animals to man.

Following the major emphasis on prevention and early detection is treatment. Support to developing and evaluating new cancer therapy is provided by the compilation of major trends in results of cancer treatment in the United States and by the development of mathematical models to guide the planning and evaluation of experimental cancer therapy in man. Some studies in cancer of the prostate, breast cancer and lung cancer are leading toward finding the characteristics of patients who do well in contrast to those who do badly.

The Third National Cancer Survey moved into full data collection in 1970 and will continue through 1971 in ten metropolitan areas across the United States, two States, and Puerto Rico. The Survey will provide up-to-date information on cancer incidence, prevalence, and some indexes of the economic and societal impact of cancer from approximately one-quarter million cancer cases in the Survey area.

The functions described above will continue at the same budgetary level in 1972, but potential for expansion is great. To be able to continue the Third National Cancer Survey, consultative service will be limited and some planned studies on pesticides and on a safe cigarette will be postponed. Activities of the Survey during 1972 will shift from the collection to the analysis of data. Computer technology will hasten the forthcoming analyses of the Survey data and thereby provide researchers with information at the time of its maximum usefulness.

Cancer Therapy

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Total.....	294	$31,582,000	294	$31,881,000	--	+$299,000
In-House.....	294	6,883,000	294	7,124,000	--	+241,000
Contracts.....	--	24,699,000	--	24,757,000	--	+58,000

Introduction

It has been proved that drugs alone can cure some forms of cancer. This has been clearly demonstrated for choriocarcinoma and Burkitt's lymphoma. There are other cancers -- (acute lymphocytic leukemia, Ewing's sarcoma, Wilms's tumor, embryonal testicular cancer) -- that are brought under complete control for years by combinations of active drugs. A percentage of these patients have been free of evidence of disease for 10 years or more and are presumably cured. As the principles of modern cancer chemotherapy have been defined, the long term survival of patients with these diseases has been sharply increased. These principles, extended recently to Hodgkin's disease, and other lymphomas, have achieved equivalent success. The road is clearly open for application of these successes to all patients with drug sensitive tumors. These tumors constitute 15% of all clinical cancer. For the 85% of tumors that are not controlled by drugs, analysis of the successful situations has led to promising hypotheses that are under study both in the laboratory and clinic.

A key element in this success has been the development of a team of scientists and physicians with the competencies and resources to apply fundamental research results to the treatment of the cancer patients and provide necessary coordination. The emphasis is on integrated research carried out in laboratories and clinics within the Federal government, contracts with industry, and with scientists and physicians in universities. The focus of drug research and development in the Institute provides nationwide and worldwide surveillance of every new lead and the capacity to exploit it quickly to the benefit of patients.

Successful drug control has occurred among the rapidly growing tumors while the failures have been among the slowly growing tumors. Progress in the rapidly growing tumors came about because of the development and study of an excellent animal model. Such models allow the scientist to discover ways in which drugs will selectively destroy tumor cells more completely than vital normal cells, and to apply these lessons in treating patients. The recent development of slowly growing animal tumor models now permits study of the principles of control of these types of tumors.

Finally, selective toxicity of drugs can be tipped in favor of the normal cells and against the tumor cells by supportive therapy. The toxicity of drugs against normal cells is manifested by hemorrhage and infection. Hemorrhage is completely prevented by platelet replacement. Infection still occurs, but recent development of white cell replacement and laminar flow germ free environments can prevent much of the mortality from infections in patients treated in such a research setting.

Program Plans in 1971 and 1972

In order to maintain the momentum for chemical control of cancer, it is essential to undertake new ventures in order to obtain full advantage as new opportunities arise from the results of recent research.

In that part of the program relating to drug development in 1972 there will be emphasis on the more intensive study of new drugs in the clinic. The results of screening over the last 5-10 years have resulted in a fairly large number of active compounds ready for clinical trial. This will mean increased chemical production so that additional chemical prep labs will be needed. It is also planned to increase contracts for the study of drug safety in animals in order to keep up with the increased flow of drugs from the screening activities.

The biggest program deficit concerns the clinical trials. With the increased ability to find active drugs in the pre-clinical studies, there are too few institutions able to study these in patients. Expansion of existing facilities and establishment of new centers has high priority.

In the drug development area there is now a large body of information relating the structure of compounds to activity. Due to work in previous years, it is now possible to automate searching and to analyze the substructures of chemical compounds in relation to antitumor activity and toxicity. It is planned to invest more effort in automated substructure search.

There are additional plans for the expansion of supportive care of patients receiving intensive chemotherapy. The laminar flow modules have in the past year shown to be feasible and additional units will be planned at the Baltimore Cancer Research Center, the Veterans Administration and in the Clinical Center. The plans for development of full nursing units using the laminar flow principles have been held up by construction delays but individual units will be added for this expanded field trial. It is planned in 1971 to let a contract for an expanded laminar flow ward at another hospital.

In addition, the ability to type platelets, white blood cells and bone marrow cells has improved. Work in these areas will expand and donors and patients types will be placed in the automated retrieval system in 1971 and will be further developed in 1972.

Study of the kinetics of tumor cells in relation to drug susceptibility have added some new conceptual dimensions to this problem requiring additional work in 1971 and 1972. Cytosine arabinoside, a drug that specifically inhibits DNA sensitivity has been found to be an extraordinary tool for the study of the relationship of concentration of drug in biologic fluids to cell kinetics, toxicology and therapeutic effectiveness. By looking at these factors in mouse, dog, monkey and man as well as in both fast and slow growing tumors, a pattern begins to emerge showing us how to maintain the right concentration for the right length of time to kill the maximum number of tumor cells with the least possible damage to normal cells. These principles will probably have general application to a number of other antitumor drugs, and it is planned in 1971 and 1972 to expand these efforts to collect data on some of the other 40 antitumor drugs and to analyze them with this pattern in mind. Most of this has been done with the L1210 tumor in the mouse, but the new tumor models, namely AKR leukemia, B16 melanoma and the Lewis' lung tumor, will be studied during the coming years.

Treatment of the highly drug susceptible tumors in man sometimes fails because the tumors reach the central nervous system where they are protected from the effects of antitumor drugs. These studies are receiving emphasis in the neurosurgical unit at BCRC and in Burkitt's lymphoma in the Lymphoma Treatment Center in Uganda. Additional work is planned in 1971 and 1972 to design drugs that will penetrate tumors within the central nervous system and to develop an animal model in the monkey that will permit studies of better ways of treating brain involvement.

Finally, one of the major obstacles in the study of the effects of drugs on solid tumors in man is the lack of an assay which will quantify the number of tumor cells remaining after each course of drug therapy. In 1972 there will be expanded efforts especially at BCRC in the fundamental aspects of developing chemical assays for surviving tumor cells.

The Cancer Therapy program will be continued at the same dollar level as 1971.

Cancer Task Forces

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Total.....	15	$4,068,000	15	$4,079,000	--	+$11,000
Breast Cancer.....	12	301,000	12	309,000	--	+8,000
Contracts.....	--	2,458,000	--	2,458,000	--	---
Lung Cancer.....	3	120,000	3	123,000		+3,000
Contracts.....	--	1,189,000	--	1,189,000	--	---

Introduction

Breast Cancer continues to be the most common type of cancer in women in the United States. Since its beginning in 1966 the Breast Cancer Task Force has stressed the need to identify the high risk patient and to develop aids for predicting recurrence of diseases, response to treatment and survival probabilities. It has probed to bring out the possibilities of advances in cell kinetics, virology and immunology for application in breast cancer.

A Lung Cancer Task Force was established in 1968. Lung Cancer is the leading cause of cancer deaths among males and is the type increasing most rapidly. The primary areas of research encompassed by the plans for this activity include: (1) smoking and tobacco; (2) lung cancer causation other than smoking, including air pollution and host modification aspects; (3) diagnosis; and (4) treatment. Initial efforts have been focused on the first and, to a lesser extent, the third areas. The Carcinogenesis Program of the Etiology Area has undertaken responsibility for the support of the second area of emphasis in the lung cancer problem. The two programs remain closely coordinated (see Carcinogenesis section of this budget justification).

The Institute has established several other task forces or study groups. They identify major problem areas, formulate general research objectives, and, as the state of the art permits, plan and recommend specific programs and projects for implementation.

Program Plans in 1971 and 1972

Breast Cancer Task Force

There has been significant change in the membership of the Breast Cancer Task Force with the appointment of a new Chairman and Vice Chairman and two new members. Based on the knowledge acquired by task force members and others, emphasis is now being directed to establishing a more comprehensive long range plan designed to develop a series of critical questions that face the physician taking care of women with breast cancer and to develop protocols for answering these questions. The clinical studies will be carried out in collaborating

institutions and where feasible in intramural clinical units. With appropriate resources it should be possible to develop a strong NCI in-house program on Breast Cancer. The Task Force will continue to advise the Institute about studies of the biology of the breast cancer in man and experimental animals.

Studies have been conducted on a limited, exploratory scale since the initiation of the Special Virus Cancer Program to determine whether evidence could be found that viruses may be the causative agents of this disease. The search for viruses, using the electron microscope, has revealed particles resembling the known RNA cancer viruses of animals in milk of: (1) women who have had breast cancer, (2) normal women belonging to families with a high risk to breast cancer, and (3) women belonging to an inbred population (the Parsi sect of Bombay, India). Similar particles have also been seen in tissue cultures of human breast cancer cells. Other evidence--such as a unique type of nucleic acid, a unique enzyme (RNA-dependent DNA polymerase), and a unique protein (an inter-species antigen), all of which are found in association with virus-induced cancers of animals--suggests that these human particles may indeed represent virus.

Although the human particles have not yet been grown successfully in the laboratory, a similar virus has been isolated from a breast cancer of a monkey and is now being grown in the laboratory.

In 1972, studies will be conducted to investigate the candidate viruses as causes of human breast cancer.

Lung Cancer Task Force

During 1972, the Lung Cancer Task Force will continue to support a part of the efforts to implement plans developed in 1969 for a major research program on the causation, treatment, and prevention of lung cancer. The program plan is designed to seek a balance between fundamental research on the mechanisms of lung cancer causation, the development of biological models reproducing the disease as seen in man, the identification and evaluation of causative agents, as well as the development and application of existing information for the direct benefit of the patient.

Following recommendations of the Tobacco Working Group, a subcommittee of the Lung Cancer Task Force, a large program has been established to develop a less hazardous cigarette. These activities involve the preparation and chemical characterization of different types of tobacco smoke and smoke condensates, selected for their importance in determining the carcinogenicity of the condensates produced. Skin application and feeding tests are underway, while intratracheal instillation tests are about to begin. Inhalation methods, adequate for large-scale animal testing, are in the stage of pilot trials.

There is some evidence that patients with lung cancer less than 2 cm in size have a 50-60% chance of surviving for at least five years. This should be compared to 5-15% 5-year survival for all lung cancer patients. X-rays annually or even semi-annually are not sufficient to diagnose patients with lung cancer before the cancer is 2 cm in diameter. Many patients with lung cancer will have cancer cells in their sputum. However, methods of procuring sputum and the interpretation

of the cells does not rest upon as sound a base as the "Pap" test for cancer of the cervix. There are patients who have cancer cells in the sputum in which the cancer cannot be found by the usual X-ray and bronchoscopic examination. The development of tantalum powder as a diagnostic aid in X-ray examination of the lung and marked improvement in bronchoscopes are being studied to improve our ability to localize lung cancers and this gives the surgeon an indication of what tissue to remove. The follow-up of early diagnosed patients and, in fact, all patients examined for cancer cells in the sputum is underway to determine how best to diagnose lung cancer and to improve the current dismal outlook for the patient with lung cancer. Much of the work described above is being conducted through a contract with Johns Hopkins University. It is planned to expand these and similar research studies by using the contract mechanism.

The 1972 budget maintains the Cancer Task Forces at the 1971 dollar level.

Cancer Research Center

During the Senate Committee Appropriation hearings last year, there was considerable discussion concerning the urgent need for greatly improved cancer treatment services in several areas of the Nation. The upper northeastern part of the United States has great need for a center which will provide patients up-to-date cancer treatment without having to travel great distances. The Committee increased the estimate for the National Cancer Institute by $3,000,000 for the development of a cancer center at the Mary Hitchcock Memorial Hospital in Hanover, New Hampshire. This action was confirmed by the Senate, the Conferee action and included in the appropriation for 1971. The National Cancer Institute is now negotiating for the award of a contract for approximately $3,000,000 in order to develop this cancer center. It is estimated that the operating cost of the center for 1972 will be $500,000. The decrease in funds of $2,500,000 in this account has been reprogrammed to meet moral commitments under regular research grants and for specialized research cancer centers to be funded through the grants mechanism.

Supporting Services

Supporting Services is primarily a service oriented unit of the Institute which provides selected administrative, office and laboratory support services. Also included in this item is the editorial review and publication of the Journal of the National Cancer Institute, a scientific publication of excellence and one of the three journals in the U.S. devoted exclusively to publication of quality cancer research results.

In 1972, the amount of funds requested will enable the Institute to continue this type of support at approximately the same dollar level as 1971.

In addition to the program changes, there is an increase of $1,101,000 which includes $231,000 for annualization of new positions in 1971, $472,000 for annualization of 1971 pay increase costs, $189,000 for within-grade pay increases, $35,000 for extra day of pay in 1972, $18,000 for FTS cost increase, and $156,000 for payment to the National Institutes of Health Management Fund for centrally furnished services.

Review and Approval of Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	110	$1,581,000	110	$1,778,000	--	+$197,000
Other expenses.....	--	1,740,000	--	1,858,000	--	+118,000
Total.....	110	3,321,000	110	3,636,000	--	+315,000

Introduction

This activity supports both the scientific and administrative staff responsible for the review of all cancer grants. The staff obtains the necessary information regarding all grant applications and in cooperation with study groups makes recommendations for the consideration by the National Advisory Cancer Council which recommends approval or disapproval of grant applications. Administrative support is provided concerning policy, planning and coordination of contract activities of the Institute.

Program Plans in 1971 and 1972

In 1971 this activity will continue to provide scientific and administrative support for the review of all Institute grants. The grant program has expanded from a $93,000,000 program in 1970 to a $108,000,000 program in 1971. The policy, planning and coordination of contract activities has increased greatly due to the increase in funds for an expanded effort in viruses as cause of cancer.

In 1972, the program increase of $50,000 will provide funds for program management in connection with the expansion in the regular research grants, specialized research centers and contract programs.

In addition to the program change there is an increase of $265,000 which includes $18,000 for annualization of new positions in 1971, $132,000 for annualization of 1971 pay increase costs, $41,000 for within-grade pay increases, $6,000 for extra day of pay in 1972, and $68,000 for payment to the National Institutes of Health Management Fund for centrally furnished services.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	56	$893,000	56	$958,000	—	+$65,000
Other expenses.....	—	744,000	—	805,000	—	+61,000
Total.....	56	1,637,000	56	1,763,000	—	+126,000

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.

In 1972, the program increase of $50,000 is requested to provide funds for the support of contracts to assist in the further development of program planning and computer applications to the research programs of the Institute.

In addition to the program change there is an increase of $76,000 which includes $13,000 for annualization of new positions in 1971, $30,000 for annualization of 1971 pay increase costs, $19,000 for within-grade pay increases, $3,000 for extra day of pay in 1972, and $11,000 for payment to the National Institutes of Health Management Fund for centrally furnished services.

Cancer Research Initiatives

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	250	---	250	$3,224,000	---	+$3,224,000
Other expenses.....	---	---	---	96,776,000	---	+96,776,000
Total.....	250	---	250	100,000,000	---	+100,000,000

Introduction

The President has called for the launching of an intensive campaign to find a cure for cancer and has stated that he will ask later for whatever additional funds can be effectively used beyond the hundred million additional dollars. He called for the same kind of concentrated effort that split the atom and took man to the moon and for a total national commitment to achieve the goal. Other groups have called for major large-scale research and development efforts for cancer and have provided extensive background on the magnitude of the problem and justification for expanded efforts. NCI staff analyses also support the concept that major expansion of R&D efforts in cancer are warranted.

The ultimate goal of a major research and development program on cancer is the prevention of all human cancers. A more realistic statement of the program goal is to develop through R&D efforts the means to prevent as many cancers as possible, cure as many patients as possible who develop cancer, provide maximum palliation in patients not cured, and restore treated patients to as nearly a wholesome state as possible through rehabilitation; the goal should be to effect improvements in the percentages of successes in each of these categories as quickly as possible.

Program Plans in 1972

In order to work toward this goal, the increased funding will allow us to expedite an R&D program consisting of the following components: (1) causation and prevention; (2) diagnosis and detection; (3) treatment; (4) programs (extended task forces) on each kind of cancer that represents a major form of human cancer defined by organ sites (lung, large bowel, breast, leukemias and lymphomas, bladder and prostate, brain and pancreas); (5) cancer centers; (6) grant-supported activities; and (7) management and coordination of the total program, including a "nervous system" with incoming sensing data inputs, central analysis and decision-making for action, and implementing communication links to the decentralized activities.

Major multidiscipline cancer centers, which generally are the major cancer institutes, are critical components in the effort. They are essential to multidiscipline cancer research, especially clinical research because sizable numbers of cancer patients are involved, and they provide an appropriate, or even a necessary, focus of joint efforts on cancer in its various aspects. Responsibility for the delivery of health care to all cancer patients is not part of this proposed program. However, a satisfactory coupling of the output of the R&D Program with the activities in the practice of medicine and public health is necessary. Major centers can play a key role in bridging the two areas, as well as providing needed

means for evaluating R&D developments. It is important that efforts be made to insure geographic distribution of the major centers in principal regions of the Nation. The program for Cancer Research Initiatives include funds for planning, renovation and construction of three major classes of centers, e.g. comprehensive cancer research centers, specialized cancer research centers and cancer chemotherapy research centers. Construction costs included will be primarily renovation and planning costs, but will involve some construction. Also included are funds for the planning of an outpatient clinic building, as well as additional laboratory facilities. If construction approval clearances can be readily secured, funds will be made available to award a construction contract to make such an addition to the NIH Clinical Center.

The estimated obligations include an expansion in Etiology activities consisting of viral oncology, chemical carcinogenesis and demography. There are now over 110 viruses which are known to cause virtually all kinds of cancer in every major group of animals including subhuman primates. The direct application of this laboratory know-how to human disease has revealed that virus particles seen in the electron microscope are of three types which can be detected and in some cases isolated from patients afflicted with different types of cancer—type C, type B and herpes type (HTV). Methods for prevention and control of virus-related human cancers are being developed, and the relation of these viruses to human cancers must be precisely elucidated. Numerous leads are available for development and exploitation as resources permit.

The major areas of opportunity and need for progress in cancer prevention through studies in Chemical Carcinogenesis are: (a) develop better means for the removal of hazardous chemicals from the environment; (b) develop means to enhance the ability of the host to detoxify environmental agents; (c) determine the extent to which chemicals act in synergistic concert with viruses or with physical carcinogens such as irradiation; and (d) develop more rapid and more sensitive means to detect and bioassay the cancer-inducing effects of chemicals for man. Plans for expanded operations in these areas are developed and await implementation.

Included in the estimated obligations are funds for expansion in the area of treatment of cancer, with emphasis on chemotherapy. Improvements in results of treatment have resulted over the past several decades. Once cancer has become disseminated throughout the body, or in the case of some forms of cancer such as leukemia and lymphoma in which dissemination begins early in the disease, surgery cannot be curative and radiation cures in only a small percentage of the cases. A major R&D thrust, therefore, for developing the means for a cure (or even improved palliation) for these kinds of patients is the development of drugs that will selectively control the cancer tissues without unacceptable toxicity and other undesirable side effects for the patient. The use of chemical agents of a great variety in this search has been a mainstay over the past decade and a half, and it is now established that several human cancers can be cured by drugs. Principles learned over the past several years can now be extended to screening of drugs for treatment of the more common tumors, and clinical evaluations of new drugs and treatment combinations can be profitably extended to more types of cancer patients. Additional possibilities are before us in the immunological treatment of cancers and in seeking ways to modify the host's resistance to cancer development and growth.

The remainder of the funds will be utilized for fundamental research; for fellowship and training programs to insure the needed additional supply of personnel needed in later years; and for the various task forces set up to perform coordinated laboratory and clinical research on the major types of human cancers, including lung, breast, colon, rectum, prostate-bladder, brain and pancreas.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Research Grants (Public Health Service Act, Title IV, Part A)

1971 Amount	1972 Authorization	1972 Budget Estimate Amount
$95,411,000	Indefinite	$97,403,000

Purpose: The National Cancer Institute, through its research grant program stimulates and supports basic and applied research activities in the broad areas of causation, diagnosis, treatment, prevention and control of cancer.

Explanation: The NCI research grant program is composed of regular program grants, general research support grants, scientific evaluation grants, specialized research centers and leukemia research support centers. Grants are awarded to public and other non-profit institutions and to outstanding individuals in support of cancer research and related activities.

Accomplishments in 1971: During 1971, a total of 1,002 regular research grants were awarded. Emphasis was placed on projects of known or potential relevance to cancer including radiation, chemical carcinogenesis, the nature of cancers and their interactions with the host organisms, immunology, drug development, and epidemiology.

Clinical investigations of new and complex anti-cancer therapies were carried out in approximately 250 institutions across the nation. The investigators at these institutions are organized in 23 cooperating groups on the basis of the therapy under study, e.g., pediatrics. urology, etc.

The NCI supported 33 Specialized Research Centers which are performing intensive, highly specialized clinical research on cancer in man.

The Institute provided support to 27 Leukemia Research Support Centers for investigators who have been obtaining, preserving, processing and administering massive platelet transfusions in the control of hemorrhage in patients with acute leukemia.

Objectives for 1972: During 1972, the funds requested will allow for the awarding of 954 regular research grants. In 1972, the program decrease of $2,651,000 includes $626,000 for general research support grants and $2,025,000 in the regular research grant program. The decrease in regular research grants will result in an overall reduction in on-going programs with the exception of the efforts in virus research. A program increase of $500,000 will serve to provide new initiatives in virology research where indications are that transformation, at least on the part of small tumor viruses, results from the attachment of one or more viral genes to cellular genes. The program increase of $1,500,000 in specialized research centers will be used to initiate one or two new centers in geographical areas where centers do not exist at this time.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Fellowships (Public Health Service Act, Title IV, Part A)

1971 Amount	1972 Authorization	1972 Budget Estimate Amount
$3,798,000	Indefinite	$3,348,000

Purpose: Fellowships are awarded to promising individuals preparing for a research career in the biomedical sciences.

Explanation: Several kinds of awards designed to meet particular objectives are granted under this program. The program provides research training to individuals whose career development extends from the immediate postdoctoral period through the advanced stages of scientific attainment. The types of awards provided are postdoctoral, special, career development awards and career awards.

Accomplishments in 1971: In 1971, 148 postdoctoral and special fellowships were awarded. Also 94 career award and career development fellowships were supported.

Objectives for 1972: For 1972, the funding level requested will support 142 postdoctoral and special fellowships as well as 74 career award and career development awards. The fellowship program will continue to provide training to promising young investigators in cancer research. Emphasis in 1972 will continue to be given to the shortage areas of medicinal and organic chemistry, epidemiology, radiation therapy, surgery, hematology, and clinical pharmacology.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Training Grants (Public Health Service Act, Title IV, Part A)

1971 Amount	1972 Authorization	1972 Budget Estimate Amount
$8,358,000	Indefinite	$8,358,000

Purpose: The National Cancer Institute awards to academic or research institutions which have demonstrated the ability to design and conduct successful training programs in such fields as surgery, pathology, radiobiology, radiotherapy, and internal medicine.

Explanation: Graduate research training grants provide support for trainees in the various fields related to cancer research and underwrite expenses for equipment, supplies, and training staff. Clinical cancer training grants are awarded to qualified institutions to provide training in the prevention, diagnosis, treatment, rehabilitation, and public health aspects of cancer.

Accomplishments in 1971: In 1971, approximately 587 full-time equivalent trainees were supported through 141 training grants.

Objectives for 1972: The estimate for 1972 will provide for 125 training grants consisting of approximately 526 full-time equivalent trainees. Emphasis will be placed on continuing training programs in disciplines where cancer researchers are in short supply, such as radiation therapy, clinical pharmacology, chemical carcinogenesis, epidemiology and training.

Activity: Laboratory and Clinical Research (Public Health Service Act, Title IV, Part A)

1971 Pos.	1971 Amount	1972 Authorization	1972 Budget Estimate Pos.	1972 Budget Estimate Amount
473	$20,518,000	Indefinite	476	$21,529,000

Purpose: Research in this activity is designed to add to our knowledge the basic processes of cancer and to improve methods of diagnosis and therapy. The types of work performed are laboratory research in the fields of biochemistry, biology, pathology, and physiology and clinical research in the fields of dermatology, endocrinology, immunology, metabolism, and surgery.

Explanation: Laboratory and clinical research is conducted in the Institute's laboratory facility and in a commonly shared clinical center facility. In addition, a limited amount of the work is performed through research contracts.

Accomplishments in 1971: Research studies ranged from a study of the processes involved in translating information in the nucleus in the form of DNA to operations within the cell by enzymes. Clinical studies ranged from those designed to improve radiation therapy and surgery as therapeutic tools to those designed to determine how cancer affects the patient.

Objectives for 1972: In 1972, the program decrease of $175,000 will result in an overall reduction in on-going programs with the exception of the virus program. The program increase of three positions and $408,000 will provide for an expanded effort directed toward applying advances in immunology as related to virus to the treatment and prevention of cancer in man.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Collaborative Research and Development (Public Health Service Act, Title IV, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
771	$97,419,000	Indefinite	778	$98,301,000

Purpose: The Institute established the Etiology and Cancer Therapy areas under this activity to provide strong central leadership and responsibility for carefully planned research activities. The programs focus on causes of cancers and their occurrence patterns and prevention, as well as finding the best methods of treating cancer through the screening, testing and clinical evaluation of drugs.

Explanation: These programs include national efforts utilizing research contracts as well as investigations carried on directly in Government laboratories and clinical facilities.

Accomplishments in 1971: The principle area of emphasis in the viral oncology program was the determination of (a) cancer-causing activity in animals of viruses already isolated from human cancer, and (b) relating this activity and other characteristics of the candidate viruses to cancer in man.

In carcinogenesis, evaluation of 150 pesticides and other environmental agents has been completed in 1971. This increased screening effort, however, covers only a small portion of the thousands of chemicals now in the environment and awaiting testing as well as the thousands newly introduced into the environment every year. A Bioassay Data System for storage and retrieval of bioassay date was developed.

In addition to studies conducted in the demography area concerning occurrence and behavior of cancers in human populations, the Third National Cancer Survey continued to collect cancer information in conjunction with the 1970 census in ten metropolitan areas, two States and the Commonwealth of Puerto Rico.

The cancer therapy program has been able to carry out fundamental research on the drug control of clinical cancer, to achieve successful drug development, and to apply the results of research and development to the control of the rapidly growing tumors.

During 1971, the Breast Cancer Task Force continued comprehensive studies of women who develop breast cancer, in particular, to determine if viruses may be the causative agents of this disease. During 1971, the Lung Cancer Task Force continued to support limited initial efforts to implement plans developed in 1969 for a major research program on the causation, treatment and prevention of lung cancer.

Objectives for 1972: The major objectives in the special virus cancer program are: (a) the determination of cancer-causing activity in animals by viruses already isolated from human cancers, (b) relating this activity, and other characteristics of the candidate viruses, to cancer in man, (c) the determination of the entire sequence of molecular events, including specific enzymatic activities (e.g., polymerases) in viral replication and tumor induction, (d) relating this information to the control of cancer in man.

The chemical carcinogenesis area will give high priority to the identification of chemical-viral interaction mechanisms, the role of various chemicals and dusts in the induction of lung cancer and the establishment of data collection and retrieval systems to improve efficiency in coordinating information generated by the program and disseminating it to the scientific community.

In demography, epidemiology studies will be made in human populations of the role of viruses and chemicals in cancer initiation. In 1972, the activities of the Third National Cancer Survey will shift from the collection of data to the analysis of the data.

The major objectives of the cancer therapy area for 1972 are the development of a biochemical assay for the number of tumor cells in the body; improvement in the treatment of cancer within the brain; further evaluation of an animal model for the small growth fraction tumors; and a continued flow of new agents to the clinic.

During 1972, the Breast Cancer Task Force will direct its efforts to investigate the candidate viruses as cause of human breast cancer. Under the Lung Cancer Task Force, the objective for 1972 is the development of a less hazardous cigarette.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Review and Approval of Grants (Public Health Service Act, Title IV, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
110	$3,321,000	Indefinite	110	$3,636,000

Purpose: This activity supports administrative staff concerning policy, planning and coordination of contract activities of the Institute. It also supports both the scientific and administrative staff responsible for the review of all grants.

Explanation: Funds are provided for the support of the in-house staff. Funds for the contract and grant programs are provided under the budget activities for research grants, fellowships, training grants, laboratory and clinical research and collaborative research and development.

Accomplishments in 1971: In 1971, this activity reviewed 2,254 grants for scientific merit and program relevance and maintained surveillance over 1,448 grants.

Objectives for 1972: This activity will continue to provide scientific and administrative support for the review of all Institute grants and will continue to establish policy, planning and coordinate contract activities. The program level for 1972 includes an increase over 1971 of $50,000 in order to provide support for the expansion in regular grants, specialized research centers and contract programs.

Activity: Program Direction (Public Health Service Act, Title IV, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
56	$1,637,000	Indefinite	56	$1,763,000

Purpose: This activity supports the Director and his immediate staff including program planning, research information and general administration. Professional leadership and technical guidance are provided to the varied activities of the Institute.

Explanation: Funding for this area provides for salaries and other operating costs for the overall administration and direction of the programs of the Institute.

Accomplishments in 1971: The planning staff of the Office of the Director has continually provided analysis, consultation and guidance to varied activities both within and outside the NCI for effective planning and operation of their programs. The production of the television program on "Progress Against Cancer" is now in process.

Objectives for 1972: Increased program planning and the development of computer applications to the programs of the Institute will be undertaken with the increase of $50,000. It is planned that the television program "Progress Against Cancer" will be televised during 1972.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Cancer research initiatives (Public Health Service Act, Title IV, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
250	---	Indefinite	250	$100,000,000

Purpose: To launch an intensive campaign for the prevention of cancer in man, to cure as many patients as possible, provide maximum palliation in patients, and restore treated patients to as nearly a wholesome life as possible.

Explanation: This major R&D effort will be carried out through the various funding mechanisms of grants, contracts and in-house activities. This will include expansion and addition of cancer research centers.

Objectives for 1972: Establishment of an organization within the National Institutes of Health for the Cancer Conquest Program; develop an effective total Program plan; expand and add cancer research centers; and expand research and development efforts in all areas of cancer research which are all encompassed under the general categories of causation, prevention, diagnosis and treatment of cancer.

New Positions Requested
Fiscal Year 1972

	Grade	Number	Annual Salary
Laboratory and clinical research			
Medical Officer	GS-15	1	$22,885
Biologist	GS-13	1	16,760
Biologist	GS-9	1	9,881
		3	49,526
Collaborative research and development			
Medical Officer	GS-15	1	22,885
Medical Officer	GS-14	1	19,643
Microbiologist	GS-14	1	19,643
Biologist	GS-13	1	16,760
Biologist	GS-9	1	9,881
Chemist	GS-7	1	8,098
Secretary	GS-5	1	6,548
		7	103,458
Total new positions, all activities		10	152,984

TUESDAY, MAY 4, 1971.

NATIONAL HEART AND LUNG INSTITUTE

WITNESSES

DR. THEODORE COOPER, DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ROBERT W. BERLINER, DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DR. ROBERT L. RINGLER, DEPUTY DIRECTOR, NATIONAL HEART AND LUNG INSTITUTE
LYMAN MOORE, EXECUTIVE OFFICER, NATIONAL HEART AND LUNG INSTITUTE
JOHN H. REEDER, FINANCIAL MANAGEMENT OFFICER, NATIONAL HEART AND LUNG INSTITUTE
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
GERALD F. MEYER, CHIEF, HEALTH BRANCH, DIVISION OF BUDGET

National Heart and Lung Institute

Object Classification (in thousands of dollars)

Identification code 09-30-0872-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	7,274	8,121	8,397
11.3	Positions other than permanent	405	405	405
11.5	Other personnel compensation	70	70	70
	Total personnel compensation	7,749	8,596	8,872
12.1	Personnel benefits: Civilian employees	781	857	877
21.0	Travel and transportation of persons	356	375	378
22.0	Transportation of things	69	75	79
23.0	Rent, communications, and utilities	279	325	325
24.0	Printing and reproduction	178	200	200
25.0	Other services	29,122	39,531	34,573
26.0	Supplies and materials	1,973	2,200	2,275
31.0	Equipment	846	1,000	1,050
41.0	Grants, subsidies, and contributions	118,904	141,288	145,818
42.0	Insurance claims and indemnities	1	1	1
99.0	Total obligations	160,258	194,448	194,448

Personnel Summary

Total number of permanent positions	570	590	607
Full-time equivalent of other positions	55	63	63
Average number of all employees	623	645	651
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0872-0-1-651		1970 actual	1971 est.	1972 est.
	Program by activities:			
	1. Grants:			
	(a) Research	96,490	116,774	126,031
	(b) Fellowships	6,904	6,871	6,195
	(c) Training	22,052	17,643	13,592
	2. Direct operations:			
	(a) Laboratory and clinical research	13,705	17,071	15,946
	(b) Collaborative research and development	25,701	30,556	26,591
	(c) Biometry, epidemiology, and field studies	1,997	1,876	1,983
	(d) Review and approval of grants	2,478	2,818	2,673
	(e) Program direction	1,095	839	1,437
	Total program costs, funded [1]	170,422	194,448	194,448
	Change in selected resources [2]	−10,164	----------	----------
10	Total obligations	160,258	194,448	194,448
	Financing:			----------
25	Unobligated balance lapsing	291	----------	----------
	Budget authority	**160,549**	**194,448**	**194,448**

Object Classification (in thousands of dollars)

Identification code 09-30-0872-0-1-651		1970 actual	1971 est.	1972 est.
	Budget authority:			
40	Appropriation	171,256	193,479	194,448
40	Portion withdrawn (Public Law 91-204, sec. 410)	−10,744	----------	----------
40	Pay increase (Public Law 91-305)	121	----------	----------
41	Transferred to other accounts	−84	−24	----------
43	**Appropriation (adjusted)**	**160,549**	**193,455**	**194,448**
46.10	**Proposed transfer for wage-board pay increases**	----------	**84**	----------
46.20	**Proposed transfer for civilian pay act increases**	----------	**792**	----------
46.30	**Proposed transfer for military pay act increases**	----------	**117**	----------

Program and Financing (in thousands of dollars)—**Continued**

Identification code 09-30-0872-0-1-651		1970 actual	1971 est.	1972 est.
	Relation of obligations to outlays:			
71	Obligations incurred, net	160,258	194,448	194,448
72	Obligated balance, start of year	112,297	109,117	127,251
74	Obligated balance, end of year	−109,117	−127,251	−138,159
77	Adjusted in expired accounts	−2,390	----------	----------
90	Outlays, excluding pay increase supplemental	161,048	175,331	183,530
91.10	Outlays from wage-board supplemental	----------	83	1
91.20	Outlays from civilian pay act supplemental	----------	785	7
91.30	Outlays from military pay act supplemental	----------	115	2

[1] Includes capital outlay as follows: 1970, $559 thousand; 1971, $846 thousand; 1972, $1,000 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $65,398 thousand; 1970, $55,235 thousand; 1971, $55,235 thousand; 1972, $55,235 thousand.

NOTES

Includes $1,309 thousand in 1972 for activities previously financed from (in thousands of dollars):

	1971
National Institute of Arthritis and Metabolic Diseases	78
National Institute of Allergy and Infectious Diseases	802
National Institute of General Medical Sciences	429

Includes $630 thousand in 1971 and $630 thousand in 1972 for activities previously financed from: Research resources, 1970, $630 thousand.

Excludes $532 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	*1971*
Office of the Director	80	71
National Institute of Child Health and Human Development	51	36
National Eye Institute	23	---
National Institute of General Medical Sciences	--	144
Health manpower	--	281

Excludes $4,051 in 1972 for activities transferred to: Health manpower, 1970, $4,051 thousand; 1971, $4,051 thousand.

INTRODUCTION OF DR. COOPER AND ASSOCIATES

Mr. FLOOD. We are continuing with the National Institutes of Health and now take up the National Heart and Lung Institute. The presentation will be made by Dr. Theodore Cooper, the Director.

We have here a biographical sketch of you which will be included in the record at this point.

(The document follows:)

BIOGRAPHICAL SKETCH OF THEODORE COOPER, M.D.

Name: Theodore Cooper, M.D.

Position: Director, National Heart and Lung Institute.

Birthplace and date: Trenton, N.J., December 28, 1928.

Education: June 1946—Graduated from High School; June 1949—B.S., Georgetown University; June 1954—M.D., St., Louis University; 1956—Ph. D., St. Louis University.

Experience: 1968–present, Director, National Heart and Lung Institute; 1967–68, Associate Director for Artificial Heart-Myocardial Infarction program—National Heart Institute; 1966–68, professor and chairman, department of pharmacology and professor of surgery, University of New Mexico School of Medicine; 1964–66, professor of surgery, St. Louis University; 1962–64, associate professor of surgery, St. Louis University; 1961–65, director, Center for Cardiovascular Research, St. Louis University; 1960–62, assistant professor of surgery, director section of surgical physiology, St. Louis University; 1959–60, Surgeon, U.S. Public Health Service, National Heart Institute; 1958–59, assistant resident in surgery, St. Mary's Group of Hospitals, St. Louis University; 1956–58, S.A. Surgeon, U.S. Public Health Service, National Heart Institute; 1954–55, intern, St. Mary's Group of Hospitals, St. Louis University.

Association memberships: American Society for Clinical Investigation, American Physiological Society, Society for Experimental Biology and Medicine, American Society for Pharmacology and Experimental Therapeutics, Society of Sigma XI, International Cardiovascular Society, American College of Chest Physicians, American Society of Artificial Organs, American Federation for Clinical Research, American Association of University Professors, American Association for Advancement of Science, American College of Cardiology.

Special awards, citations, or publications: Borden Award—St. Louis University, 1954; Who's Who in American Colleges and Universities, 1956; Research Development Award, USPHS, 1962–66; Author or coauthor of approximately 150 publications. Editorial board, circulation, American Journal of Physiology, Journal of Applied Physiology, editorial board—Journal of Pharmacology and Experimental Therapeutics, circulation research, Journal of Molecular Cardiology.

Dr. COOPER. We have with us the new executive officer of the National Heart and Lung Institute, Mr. Lyman Moore on my far left and the Deputy Director of the Institute, Dr. Robert Ringler to my near left.

Mr. FLOOD. We would like biographical sketches of both of these gentlemen.

(The documents follow:)

BIOGRAPHICAL SKETCH

Name: Robert L. Ringler, Ph. D.

Position: Deputy Director, National Heart and Lung Institute.

Birthplace and date: Chase, Mich., March 27, 1922.

Education: A.B., Central Michigan College, February 1951; Ph. D. (biochemistry), Michigan State University, August 1955.

Experience: 1961–present, National Heart and Lung Institute, NIH, Bethesda, Md.; 1969–present, Deputy Director; 1969–70, Acting Associate Director for

Collaborative Research and Development; 1968–69, Special Assistant to the Director; 1967–68, Chief, Institutional Research Programs; 1967–68, Acting Chief, Program Projects Branch; 1966–67, Head, Task Force on Cardiovascular Research Centers; 1962–66, Chief, Program Projects Branch; 1961–62, Scientist Administrator; 1957–61, Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit, Mich., Senior Associate, Enzyme Division; 1955–57, North Carolina State College, Raleigh, N.C., Assistant Professor, Department of Biochemistry; 1951–55, Michigan State University, East Lansing, Mich. graduate assistant.

Association memberships: American Society of Biological Chemists, American Heart Association, Fellow, American College of Cardiology, Sigma Xi.

Special awards citations, or publications: 75th Anniversary Award, Central Michigan University, 1967; DHEW Superior Service Honor Award, June 1970; Author or coauthor of approximately 25 scientific publications.

BIOGRAPHICAL SKETCH

Name: Lyman Moore.

Position: Executive Officer, National Heart and Lung Institute.

Birthplace and date: Elizabeth, N.J., January 16, 1916.

Education: 1932–1936 Princeton University—A.B.; 1939–1940 University of Minnesota—M.A.

Experience: 1970-present, Executive Officer, National Heart and Lung Institute; 1970, Regionalization Coordinator, Office of the Administrator, Health Services and Mental Health Administration; 1968–1970, Acting Executive Officer, National Center for Health Services Research and Development, Health Services and Mental Health Administration, DHEW; 1967–1968, Executive Officer, Bureau of Disease Prevention and Environmental Control, PHS, DHEW; 1960–1966, Executive Officer, BSS/Environmental Health, PHS, DHEW; 1958–1960, Assistant Executive Officer, Public Health Service, DHEW; 1954–1958, Consultant, Booz, Allen & Hamilton; 1951–1954; 1958–1966, Professorial lecturer, The American University; 1949–1954, Executive Officer, National Institute of Mental Health, NIH; 1940–1949, Budget Examiner, U.S. Bureau of the Budget; 1937–1939, Program Officer, International House, New York N.Y.; 1936–1937, Assistant in Instruction, Woodrow Wilson School of Public and International Affairs, Princeton University.

Association memberships: Society for Advancement of Management—Vice president-membership—1966–1968; vice president, intersociety relations—1968–1969 past president, Washington Chapter, American Society for Public Administration, American Public Health Association (Fellow), Association for Management in Public Health—member board of directors—1967—present.

Special awards citations, or publications: Phi Beta Kappa—Princeton University, American Youth Hostels National Award for Distinguished Service to Hosteling—November 1963.

GENERAL STATEMENT

Mr. FLOOD. I see you have a prepared statement. How do you wish to proceed?

Dr. COOPER. I would like to read my prepared statement first, Mr. Chairman.

Mr. FLOOD. All right, suppose you do that.

Dr. COOPER. Mr. Chairman and members of the committee: I am pleased to have this opportunity to discuss with you what we, at the National Heart and Lung Institute, are trying to do to prevent diseases of the heart and lungs, as well as to detect and treat diseases of these systems which have already developed.

This Institute supports research on diseases of the heart, lungs and vascular systems in its own laboratories and clinics in Bethesda and through grants and contracts to universities, medical schools and other institutions. While I am happy to detail any of these for you, I would

like in this opening statement to highlight particularly new programs which we have started in three areas of major concern: heart attacks, diseases of the blood, and diseases of the lung.

HEART ATTACKS LINKED TO BLOOD FAT DISORDERS

We place our major emphasis on heart attacks because they represent the Nation's No. 1 killer. Fundamental research has shown us that two groups of patients are at particularly high risk of heart attack early in their adult life. These two groups of patients (known scientifically as type II and IV hyperlipoproteinemia) have different types of disorders of their blood fats. Both types, but particularly the first type, seem to pass the disorder from parents to children, and hence whole families may be affected.

Mr. FLOOD. They seem to?

Dr. COOPER. We do not know the extent to which this is actually transmitted and to what extent this is actually prevalent in the open community.

Mr. FLOOD. From parents to children? How about Mendel's law?

Dr. COOPER. We do not know this information.

Their blood fat levels can be reduced by specific diets and by drugs. The second group, type IV hyperlipoproteinemias, can also be treated by proper diet, but a diet different from the type II's, and their lipids further lowered, if necessary, by drugs, but again by a different drug from the type II's.

Mr. FLOOD. What are lipids?

Dr. COOPER. Lipids are fatty substances and these can be found in the blood of all people, both normal and abnormal.

With our new Lipid Research Clinics, the Institute is beginning studies to determine how many such people there are in the population at large, how best to diagnose their abnormality, and most importantly, determine just what effect lowering the blood fats has on their risk of a heart attack. We expect that reduction of blood lipid levels will reduce the risk of heart disease in these patients but this fact remains to be proven. Since they would be expected to remain on the special diet and drug therapy for life, it is very important to be sure that the drug has no unexpected, and unwanted, side effects and it is equally important to know when, in the life of the individual, the diet should be started.

CONTROLLING HIGH BLOOD PRESSURE

The Institute also has plans for studies in the prevention of heart disease through control of high blood pressure in patients in the community. Studies conducted in Veterans' Administration hospitals have provided strong indications that under the particular conditions of the VA study, blood pressure can be controlled and the complications of persistent high blood pressure prevented. Proof that controlling blood pressure will reduce heart attacks has yet to be established as has the feasibility and the efficacy of giving the drugs to patients who are living in different parts of the country, working at many different types of jobs, being of different ages, and, perhaps most importantly

of all, not being under the strict management of a controlled clinical trial as was the case in the VA study.

POSSIBILITY OF INHERITING BLOOD FAT PROBLEMS

Mr. FLOOD. I want to go back to the top of the page where you say these people would be expected to remain on the special diet and drug therapy for life.

That suggests this is either (1) inherent or (2) acquired at a very early age and continues through life.

Dr. COOPER. Yes, sir. We feel there is some indication, particularly in the type II condition, that if it is transmitted the disease may have an incubation period of 20 or 30 years. Therefore we need to detect it early in life and perhaps begin to ameliorate or modify the life style of these patients early on, but the basic information for this is not yet available.

Mr. FLOOD. Is this type of disease, in that type II class, one that becomes progressively worse?

Dr. COOPER. Yes, it does. Vascular lesions become progressively worse and perhaps 50 percent of the people with type II disease may have had a heart attack before the age of 50.

MYOCARDIAL INFARCTION UNITS

I have described our myocardial infarction research units in previous appearances before this committee. These units are continuing to provide new knowledge as to how best to care for patients who arrive at a hospital having had a heart attack. These units have developed new methods for determining the size of the infarct, new ways of measuring changes in the patient's blood pressure, his cardiac output and the amount of oxygen carried in his blood, as well as new methods of determining how well the patient is responding to treatment.

Mr. FLOOD. What is myocardial infarction as opposed to other types of attack?

Dr. COOPER. Very often in the common parlance a heart attack means an episode in which there is acute failure of the heart, where people become short of breath and have to sit up and gasp for breath, but a myocardial infarction is the crushing, subexternal pain that occurs when the muscle is deprived of blood supply.

Mr. FLOOD. Does it actually damage the physical heart?

Dr. COOPER. Yes, sir; considerably.

We also have a number of programs directly concerned with those patients who do not live long enough to get to a hospital to have their heart attack cared for. In a variety of different ways, we are trying to determine who is likely to die suddenly due to unsuspected heart disease. We are trying to find out what can be done on the spot for these people whose life expectancy may be less than an hour and who must therefore have immediate treatment if they are to survive. We are working on new ways of getting the therapy to them, new drugs which may prevent their attack in the first place, new tests which will identify those at risk before their disease becomes apparent.

THE MEDICAL DEVICES APPLICATION PROGRAM

The mandate of what was formerly called the artificial heart program has been broadened to include the development of devices needed to support patients with chronic lung disease and the name of the program has been changed to the medical devices applications program. New materials have been developed that are of particular importance to the program. These materials minimize blood clotting, damage to blood cells and denaturation of blood proteins; all things which could make the patient worse, not better.

We now have a number of new materials such as anionic polymers, modified silicones, hydrogels and block polymers which seem to not only work well when made up into these devices but they possess that most critical property, they do not cause major damage to the blood.

Mr. FLOOD. All through your testimony I find a theme, or motif of uncertainty. You have an idea but you are uncertain about these things?

Dr. COOPER. Yes, sir. These are new leads which we have identified in recent years that would seem to offer a great deal of promise and what I am trying to avoid is overpromise in this presentation. These are all things that need further study and clinical trial.

TESTING THE EFFICACY OF NEW MEDICAL DEVICES

The next hurdle to be met with these materials is to determine how well they stand up under use and how well the body stands up after having had them implanted.

Mr. FLOOD. Any danger of fallout from any of these things?

Dr. COOPER. We have learned that substances which used to be called inert, that would not have effects on the body, seem to have toxic effects that could have some dangerous fallout on the systems. This is why certain types of devices, when implanted, do not seem to sustain life for more than several days or weeks.

To study the performance of these devices, two Test and Evaluation Centers have been developed for subjecting materials and the devices to bench tests, tests in animals, and finally, to carefully controlled clinical trials prior to general use.

Now, these devices, if they should prove out to the effective and safe, would help rehabilitate patients with chronic serious lung disease, as well as those with heart attack.

Recently a surgical procedure has been developed for restoring blood supply to the heart itself in patients who have diseases or blockage of the coronary arteries or who have already had a heart attack. The procedure involves bypassing the obstructed segment of the coronary artery with either a natural vessel from elsewhere in the patient's body or with a synthetic vessel.

Mr. FLOOD. What do you mean by a vessel?

Dr. COOPER. An artificial artery or tube made out of a plastic.

We estimate that the procedure has been performed in approximately 12,000 patients. Early results have been most encouraging.

NATIONAL BLOOD RESOURCE PROGRAM

I mentioned the problem of blood clotting. This is a problem not only in heart disease but in lung disease as well since a clot in a vessel to the lung can also be lethal. The Institute's national blood resource program has just completed a clinical trial of substance called urokinase which dissolves blood clots. The results of this trial have been so promising that we are moving forward to the second phase of the trial to compare urokinase, which is a drug isolated from human urine, with another clot-dissolving drug, streptokinase, which is made from a particular species of bacteria. Streptokinase is much easier to manufacture and, hence, would be much less expensive, though similarly effective.

The national blood resource program has also been successful in attacking the problem of hepatitis, a serious liver disease, which can be acquired from blood transfusions. New tests are being refined which will detect the presence of hepatitis virus in blood so that contaminated blood will not be used for transfusions.

Mr. FLOOD. Is that clear, that test? Is that firm?

Dr. COOPER. There are five different tests which at their own level of sensitivity are firm. The question is whether or not they are specific enough or whether their sensitivity is good enough to detect all the cases.

Mr. FLOOD. It is unlikely that it would hurt anybody anyhow.

Dr. COOPER. The tests do not hurt anybody. Of course, the blood transfusion, if the virus is present, can cause a serious disease which can be lethal.

As you all know, the supply of human blood for transfusion is always going to be limited. Thus, the national blood resource program is working actively on improving methods of storing blood, and improving ways of breaking the blood up into its component parts so that patients who do not need whole blood but who need only one fraction can receive only the required fraction, leaving the rest for other patients who need other fractions.

RESEARCH ON ARTIFICIAL BLOOD

Mr. FLOOD. Does anybody pay any attention to inventing artificial blood?

Dr. COOPER. Yes, we are. We are supporting some work on fluorocarbons which are oxygen-carrying substances which in certain limited circumstances for short periods of time could be used as substitutes for blood to vital organs. We are also working on artificial systems of profusion.

LEADS IN TREATING SICKLE CELL DISEASES

One particular group of individuals who often need large numbers of transfusions of whole blood are patients with sickle cell disease This disease is limited to black people and a severe form may affect as many as 1,000 babies born each year, perhaps 30,000 to 50,000 other persons may be at risk with a less severe form of the disease.

Until recently, the only therapy available was massive blood transfusion and, as I have indicated, this was not without some hazard. Within the last few months new leads have emerged for treating patients with this disease. The Institute plans to initiate clinical investigations to assess a number of presently proposed therapeutic regimens. We plan to coordinate our efforts in this area with the National Institute of Arthritis and Metabolic Diseases and with the Institute of General Medical Sciences, as well as with the Health Services and Mental Health Administration. We hope that this coordinated effort will assume dimensions of some $5 million.

Mr. FLOOD. Why does this sickle cell disease affect only black people?

Dr. COOPER. This seems to be genetically determined and transmitted as an inherited disease. This particular abnormality of hemoglobin seems to be limited to that population.

ORIGIN OF THE SICKLE CELL GENETIC CHARACTERISTICS

Mr. FLOOD. Merely because they are black?

Dr. COOPER. I don't think it is because they are black but in association with their other genetic makeup. This would be the familial transmission.

Mr. FLOOD. What would be the difference in genetic makeup other than color?

Dr. COOPER. In the treatment of disease or in the study of disease there are other abnormalities in our area of mandate in which the black population seems to have a predisposition to disease patterns which are different from that of Caucasians or other nonwhite groups. For example, in hypertension, the white male has perhaps half as much hypertension as the black, particularly in the younger age groups.

Mr. FLOOD. Would the roots of this lie in the fact that they came from certain sections of the world, or would their life in this new section contribute?

Dr. COOPER. I think both would. We are not certain as to what the environmental influences are on this pattern at this point in time.

There is an interesting hypothesis about why sickle cell anemia occurs among black people. It has been shown that the presence of a sickle cell trait—that is, the carrier state for sickle cell anemia, increases the body's ability to cope with malaria. Certain types of malaria are prevalent in Africa, and it is believed that the persistence of this trait in the black population has been due to a selection for an increased survival of those people with sickle cell anemia.

Mr. FLOOD. How would susceptibility to infection by malaria be genetic?

Dr. COOPER. The point is that the malaria is more likely to kill those people who did not have the trait than those who do, and consequently to increase the fraction of the people who have the trait.

Mr. FLOOD. Genetically the black people built up their resistance to malaria by this cell?

Dr. COOPER. That is right. That is the hypothesis which I think is generally accepted as the probable explanation. Some forms of

natural selection would make carriers of the trait more resistant to the infection.

Acceleration of Research on Lung Diseases

As you remember, last year I told you that we had become the National Heart and Lung Institute in order to accelerate research dealing with lung diseases. We now have on board an Associate Director for Pulmonary Programs, Dr. Claude Lenfant, and we have moved rapidly ahead with scientists and doctors in the community to identify critical problems in this area.

Genetic Predisposition to Lung Disease

One of these problems which is of critical importance is the need for more doctors well-trained to treat lung diseases. Accordingly, we have established a pulmonary academic award program which will enable young physicians who have already had training in lung diseases to pursue the solution of these problems and to teach others how to deal with patients who suffer from them.

We are also planning a study to determine how many people there are in the community who have a genetic predisposition to lung disease by virtue of the fact that they lack a particular enzyme called alpha antitrypsin.

Mr. Flood. What community?

Dr. Cooper. The general community at large. Different population groups scattered throughout the country on a general demographic basis. The lead here is that certain patients inherit an abnormality where there is a deficiency of this enzyme which is necessary to combat the results of infection in the lung and when this enzyme doesn't work the lung scars at an abnormally fast rate and therefore the chronic scarring and destruction of lung tissue which we call chronic lung disease occurs more frequently and more rapidly in this population.

Mr. Flood. But you are not here involved in genetics again, are you?

Dr. Cooper. Yes, sir.

Geographic and Environmental Factors

Mr. Flood. How about geography?

Dr. Cooper. Again, the effect of geography on this has well been observed on an empirical basis, and that is why for many years people who have had chronic lung disease have been advised to go to southern climes away from cold, wet weather, which seems to help their ability to withstand repeated infection and susceptibility to or acceleration of the disease process.

Mr. Flood. Anything in the environs of the homeland from which their parents came that would contribute to that, as perhaps applies to the black people with the sickle cell anemia?

Dr. COOPER. There is some occupational suggestion——

Mr. FLOOD. That would be immediately environmental—not derivative by race.

Dr. COOPER. I know of nothing derivative by race. It is known that patients who inherited this abnormality from both parents have more lung disease than other people in the community, but we have not yet determined how many people there are who inherited it from only one parent, and why only some of them have lung diseases. It appears that certain factors in the environment, particularly certain kinds of work, may be especially harmful for these individuals.

We are also implementing research on how to use oxygen therapy in the treatment of acute respiratory failure in a more effective way. There are more advances which I would like to note, particularly those from our own research laboratories in Bethesda, in the area of the effects of calcium metabolism on brittle bone disease and on the progress which has been made in detection and treatment of painful kidney stones, as one example.

LIMITING ENVIRONMENTAL HAZARDS

Mr. FLOOD. Certainly nobody with this potential for infection of the lung should work in any mine of any kind. Asbestos, soft coal, hard coal. That would be the last place in the world they should work?

Dr. COOPER. Yes; I think if the protection of these individuals by appropriate public health maneuvers to reduce contamination of the area is not effective, it might be well to advise these patients about the hazard to which they are exposed in their occupation and allow them to choose their occupation on that basis.

NEW SPECIALIZED RESEARCH CENTERS

The programs I have described involve our intramural research laboratories as well as those supported by grants and contracts. We are extremely pleased to be able to announce that during the current year new specialized centers of research in four important areas—arteriosclerosis, hypertension, thrombosis, and pulmonary diseases—are being established.

We anticipate that these centers will make an important contribution to many of the unsolved problems that I have identified in these remarks.

In conclusion, Mr. Chairman, what I have been describing for you has been almost entirely related to the $22 million of "new money" which you awarded us last year. We are asking to maintain this level of funding in 1972 so that we can pursue these new initiatives. The request for the National Heart and Lung Institute is $195,592,000 for 1972 as compared with $191,627,000 in 1971, an increase of $3,865,000.

I shall be happy to answer any questions you or the committee may have.

FUNDS ALLOCATED FOR LUNG RESEARCH

Mr. FLOOD. Doctor, there were an awful lot of people, including me, who thought that the expansion of your name to include "and Lung" would mean an expansion of your program. We were all a little naive about that, weren't we?

Dr. COOPER. No, sir. I think in comparing 1971 to 1970, the expenditures by this Institute for work on lung diseases has gone from a level of about 10 or 11 million to some 20 million during the current year. Therefore, I think that with the added resources that you gave us last year, we have been able to double the research effort during the past year so I think we have effected some meaningful increase.

Mr. FLOOD. The appropriation for your Institute for 1970 was $171,377,500. For 1972 you are requesting $195,492,000, an increase of 14 percent.

Now, according to what you people have been telling us for the last several years, this is hardly enough to cover increased costs of research and research training, is it?

Dr. MARSTON. You were comparing 1971 and 1972.

Mr. FLOOD. No, 1970 with 1972.

Dr. COOPER. In 1970, despite the fact the appropriation was $171 million plus, we obligated $160.5 million.

Although the President's initial request was $171 million, we obligated in 1971 $194 million.

The 1972 request is essentially at the same level as what finally turned out to be the appropriation and obligation rate for the Institute in 1971. Therefore, between 1971 and 1972 the funding is level.

PRIORITY IN FISCAL YEAR 1971 GIVEN TO LUNG RESEARCH

Mr. FLOOD. That puts it in a little better perspective but that still does not allow funds for the dramatic increase that these people thought there would be when you added "and Lung".

Dr. COOPER. Between the $171 million and the $194 million, within that level of increase which you allowed us last year, we were able to effectively double the research resources for lung disease from about $11 million to about $20 million during the current year.

Mr. FLOOD. I have just stated what your appropriation was. You stated the obligated amounts, which are different of course. And then you tell me the dramatic increase for lung. Where did you get the money—by shorting heart research? What did you do with the increase for lung?

Dr. COOPER. We took that portion of the increment which you allowed us in 1971 to apply to the development of the new pulmonary academic award, the new collaborative program, and the new specialized centers.

Mr. FLOOD. You took 6 inches off the bottom of the blanket and sewed it on the top because the blanket wasn't long enough, or do you feel it is more appropriate to say that you robbed Peter to pay Paul?

Dr. COOPER. I think we have to choose at the time from the resources available what the most appropriate opportunities are.

NEW LUNG DISEASE THERAPY AND PREVENTION ACTIVITIES

Mr. FLOOD. Now, you indicated in your testimony last year that it hasn't been possible to offer people much in the way of therapy for lung disorders, or in prevention because PHS has not had a focused attack. You didn't have a rifle on these conditions until the expansion of NHLI, which took place a little over a year ago.

We would be interested to know what activities were started during the past year as a part of your new attack upon emphysema and black lung and asthma and what expansion you anticipate in these activities. Do you propose to start some new ones?

Dr. COOPER. Yes, sir. In the past year with the new attack on lung disease, we have experienced a doubling of the request for research grants in emphysema; we have had an extensive increase in the applications for training for lung disease; we have implemented a new pulmonary academic award program in order to teach physicians both in the undergraduate sense, but also in the continuing and specialty sense, the problems related to emphysema and other forms of chronic lung disease. We anticipate within a week we will implement awards for approximately 10 specialized centers of research, which will focus on chronic lung disease with the predominant emphasis on emphysema, and in the future I think our most important need will be to establish a program of what we call epidemiology of the chronic lung diseases. This has been identified as a high need by the people in the community, by the physicians who treat the patients in order to study the natural history of this disease from childhood on.

IMPACT OF LUNG PROBLEMS ON HEART DISEASES

Mr. FLOOD. Now, you know of the Federal Coal Mine Safety and Health Act of 1969?

Dr. COOPER. Yes, sir.

Mr. FLOOD. Now, we have thousands of widows applying for the benefits. Their husbands worked in the mines 30 years and you don't need a doctor to diagnose or identify what we now call black lung. He died. Now his wife, to file an application, has to get a certificate. The death certificate says, "arteriosclerosis" or "heart failure."

I suppose people, when their heart stops, die. But no hospital records, no X-ray records and sometimes the doctors are dead, and there it is.

Now, what connection is there between emphysema or black lung, and arteriosclerosis or heart failure and any one of the different kinds of heart attacks?

Dr. COOPER. There is no direct causal relationship between emphysema and arteriosclerosis. However, it is true if one is subjected repeatedly to inadequate oxygenization as a result of chronic lung disease, this produces a stress on the heart which may accelerate or aggravate preexisting disease and may precipitate the lethal event.

Now, again, the association of other factors which the miners may be involved with may be dually responsible for the genesis of disease, both of the lungs and of the heart. For example, exposures to tobacco.

Mr. FLOOD. Certainly it is not beyond the realm of imagination for it to be fatal.

Dr. COOPER. It is quite possible.

NHLI LIAISON WITH SSA ON LUNG DISEASES

Mr. FLOOD. Have you had any relations with the social security people about this problem at all?

Dr. COOPER. We have had a relationship with the new Institute of Occupational Health and Safety; previously a bureau, and its relationships with Social Security as the NIH representative to their National Advisory Committee to the Secretary, and we have been directly involved in the evaluation of their program and in formulating plans.

Mr. FLOOD. Will you have a meeting with them tomorrow and tell them you have talked to me about this and watch the expression on their face?

Dr. COOPER. As a matter of fact, the committee meets on the 5th and 6th in Morgantown, W. Va.

Mr. FLOOD. It is almost as bad as the safety inspector from the soft coal area going into the anthracite area. Some of them can't even spell anthracite.

As far as you are concerned, preach the gospel in their ear. They need it. I intend to meet with them too. I have received the impression from some things you and others have said that the administration is not committed to advancing research and training in pulmonary diseases half as much as Congress is. There were a number of bills introduced in 1969 calling for a separate lung institute. We talked about that last year.

RESOURCES FOR MAXIMUM ATTACK ON LUNG DISEASE

I would like to know exactly what you think is needed if we are to exert a maximum effort in pulmonary diseases, and if the kind of support being proposed would allow that kind of program.

Dr. COOPER. I think what is needed is a program of total scope, dealing with the development of the needs in the field from basic research through clinical application, and a community program. Whether or not this Institute actually implements it or not, the Department must be concerned with the total spectrum of all chronic lung disease through its total continuum.

Mr. FLOOD. That was the reason for the change in the title.

Dr. COOPER. Yes, and what we are trying to accomplish in that regard is the development of an overall plan in which we could include the development of the total resources, people as well as the immediate information, plus the needed programs of screening and application for this effort.

NHLI COMMUNITY SERVICES FOR LUNG DISEASE

Mr. FLOOD. Now, that suggests this question: One of the functions listed for the NHLI, when it was set up by the Secretary of HEW, was

the application of the results of research and other activities being conducted by the Institute.

We interpreted this to mean there could be support of community demonstrative programs, in diagnosis and treatment of emphysema, and asthma which, believe me, are very much needed. Now, since you are the only Federal agency I can find which includes reference to lung disease in the title, it seems to me that your responsibility should extend beyond mere research.

What are you doing in the matter of community service for emphysema, black lung, and asthma, or don't you think that is important?

Dr. COOPER. I do think it is important, Mr. Flood, and I think the most important thing that we have identified is that there is a shortage of people to perform this service in the community. Therefore, we are embarked on a commitment to develop the needed manpower in the specialty area and to make these available to the needed community programs.

Mr. FLOOD. You haven't realined the priorities have you?

Dr. COOPER. No, sir; I think we are adhering to the original commitment, to develop all areas of research, training, and community activity.

Dr. MARSTON. Mr. Chairman, could I comment?

Mr. FLOOD. Of course.

Dr. MARSTON. On the question whether enough was being done in the pulmonary area, we did undertake, at NIH, a fair evaluation of emphasis on the area of pulmonary disease in the Institutes and we concluded that we were not doing as much as we should do. This was the reason for recommending increased activities in the pulmonary area, and for changing the name of the Heart Institute to Heart and Lung Institute.

On the question of NIH responsibility in terms of community service, I would certainly agree with what Dr. Cooper has said about the responsibilities for conducting research for looking to the needs for trained people for looking to the expertise in these categorical areas. But, as you know, the Health Services and Mental Health Administration is the part of the Department that has responsibility for the organization and delivery of health services, to the extent that this is a Federal responsibility, rather than NIH itself.

Mr. FLOOD. We feel, some of us, that you should do more in this community services kind of thing. We feel you are not breathing deeply enough.

SICKLE CELL ANEMIA

Now, the President made a point in his health message concerning increased attention to research on sickle cell anemia. It appears to me that is the only increase of any consequence in your budget. Tell us why this is so particularly important. Tell us what you know about prevention, and what you know about cure, and what you hope to accomplish with this increase of $5 million for this purpose.

Mr. COOPER. This represents the confluence of both scientific and social concerns in my opinion in an area of a specific section of the population in which there have been recent scientific advances which

have offered the hope that this disease, which is limited to the black people, could be dealt with in an effective way across the board.

As I mentioned in my opening statement, we do intend to involve in this particular effort a coordinated attack which will involve both the research development, clinical trial assessment, screening, counseling and public education in order to accomplish meaningful control of this unique disease. There are three or four areas that offer promise. One is the administration of urea, a substance which is found naturally in the body. One is the use of what is called hypertransfusion, the administration of large amounts of blood, and another the administration of bicarbonate or alkalinizing solution. It is felt that this type therapy may offer the prospect not only of relieving the painful and tragic crisis which accompanies these diseases in the young people, and results ultimately in their death before the age of 30, but also offers some possibility of prolonged treatment in this young phase which may be a preventive to these crises and therefore prolong life.

Mr. FLOOD. Are you concerned with prophylactics to prevent these things?

Dr. COOPER. Yes, sir, we intend to explore that possibility.

CUTBACK IN HEART COOPERATIVE DRUG STUDY

Mr. FLOOD. Now, you are cutting back by $1,324,000 in the budget for the "Heart cooperative drug study." How much will that leave for this purpose in 1972?

Dr. COOPER. It will leave $3,255,000 in the research grant category. We feel as an initial estimate we can carry on the total objectives of this program without infringing on its scientific accuracy or long-term result because over the past year we have found that part of the cost of the study related to the hospitalization costs of patients with acute heart attack, was being covered by third party payments and other sources of funds. Therefore we calculate we may be able to save those costs.

Mr. FLOOD. We have been led to believe, by both you and the public witnesses who were here in support of this program that it was one of your most important activities. Why did you cut it back?

Dr. COOPER. I think our commitment and enthusiasm for the study is not necessarily directly related to the cost of it. I think we have to be candid about our commitment to see it through and it is one of our gung ho projects, but I think if we do not need to spend the additional clinical cost, then we should not do so. We intend to try to make those savings as reasonable as we can while continuing our commitment to this because I do think this is one of the most important projects and one which we must see through.

ADVANCES IN HEART DRUG RESEARCH

Mr. FLOOD. What important results have we so far?

Dr. COOPER. As you may recall we have been using four drugs on five different dose regimens in the treatment of patients who have

already had one heart attack, some 8,300 males who have already had a heart attack.

Two-fifths of this group are on what is called placebo. They are on good medical treatment, but not on any of the other four drugs being tested. We have found thus far that one of the drug regimens we had started with is probably not effective and so we have discontinued it.

Therefore, we are now assessing at midpoint—this is scheduled to go to 1974—what other conclusions we can draw at the present time.

Of the other four regimens that are currently available we have not yet had any critical information which would allow us to draw this conclusion. This is not unusual in view of the fact that to induce the effect with these remaining drugs may take as long as three years. We are now at about the 30 or 32 month period in this study.

EQUIPPING AMBULANCES FOR HEART CARE

Mr. FLOOD. I have here a story from the Washington Post of July 5, 1970. The headline is "Making Heart Centers of Ambulances." In this article they go on to say that certain leaders in the field have been sponsoring this cause of making every ambulance a heart center to save some of those you told us a few minutes ago never make it to the hospital because of lack of care and attention.

Suppose you comment on that for the record.

(The information follows:)

RESPONSE TO REQUEST FOR NHLI POSITION ON WASHINGTON POST ARTICLE: MAKING HEART CENTERS OF AMBULANCES URGED, PUBLISHED ON JULY 5, 1970

The problem of sudden unexpected death in adults, which is usually due to coronary artery or myocardial disease, is a serious and an important public health problem in the United States. Some 80,000 lives of people under 65 years of age are lost each year in this way and the National Heart and Lung Institute not only endorses but supports various activities aimed at reducing this toll. Therefore, mechanisms to bring better care to the patients, sooner after the onset of their heart attacks, are greatly to be desired. The creation of heart mobiles and the conversion of ambulances into coronary care units can have impact on several key facets of this problem. However, it is clearly not the total solution.

In the first place, there are many reasons why these 80,000 people succumb before they can be admitted to a hospital and not all of them are due to lack of resources and expertise during the ambulance ride to the hospital. Some of the patients die within a few minutes of the onset of their distress and hence have no time to summon aid or benefit from it. Others experience difficulty but fail to seek aid for reasons which are both complex in any one patient and quite different from patient to patient. These patients who wait too long before requesting coronary care will not be benefited even by the most elaborate mobile unit. Furthermore, many patients who suffer a sudden unexpected cardiac death have had premonitory symptoms and sometimes even signs prior to their fatal event. Education of these people to seek prophylactic treatment would be much more effective and ever so much cheaper. Thus it is clear that not all the sudden unexpected cardiac deaths will be prevented by the availability of well-equipped mobile coronary care units staffed with suitably knowledgeable personnel.

Important as cardiovascular diseases are, and large as they loom as a cause of premature mortality and morbidity, they are not the only reason why patients may suddenly find themselves in need of acute, expert, immediate, and hence mobile intensive care. To ignore such disorders as acute respiratory problems,

natural and unnatural disasters such as suffocation, burning, and vehicular trauma is to overlook an important public health problem.

Thus the National Heart and Lung Institute takes the position that what communities require in the way of mobile coronary care is a vehicle, whether ambulance or helicopter, which is appropriately equipped and suitably staffed to manage, on what is essentially a sophisticated first aid level, many different life-threatening disorders and diseases. Certainly these facilities and the expertise should encompass all manner of cardiac monitoring, cardiac massage, mouth-to-mouth resuscitation, etc., but they should also be equipped to give emergency aid to patients in shock due to blood loss, in acute respiratory arrest due to electrocution, etc.

Finally, if a real saving in lives is to be accomplished, then it is imperative that the mobile unit be backed by adequate and ever ready stationary resources to which the patients may be taken for continuing emergency care and in-depth therapy. In most instances these stationary units will be community or city hospitals but they must be hospitals or clinics or other units manned on a round-the-clock basis by trained, experienced personnel. Unless this is provided for in advance, the potential of the mobile unit will not be realized and the lives saved in the street will be lost in the hospitals.

HEART AND LUNG TRANSPLANTS

Mr. FLOOD. I would like some comment from you about heart transplants. So that you don't feel any time constraints on your answer, would you prepare something for the record?

Dr. COOPER. Yes, sir; we will be glad to provide for the record an up-to-date assessment.

Mr. FLOOD. We haven't heard much about lung transplants. Will you develop that for the record, also?

Dr. COOPER. Yes.

(The information follows:)

HEART AND LUNG TRANSPLANTS

The National Heart and Lung Institute is one of the six categorical Institutes contributing to the support of a transplantation registry at the American College of Surgeons. One of the functions of this registry is to maintain a running tally on the number of transplants performed both in this country and to some extent abroad, as well as to monitor, within the limits of feasibility, the clinical course of the recipients of these grafts. A detailed roster of the numbers of cardiac transplants is inserted elsewhere in this testimony. In total, there have been 171 heart transplants with 168 recipients, and, as of spring, 1971, the longest time that a functioning graft had remained viable in support of the life of the recipient was 31 months.

Only with the initiation of the lung component of the National Heart and Lung Institute was a formal attempt made to identify the number of lung transplants. According to the registry, there have been 25 such transplants with 25 recipients. The longest time that one of these survived was 10 months and, as of the spring, 1971, no lung transplant was continuing to function. Throughout the world there are some 18 transplant teams performing lung transplants.

While some of the problems encountered in cardiac transplant are also experienced in lung transplant, there are additional problems with the lung grafts, inasmuch as the graft is immediately and continuously exposed to the external air and it is difficult, if not almost impossible, to establish and maintain this as germ free. A germ-free atmosphere can be provided but the donor lung is sure to contain some infective agents at the time of transplantation.

The Associate Director for Pulmonary Programs of the NHLI, Dr. Claude Lenfant, serves as the project officer to the registry for lung transplant. An

advisory committee for this particular organ is being assembled, and it is anticipated that within the next year or so data on lung transplants comparable to that now available in cardiac transplants will be compiled by the registry.

ARTIFICIAL HEART DEVELOPMENT

Mr. FLOOD. Would you also comment on the development of an artificial heart for the record?

Dr. COOPER. Yes, sir.

(The information follows:)

ARTIFICIAL HEART DEVELOPMENT

The medical devices applications program (MDAP) of the National Heart and Lung Institute is aimed at the development of devices to assist or replace the heart and/or lungs in diseased patients. The goal is to achieve maximum rehabilitation of cardiac and pulmonary disease patients through the development of a family of devices designed to render emergency, temporary, or permanent assistance, or total heart replacement with a permanently implanted artificial heart.

A goal-oriented program of contractual research, the MDAP uses a modified systems development approach whereby all subsystems are considered concurrently and their design, development, testing and assemblage into complete, workable systems is achieved by the coordinated efforts of various contractors, each concentrating on specific problems lying within a particular area of expertise. By thus bringing together the biomedical skills in the medical schools and hospitals and the talents of university scientists in physics and engineering, the chemical industry, engineering and actuarial firms, and other groups from private industry—and coordinating the efforts of these participants—the MDAP hopes to produce the most reliable and beneficial types of systems at minimal cost in time and money.

Areas of research and development by investigators working under the terms of 78 currently active MDAP contracts include: development of circulatory and pulmonary assist devices, physiologic effects of devices in animals, development and evaluation of materials for use in assist devices, effects of additional endogenous heat, cardiac control parameters, blood flow studies, development and testing of oxygenators, instrumentation, biological fuel cells, and energy systems, among others.

Although progress has been made in all areas under investigation, the following two developments are of particular interest: permanent heart-assist devices and a new capillary blood oxygenator (artificial lung).

An important goal of the MDAP is the development of improved blood oxygenators for the heart-lung machines used in open heart surgery and also oxygenators suitable for use with heart assist devices in patients requiring not only circulatory support but also temporary respiratory assistance as well. This is often the case in victims of massive heart attacks or with heart conditions resulting from or complicated by chronic respiratory disorders such as emphysema. The aim is to develop oxygenators with very high gas-exchange efficiencies that also cause very little damage to blood. In addition, they should be light, compact devices that require very little blood for priming, are easily sterilized, and, ideally, cheap enough to be disposable.

A membrane capillary blood oxygenator which may meet these specifications has been developed and evaluated under a program contract to the point where limited clinical trials are anticipated in the next several months. The device has been demonstrated to function adequately as a gas exchanger, to be atraumatic to blood for total heart-lung bypass for 8 hours, and for partial heart-lung bypass for 36 hours.

In the capillary oxygenator, blood entering the device is forced to flow through thousands of tiny, gas-permeable tubes—only a few thousandths of an inch in diameter. The capillary tubes are surrounded by a moving atmosphere of pure oxygen, which diffuses through the tubing to refresh the blood flowing through them. Carbon dioxide from the blood diffuses out through the tubing and is swept

out of the oxygenator on the moving oxygen stream. The capillary oxygenator thus works very much like the human lung.

The capillary oxygenator provides a very large surface area for gas exchange in a compact package and eliminates a direct blood-gas interface, which is damaging to blood components. Also damaging to blood, but unavoidable, is blood contact with the foreign surface of the gas-exchange membrane. Surprisingly, however, compared with conventional membrane oxygenators, the capillary oxygenator actually may reduce the extent of blood-membrane contact.

Implantable heart assist devices have been developed which function synchronously with sick and irregular hearts, and are capable of reversing the lethal hemodynamic problems resulting from heart failure. The hydraulically driven blood pump components of these systems have been designed to render permanent assistance to either or both of the heart's main pumping chambers, the ventricles.

One of these devices is a double-valved blood pump that is connected at its inlet end to the left ventricle and at its outlet end to the body's main artery, the aorta. The pump is synchronized with the heart so as to effect counterpulsation, i.e., the assist pump ejects blood into the aorta while the left ventricle is filling and receives blood during the ventricle's pumping phase. The device thus minimizes left ventricular work by reducing the pressure against which the ventricle must pump.

The pump's ability to reduce left ventricular pressures in both normal and failing hearts was established by implantation experiments in 124 calves. The investigators achieved continuous pumping with the left ventricular assist pump for periods up to 140 days with no significant damage to blood, other tissues or organs, and with no evidence of thromboembolism (formation on pump surfaces of blood clots that break loose to block arteries "downstream" from the pump).

Similar results, with survival times of up to 92 days, have been achieved with a right ventricular assist device (connecting the right ventricle to the pulmonary artery which leads to the lungs); and of up to 60 days in calves equipped with a combined right- and left-sided circulatory assist device.

Future research includes the development of nuclear powered heart pacemakers and instrumentation (flowmeters, pressure transducers, and so forth) for monitoring the performance of pulmonary and heart assist devices. Additional research is needed for the clinical evaluation of these devices as well as of artificial heart valves, blood oxygenators, and intraaortic balloon pumps for providing temporary assistance to failing hearts.

INFORMATION ON OTHER HEART AND LUNG DISEASES

Mr. FLOOD. I think I should add emphysema, black lung, miner's asthma and arteriosclerosis. Develop them at your leisure in the record.

Dr. COOPER. Yes.

(The information follows:)

ARTERIOSCLEROSIS

A degenerative blood-vessel disease characterized by the deposition in the inner walls of arteries of fatty materials and other substances from the blood, arteriosclerosis is present to a greater or lesser degree in most American adults. Arteriosclerosis of the arteries that nourish the heart muscle, or coronary heart disease, is the primary cause of an estimated 1.25 million heart attacks and nearly half a million heart-disease deaths each year. Arteriosclerosis of vessels supplying the brain, or cerebral vascular disease, is the major cause of strokes that cause nearly 300,000 deaths annually and disable two to three times as many others.

Last year, the NHLI Task Force on Arteriosclerosis, a 13-member panel of experts drawn from key cardiovascular research and clinical fields was convened to develop plans for a comprehensive, integrated research assault on arteriosclerosis to be waged by the Institute during the next decade. The final report, due this July, is expected to figure importantly in future decisionmaking and program planning by NHLI and its advisory bodies.

Present NHLI programs aimed at reducing morbidity and mortality from arteriosclerosis and its clinical consequences are emphasizing the development and wider application of countermeasures against factors known to increase susceptibility to the disease. Two of the most potent risk factors are elevated blood lipids and high blood pressure.

Elevated blood lipids may stem from any of five distinct lipid-transport disorders called hyperlipoproteinemias. These are readily identifiable—sometimes from birth and almost invariably by age 40—and once the specific hyperlipoproteinemia has been identified, the associated blood-lipid abnormality can nearly always be corrected or substantially improved by appropriate therapy. The newly established NHLI Lipid Metabolism Branch will attempt to improve the detection and clinical management of hyperlipoproteinemias in the U.S. population through the establishment and support of lipid research clinics at a number of medical centers around the country. Also scheduled to get underway in the near future at NHLI is a definitive study to determine whether correcting or ameliorating the elevated blood cholesterol levels of type II hyperlipoproteinemia reduces the threat of clinical coronary heart disease in type II subjects or favorably affects the clinical course of the established disease.

Elevated blood pressure greatly increases susceptibility to coronary heart disease and is more important than elevated blood lipids as a determinant of stroke risk. The Institute proposes to support clinical trials to determine whether and to what extent the detection and control of hypertension by blood-pressure-lowering drugs during its early, milder stages reduces the subject's risk of developing coronary heart disease and cerebral vascular disease.

Sudden cardiac death, occurring before the patient can be hospitalized, currently account for nearly half of all deaths from arteriosclerotic heart disease. In order to develop new knowledge needed to cope with this catastrophic consequence, the NHLI Myocardial Infarction Branch has awarded research contracts to (1) learn more about factor underlying sudden, unexpected cardiac death; (2) seek means of identifying the high-risk individual before he is stricken; (3) identify "trigger" factors that convert coronary arteriosclerosis into a full-blown heart attack; and (4) seek out warning symptoms that may alert the individual or his physician of a threatened attack, or, failing that, hospitalize the patients before it occurs.

The NHLI Medical Devices Applications Branch continues their support of research to develop effective devices to provide temporary or permanent assistance to hearts heavily damaged by acute heart attacks or chronic heart failure due to any number of cardiovascular diseases. Various types of intra-aortic balloon pumps for providing temporary circulatory assistance have been developed and clinically tested against cardiogenic shock, currently the leading cause of death among hospitalized heart-attack victims. Results thus far, while not spectacular, have been sufficiently promising to warrant further evaluation of these and similar heart-assist devices.

The individual who has experienced and survived an acute heart attack remains a prime candidate for recurrent attacks. The NHLI Coronary Drug Project is evaluating the effectiveness of lipid-lowering drugs as a means of protecting against recurrent heart attacks and reducing 5-year mortality rates among recovered heart-attack victims, hopefully by 25 percent or more.

During the most recent fiscal year for which figures are available (1970), NHLI also awarded 312 research grants totaling $14,234,160 for studies on arteriosclerosis. Major research areas included:

Studies on lipid metabolism and metabolic disorders that predispose to the development of arteriosclerosis;

The development and/or evaluation of therapeutic diets and drugs for the correction of blood-lipid abnormalities;

Epidemiological studies to identify and quantitate factors increasing risk of coronary heart disease and assessment of the effectiveness of countermeasures against salient risk factors;

Studies to develop and evaluate improved techniques for detecting and following the progress or regression of arteriosclerosis, especially in asymptomatic individuals;

Improved monitoring techniques, resuscitation procedures, drugs, and other therapeutic measures for coping with the acute heart attack and its

complications, such as cardiogenic shock, acute heart failure, and arrhythmias; and

Development and clinical evaluation of drugs and surgical procedures for the relief of angina pectoris, a common clinical manifestation of coronary artery disease.

During 1971 a new "managed" grants program was initiated to establish specialized centers of research. Four particular disease areas are to be attacked via this mechanism. Something more than 40 percent of the available dollars in this line item will be awarded to centers approaching the problem of arteriosclerosis in many different ways. While not a geographic network, such specialized research programs will be established in at least nine States.

Emphysema and Other Chronic Respiratory Diseases

Chronic respiratory diseases, mainly emphysema and chronic bronchitis, afflict an estimated 5.3 million Americans and currently cause more than 33,000 deaths per year. Emphysema ranks second only to coronary heart disease as a cause of disability among the Nation's workers, incapacitating approximately 1 out of 14 persons aged 40–65.

In December 1969, the National Heart Institute was redesignated the National Heart and Lung Institute and assigned broadened responsibility for the conduct, support, and coordination of research and training activities directed against chronic lung disease. During the past year, the Institute appointed an associate director for lung programs to plan, organize, and administer an expanded NHLI effort against chronic lung disease.

In June of last year, the Institute sponsored a meeting of pulmonary program directors that was attended by 150 biomedical scientists from 97 medical schools and 12 Federal agencies to discuss current and foreseeable research and training needs in the pulmonary disease field. The report and recommendations of this group should prove highly useful to the Institute in shaping its pulmonary disease programs, and the Institute is hopeful that this meeting will be the first in what will become a continuing dialog between the Institute and all segments of the pulmonary-disease community.

A critical and steadily increasing need is evident for additional highly trained research workers, clinicians, and teachers in the field. To help meet this need, the Institute is currently inaugurating a program of pulmonary academic awards to schools of medicine or osteopathy to (1) attract high-quality students into this field to provide them with superior training in the most modern techniques of prevention, diagnosis, and treatment and (2) strengthen the pulmonary training staffs of recipient institutions by attracting promising young teacher-investigators into academic careers in the respiratory-disease field.

Collaborative research activities planned for the near future include—

Epidemiological studies on hereditary deficiencies of the plasma protein alpha-1-antitrypsin, which appear to predispose to the development of emphysema and to render persons with this deficiency unusually susceptible to the harmful effect of cigarette smoking. These studies will attempt to ascertain the prevalence of this deficiency in the U.S. population and to assess its importance in the genesis of emphysema and also as a factor to be considered in preventive measures and in the treatment and rehabilitation of emphysema patients.

Studies seeking improved procedures for the rehabilitation of patients partially or completely disabled by emphysema, currently estimated to number more than 200,000.

Establishment of pulmonary intensive care units (1) to develop new clinical knowledge about acute respiratory crises resulting from chronic lung disorders, hyaline membrane disease in the newborn, and other causes and (2) to evaluate new or improved modes of therapy, including respiratory-assist devices.

The NHLI Medical Devices Applications Branch is supporting research to develop respiratory assist devices and blood oxygenators for heart-lung machines; for use with heart-assist devices in victims of massive heart attacks or heart failure resulting from or complicated by chronic respiratory disease; and for temporary respiratory support during acute respiratory crises, such as respiratory distress resulting from hyaline membrane disease, which causes some 25,000 in-

fant deaths per year. The goal is light, compact devices that do not damage blood, have very high gas-exchange efficiencies, require very little blood for priming, are easily sterilized, and hopefully cheap enough to be disposable.

During 1970 NHLI also supported 152 research grants totaling $5,594,436 for research into the causes, prevention, diagnosis, and clinical management of emphysema and related lung disorders. Major research areas included:

Epidemiological studies to identify factors in the person or his environment that increase his susceptibility to emphysema or aggravate the course of the disease.

Development of techniques for evaluating lung function, measuring pulmonary gas exchange and bloodflow, and other parameters useful in detecting chronic lung disease, assessing the extent of the resulting damage, and evaluating the results of therapy.

Development and evaluation of drugs and other therapeutic procedures for relieving the distressing symptoms of emphysema and for the rehabilitation of patients partially or completely disabled by this disease.

Development of more effective means of dealing with circulatory complications of chronic lung disease, such as right heart failure and/or pulmonary hypertension.

Basic research on pulmonary physiology and biochemistry and on the interrelationships of the pulmonary and cardiovascular systems in health and disease.

Research on lung transplantation and associated surgical, immunological, and organ-storage problems.

The particular problems of miner's asthma and black lung disease are of interest and concern to several different agencies and divisions within the Federal Government. Within the context of its lung program, the National Heart and Lung Institute is concerned with basic studies which may help to identify those at particular risk of developing the diseases, of determining how many such people there are in the country and where they tend to live, how their predisposition may be determined before the disease sets in so that prevention rather than therapy may be offered to them. While the elimination of asthma-producing antigens and the control of air pollutants contributing to black lung disease are of categorical concern to other Institutes in the NIH, the patient with lung disease is of prime interest to the NHLI, not solely because his disease is undoubtedly interrelated with other lung diseases such as chronic bronchitis and emphysema, but because once his illness is manifest, he will require the services of highly trained pulmonary specialists and the resources of pulmonary care units to alleviate his suffering.

Thus many of the Institute's current lung programs are of direct relevance to miners' asthma and black lung as well as to chronic bronchitis emphysema, and respiratory distress syndrome. However, by no means do we feel that all of the potentially fruitful research is being undertaken nor that more effective and more efficient screening systems, prevention programs, and therapeutic modalities could not be instituted. In this context it might be noted that in the NHLI's new line item for specialized centers of research, some 11 pulmonry centers are being established at a cost of approximately $4,700,000 per year. While these are in no way intended to be primarily a regional network, they are located in some 10 of the 50 States, are concerned with a multiplicity of pulmonary problems, and will have the potential to serve many different groups of patients in the country with many different types of pulmonary disorders.

Mr. FLOOD. Mr. Michel.

INCIDENCE OF HEART FAILURE DEATHS

Mr. MICHEL. Doctor, how many people died last year because of heart failure?

Dr. COOPER. The usual designation on a death certificate is coded as probably not heart failure but arteriosclerotic heart disease. Of that total number of 800,000 to 900,000, probably the predominant group would be due to what is called heart attack, some of which may be

associated with heart failure and some not. There are undoubtedly many in that group that have associated severe heart failure.

FEMALE HORMONE THERAPY FOR HEART ATTACKS

Mr. MICHEL. Several years ago I recall a witness—a woman doctor—who told us about what she was doing in the area of using female hormones in the male as a means of reducing the incidence of heart attack.

Was that a study funded in any part through the Heart Institute?

Dr. COOPER. The then Heart Institute and now the Heart and Lung Institute has supported studies on the effects of hormones and arteriosclerosis and heart attacks.

Mr. MICHEL. What have we found?

VARIATION IN INCIDENCE OF HEART ATTACKS BETWEEN MEN AND WOMEN

Dr. COOPER. The drug which I mentioned to Mr. Flood that we have discontinued in one dose level in the coronary drug study was the high dose estrogen, a female hormone, which was used in an attempt to prevent heart attacks in males. We are continuing to assess the administration of a low dose of female hormones for the prevention of heart attacks in males. This comes from the old observation that prior to menopause, the female in this country, at least the white female. seems to be much less susceptible to a heart attack than the male.

Then after the menopause the curves seem to come together and the attack rate becomes similar. We are continuing to explore this area.

Mr. MICHEL. Is that overall death rate you talked about a moment ago about equal for men and women? How does it break down?

Dr. COOPER. Before the age of 55 to 65, the attack rate in the male is considerably higher than in the female. As you approach the post-65 age and go up to 70 or 75, the numbers seem to be more akin to each other.

HEART ATTACK DEATH RATE SINCE 1940

Mr. MICHEL. Related to the population growth in the country, how is the curve on the death rate with respect to heart ailments?

Dr. COOPER. It depends on the decades you compare. If you compare 1940, for example, with 1968 and observe the heart attack rate during this period of time, you will see that overall there is a tendency for the attack rate in all groups to level off, but not a gross diminution of the overall death rate from the arteriosclerotic group of diseases.

If you age-adjust all the death rates and compare 1940 with 1968 across all cardiovascular diseases, there seems to be a significant decrease between 1940 and 1968. Perhaps 10 or 11 percent.

HYPERBARIC OXYGENATION FOR EMPHYSEMA

Mr. MICHEL. Within the last several years we have had 2 distinguished Senators, Dirksen and Russell who have suffered from emphysema. I recall their having gone to a place in New Jersey for a special kind of treatment that wasn't available generally throughout the country.

What kind of treatment specifically was that for emphysema?

Dr. COOPER. That is called hyperbaric oxygenation, the administration of oxygen at high pressure to induce into the blood a higher quantity of oxygen, by physical processes, than the blood would ordinarily carry.

Since the lung is diseased, the exposure to this high pressure oxygen would allow them to get better oxygenation and suffer less from failure of the lung function.

This is occasionally effective in acute episodes and may have effects that will last a day or two, but is not an effective deterrent over the long range.

In addition the use of large amounts of oxygen of high purity can be of itself injurious to the lungs. So there is an appropriate balance that has to be sought for the use of this type of special therapy. It is not widely used for the amelioration of the crisis in this condition. In given selected cases it can have dramatic results.

SMOKING AS A FACTOR IN LUNG AND HEART DISEASE

Mr. MICHEL. Do you take the position, or do you have the same position as the Surgeon General and Dr. Baker of the Cancer Institute with respect to smoking?

Dr. COOPER. We feel that the evidence thus far in relation to cardiovascular and pulmonary disease aside from cancer indicates there is a correlation between cigarette smoking and the incidence of chronic diseases of the heart and lungs. It is not of the dimensions of the cancer risk where it might be 10 or more fold greater.

In heart attacks, for example, we feel the risk induced by smoking more than 10 or 20 cigarettes a day may be in the order of 1.7 to 2 fold greater. There is a considerable difference between the epidemiological statistics for lung disease as compared to heart disease. It does indicate, probably, a noxious influence.

EFFICACY OF ANTI-SMOKING PRODUCTS

Mr. MICHEL. There are several products on the market that are advertised to help people quit smoking or reduce their amount of smoking. Do you folks make any studies of those products as to whether or not they are really effective whether their advertising claims are valid?

Dr. COOPER. No, sir; we do not conduct studies on those proprietary products. We are interested, however, in the factors which induce people to smoke or induce them to give it up as psychologic and behavioral influences in the determinants of chronic heart and lung disease.

LIST OF ALL HEART TRANSPLANTS

Mr. MICHEL. Last year you provided us with a list of all heart transplant patients, the date, and pertinent facts and statistics on each case. I think it would be well if you would bring that up to date.

(The information follows:)

Report of Human Heart Transplants - As of May 1, 1971

Summary:

Total No. of Transplants: 171
U.S. : 109
Foreign: 62

Total No. of Recipients: 168

Total No. of Deaths: 145
Number of Survivors: 23
U.S. : 17
Foreign: 6
Total Number of Countries: 20
Total Number of Surgical Teams: 65
U.S. : 29
Foreign: 36

Of Those Recipients Still Surviving:

6 months+:	21	18 months+:	16
7 months+:	20	21 months+:	13
8 months+:	20	24 months+:	12
12 months+:	19	27 months+:	11
15 months+:	17	30 months+:	7

Detail:

#	Recipient Age	Sex	Donor Age	Sex	Date of Tx	Survival	Reported Cause of Death	Country
1	53	M	25	F	12-3-67	18 days	infection/rejection	South Africa
2	17da	M	2 da	M	12-6-67	6-1/2 hrs.	metabolic/respiratory acidosis	U.S.
3	58	M	24	M	1-2-68	593 days	chronic rejection	South Africa
4	57	M	43	M	1-6-68	15 days	internal hemorrhage	U.S.
5	58	M	29	F	1-10-68	8-1/2 hrs.	left ventricular failure	U.S.
6	27	M	20	F	2-16-68	3 hrs.	pulmonary hypertension	India
7	66	M	23	M	4-27-68	2 days	embolism/brain damage	France

#	Recipient Age	Sex	Donor Age	Sex	Date of Tx	Survival	Reported Cause of Death	Country
8	40	M	43	M	5-2-68	3-1/2 days	deprivation of oxygen/ pulmonary embolism	U.S.
9	47	M	15	F	5-3-68	204 days	rejection	U.S.
	(received second heart 11/18/68, see #86)							
10	45	M	26	M	5-3-68	45 days	multiple pulmonary emboli	England
11	48	M	15	M	5-5-68	3 days	leukopenia/pneumonia	U.S.
12	62	M	36	M	5-7-68	7 days	renal and hepatic failure	U.S.
13	65	M	35	M	5-8-68	2 days	pulmonary injury/cerebral air embolism	France
14	56	M	39	M	5-12-68	523 days	rejection	France
15	54	M	17	M	5-21-68	146 days	cardiac arrest/rejection	U.S.
16	53	M	48	M	5-25-68	7 days	total rejection	U.S.
17	24	M	40	M	5-26-68	28 days	rejection	Brazil
18	54	M	47	M	5-31-68	5 days	cerebral embolism	Argentina
19	59	M	38	F	6-1-68	1 day	low-output heart failure	Canada
20	39	M	29	M	5-31-68	0 hrs.	malfunction of right ventricle	U.S.
21	41	F	26	M	6-7-68	1-1/2 hrs.	acute rejection	U.S.
22	49	M	23	M	6-28-68	156 days	asphyxiation following indigestion	Canada
23	24	F	32	M	6-28-68	133 days	cerebral embolus	Chile
24	48	M	50	M	7-2-68	149 days	chronic rejection	U.S.

#	Recipient Age	Recipient Sex	Donor Age	Donor Sex	Date of Tx	Survival	Reported Cause of Death	Country
25	49	F	46	M	7-9-68	5 hrs.	?	Czechoslovakia
26	58	M	33	F	7-20-68	266 days	probable arrhythmias	U.S.
27	57	M	16	M	7-23-68	170 days	chronic rejection	U.S.
28	47	M	34	M	7-26-68	2 days	ventricular failure	England
29	49	F	40	F	7-29-68	56 days	sepsis/GI hemorrhage, thrombocytopenia	U.S.
30	18	M	21	M	8-8-68	82 days	acute respiratory infection	Japan
31	5	F	11	M	8-18-68	7 days	cardiac arrest/acute rejection	U.S.
32	50	M	37	F	8-19-68	68 days	herpes sepsis, penumonia	U.S.
33	43	M	21	M	8-22-68	46 days	pneumonia	U.S.
34	43	M	17	M	8-24-68	Surviving	-	U.S.
35	58	M	35	?	8-30-68	11 days	stroke	Canada
36	50	M	39	M	8-31-68	624 days	?	U.S.
37	50	M	20	F	8-31-68	Surviving	-	U.S.
38	46	M	22	M	9-1-68	443 days	rejection	U.S.
39	48	M	39	M	9-2-68	409 days	rejection	Brazil
40	50	M	25	F	9-4-68	476 days	acute M.I.; chronic rejection	U.S.
41	47	M	17	M	9-5-68	8 days	cardiac arrest	U.S.
42	52	M	36	F	9-8-68	621 days	cancer of stomach	South Africa

#	Recipient Age	Sex	Donor Age	Sex	Date of Tx	Survival	Reported Cause of Death	Country
43	48	F	27	M	9-10-68	132 days	hepatitis	U.S.
44	58	M	16	M	9-11-68	117 days	pulmonary infarction	Canada
45	21	M	25	F	9-13-68	14 hrs.	renal failure	India
46	52	M	20	M	9-15-68	111 das	monelia brain abscess	U.S.
47	2mo.	F	1 da	F	9-15-68	14 hrs.	pulmonary insufficiency	U.S.
48	44	M	46	F	9-17-68	2 days	acute kidney insufficiency	Spain
49	45	M	27	F	9-18-68	6 hrs.	irreversible ventricular fibrillation	Venezuela
50	16	M	36	M	9-18-68	Surviving	-	U.S.
51	51	M	19	M	9-18-68	62 days	herpes viremia and cerebral pseudomonas abscess	Canada
52	57	M	46	M	12-16-68	88 days	lung infection	U.S.
53	50	M	37	M	9-20-68	446 days	pneumonia	U.S.
54	46	M	17	M	9-23-68	22 days	cardiac arrest	U.S.
55	21	M	17	M	10-1-68	Surviving	-	Chile
56	46	M	43	M	10-2-68	5 days	acute rejection	U.S.
57	54	F	28	F	10-5-68	61 days	penumonia	U.S.
58	42	M	33	M	10-9-68	204 days	rejection	Canada
59	54	F	28	F	10-12-68	157 days	bowel perforation	U.S.
60	19	F	35	?	10-15-68	15 hrs.	complication in blood coagulation	Argentina

#	Recipient Age	Recipient Sex	Donor Age	Donor Sex	Date of Tx	Survival	Reported Cause of Death	Country
61	50	M	20	M	10-18-68	177 days	ruptured colon	U.S.
62	45	F	20	?	10-20-68	60 days	acute rejection	Canada
63	49	F	30	M	10-21-68	Surviving	-	U.S.
64	57	M	30	M	10-23-68	45 days	hemorrhage following surgical complications	Australia
65	19	F	19	M	10-23-68	7 days	acute rejection	U.S.
66	42	M	41	F	10-24-68	6 hrs.	cardiac arrest	U.S.
67	52	M	49	F	10-25-68	126 days	chronic rejection	U.S.
68	35	?	25	?	10-25-68	54 days	rejection	Canada
69	54	M	20	?	10-26-68	Surviving	-	U.S.
70	45	M	20	M	10-29-68	9 days	pneumonia/infection	Canada
71	23	M	24	M	10-30-68	18 days	rejection	U.S.
72	40	M	42	M	11-3-68	4 days	failure of liver/kidneys	U.S.
73	52	M	28	F	11-3-68	Surviving	-	Canada
74	50	M	27	M	11-5-68	7 days	rejection	U.S.
75	25	F	19	M	11-5-68	1 day	acute rejection	Russia
76	55	M	27	F	11-9-68	47 days	bacterial pneumonia	U.S.
77	44	M	15	?	11-11-68	38 days	acute rejection	Canada
78	34	M	50	M	11-11-68	13 days	acute rejection	France

#	Recipient Age	Sex	Donor Age	Sex	Date of Tx	Survival	Reported Cause of Death	Country
79	54	M	22	M	11-13-68	7 days	cerebral embolism	Canada
80	44	M	44	M	11-13-68	14 hrs.	ventricular fibrillation	Australia
81	50	M	38	F	11-16-68	497 days	penumonia/rejection	U.S.
82	53	M	50	F	11-17-68	40 days	rejection	France
83	54	M	18	M	11-17-68	Surviving	-	Canada
84	56	M	?	?	11-20-68	3 days	stroke	U.S.
	(received second transplant 11-20-68, see #85)							
85	56	M	?	?	11-20-68	3 days	stroke	U.S.
86	47	M	47	F	11-20-68	3 days	cardiac failure/rejection	U.S.
	(received first transplant 5-3-68, see #9)							
87	49	M	?	?	11-22-68	281 days	irregular heart action	U.S.
88	30	F	14	M	11-22-68	3 hrs.	?	Chile
89	33	F	18	M	11-22-68	18 hrs.	liver ceased functioning/ failure of blood to clot	Turkey
90	37	M	47	?	11-24-68	14 hrs.	irreversible kidney failure	France
91	48	M	46	?	11-24-68	400 days	rejection	France
92	26	M	50	M	11-25-68	1 day	cardiac insufficiency	Turkey
93	56	M	26	M	11-25-68	70 days	rejection	U.S.
94	56	M	33	M	11-26-68	20 hrs.	cardiac arrest	France

#	Recipient Age	Sex	Donor Age	Sex	Date of Tx	Survival	Reported Cause of Death	Country
95	48	M	25	M	11-27-68	Surviving	-	France
96	54	M	40	M	11-29-68	13 days	rejection	U.S.
97	54	M	23	?	11-29-68	105 days	cerebral thrombosis	Canada
98	38	M	22	?	12-1-68	Surviving	-	U.S.
99	43	M	?	M	12-5-68	14 days	kidney failure/pneumonia/ rejection	Israel
100	22	M	21	?	12-16-68	43 days	congestive heart failure	U.S.
101	28	M	30	?	12-22-68	225 days	?	France
102	8da	M	2da	M	12-25-68	5 hr.	cardiac failure	U.S.
103	50	M	24	M	12-27-68	91 days	rejection	U.S.
104	64	M	48	M	1-1-69	114 days	acute rejection	U.S.
105	35	M	26	M	1-4-69	0 hrs.	right ventricular failure/ pulmonary hypertension	Poland
106	59	M	14	M	1-5-69	37 days	rejection	U.S.
107	44	?	54	?	1-5-69	7 days	pulmonary hypertension	U.S.
108	49	M	44	M	1-6-69	7 days	brain hemorrhage/pneumonia	U.S.
109	52	M	28	M	1-6-69	83 days	pulmonary embolus	Brazil
110	49	M	38	M	1-17-69	4 hrs.	progressive pulmonary hypertension	U.S.

#	Recipient Age	Sex	Donor Age	Sex	Date of Tx	Survival	Reported Cause of Death	Country
111	47	M	13	?	1-23-69	2 days	brain damage/edema of brain	U.S.
112	7	F	8	M	2-8-69	30 days	lung infection/rejection	U.S.
113	43	M	?	?	2-8-69	Surviving	-	U.S.
114	36	M	39	F	2-13-69	1 day	traumatic coronary thrombosis pre-transplant	Germany
115	55	M	24	M	2-15-69	10 days	rejection	U.S.
116	36	M	57	M	2-20-69	64 days	rejection	U.S.
117	58	M	23	F	2-20-69	41 days	hemorrhagic pneumonitis	U.S.
118	56	M	26	M	3-4-69	99 days	hepatitis	U.S.
119	43	M	24	M	3-16-69	306 days	kidney/liver failure	U.S.
	(received second transplant 1-16-70, see #154)							
120	38	M	28	M	3-22-69	1 day	cardiac arrest	Germany
121	42	M	?	?	3-29-69	39 days	?	U.S.
122	40	F	?	?	4-3-69	5 days	rejection/hepsis	U.S.
123	35	M	41	F	4-4-69	49 days	acute rejection	Canada
124	47	M	40	F	4-7-69	1 day	pseudomonis septicemia	U.S.
125	63	M	43	F	4-7-69	64 days	rejection	South Africa

#	Recipient Age	Recipient Sex	Donor Age	Donor Sex	Date of Tx	Survival	Reported Cause of Death	Country
126	54	M	27	M	4-14-69	91 days	unidentified infection	Switzerland
127	58	M	20	M	4-14-69	729 days	?	U.S.
128	44	M	30	M	4-15-69	31 days	acute rejection	U.S.
129	38	F	33	M	4-17-69	Surviving	-	South Africa
130	55	M	29	F	4-24-69	14 days	parasitic pneumonia/rejection	U.S.
131	35	M	35	F	4-26-69	6 days	acute rejection	South Africa
132	48	M	16	F	5-11-69	35 days	rejection	U.S.
133	59	M	29	F	5-16-69	107 days	cardiac arrest	England
134	?	?	?	?	5-22-69	Surviving	-	U.S.
135	54	M	20	M	6-2-69	41 days	rejection reaction	U.S.
136	52	M	25	M	6-3-69	142 days	systemic infection	U.S.
137	56	M	32	F	6-28-69	42 days	pneumonia/renal failure	U.S.
138	46	M	28	M	7-7-69	74 days	arrythmia	Switzerland
139	46	M	31	M	7-10-69	9 hrs.	fibrinolysis and irreversible bleeding	Germany
140	52	M	?	?	7-16-69	136 days	rejection	U.S.
141	59	M	17	F	7-25-69	4 days	pulmonary emboli/ renal failure	U.S.

#	Recipient Age	Sex	Donor Age	Sex	Date of Tx	Survival	Reported Cause of Death	Country
142	47	M	18	M	7-28-69	5 days	pneumonia/renal failure	U.S.
143	58	M	35	M	8-13-69	Surviving	-	U.S.
144	54	M	?	?	8-16-69	10 hrs.	high blood pressure in lungs/lack of oxygen	U.S.
145	45	F	?	?	9-3-69	Surviving	-	U.S.
146	64	M	32	M	9-14-69	60 days	?	U.S.
147	54	M	41	F	9-25-69	26 days	pneumonia	U.S.
148	48	M	24	M	9-29-69	Surviving	-	U.S.
149	44	M	20	M	10-13-69	29 hrs.	?	South Africa
150	43	M	50	F	12-25-69	8 days	lung rejection/pneumonia	U.S.
	(note: also received two lungs)							
151	40	M	?	?	1-4-70	Surviving	-	U.S.
152	52	M	36	F	1-8-70	116 days	massive respiratory infection	U.S.
153	34	M	?	?	1-13-70	4 days	rejection	U.S.
154	44	M	24	M	1-16-70	13 days	kidney/liver failure	U.S.
	(received first transplant 3-16-69, see #119)							
155	49	M	?	?	1-16-70	Surviving	-	U.S.
156	49	M	?	F	2-10-70	58 days	rejection	U.S.

#	Recipient Age	Recipient Sex	Donor Age	Donor Sex	Date of Tx	Survival	Reported Cause of Death	Country
157	54	M	43	M	4-18-70	0 hrs.	heart could not function	U.S.
158	50	M	?	F	4-28-70	Surviving	-	Canada
159	41	M	?	?	6-10-70	0 hrs.	?	U.S.
160	37	F	45	M	6-13-70	24 days	pancreas involvement	U.S.
161	62	M	?	?	6-13-70	47 days	?	U.S.
162	49	M	?	?	6-19-70	55 days	?	U.S.
163	50	M	?	?	6-22-70	52 days	?	U.S.
164	48	M	?	?	7-4-70	Surviving	-	U.S.
165	48	M	23	M	7-21-70	45 days	?	U.S.
166	45	M	?	?	10-15-70	Surviving	-	U.S.
167	21	M	?	?	10-23-70	12 days	rejection	U.S.
168	36	M	16	F	1-5-71	48 days	?	U.S.
169	48	F	?	?	1-11-71	Surviving	-	U.S.
170	47	M	26	M	2-24-71	50 days	?	U.S.
171	35	M	?	?	3-23-71	Surviving	-	U.S.

Summary: 171 transplants (168 patients) Surviving: 23

DECREASING NUMBER OF HEART TRANSPLANTS

Mr. MICHEL. While the number of heart transplants has gone down there still have been some during the last year, have there not?

Dr. COOPER. Yes, sir, there have been. At the peak time in 1968 when heart transplants were being performed at their greatest rate in man, some 26 or 27 per month were being done. What we are observing now is an operation rate of maybe 1 or 2 a month.

In this country the most active team which is conducting research with the support of the Institute and doing an exemplary job is Stanford University in Palo Alto, Calif. Their results continue to show that in properly selected cases the possibility of rehabilitation is encouraging, although the immunologic problem and the problem of rejection as well as the selection of donor and organism preservation remain very much with us.

RESEARCH ON ARTIFICIAL HEARTS

Mr. MICHEL. Then on the artificial heart, is that being used?

Dr. COOPER. There have been no further occasions that I am aware of, of the actual implantation in man of an artificial heart or two pumping cylinders for the heart. However, in large animals, particularly the calf, there have been experiments in which the calves have been sustained totally on devices and these were able to carry the full blood flow.

Mr. MICHEL. Are we funding research in that area through your shop?

Dr. COOPER. Yes.

Mr. FLOOD. What happened to the sheep?

Dr. COOPER. We have tried it in sheep and goats as well. The most successful experiments have been done with 200-pound calves.

Mr. MICHEL. Why do the calves do better?

Dr. COOPER. They tolerate the operative procedure and the anesthesia better. Why certain species seem more vulnerable to certain types of anethesia is not well understood. Even in smaller animals, the rabbit compared to cat or dog, for example, has a different tolerance for biologic experimentation.

Mr. SMITH. A 200-pound calf is very young. Does the age have something to do with it?

Dr. COOPER. We select the size and age because of the dynamic level, that is the amount of the blood that must be pumped for the size of the vessel. When the calves get further grown we have a different amount of blood that has to be pumped. The size of the vessels and the thickness of their walls are different and therefore they do not provide an appropriate animal model in relation to man.

One of the things we need to test in this is the capability of the device to carry a load which is comparable to the human load.

Mr. SMITH. It seems to me it would be kind of hard to compare an organ of a 2-month old animal of any kind with an adult human.

Dr. COOPER. We have not done the experiment in which we have induced chronic disease in the animals and tried to rehabilitate them

The experiments are at the stage where we are trying to test devices, the practicality of developing a pump that could be implanted in man.

We are at a size now which would be little more than a quart and weigh about 4 or 5 pounds. It is pushing the state of the art but we are approaching the stage where we could probably settle for further engineering expertise to develop that.

COSTS AND DEMAND FOR HEART PACEMAKERS

Mr. FLOOD. Do you know Dr. Hufnagel of Georgetown?

Dr. COOPER. Yes, sir; we do, very well.

Mr. MICHEL. How many patients in the country are using pacers would you say?

Dr. COOPER. The estimates on this range from 50,000 to 100,000 depending on type of pacer which you would like to consider. If you are talking about the chronically implanted, permanent type of pacemakers, it is probably in the range of about 50,000 at the present time.

Mr. MICHEL. Are you keeping statistics on those individuals?

Dr. COOPER. We do not have a formal registry in which we are following each one as a Federal responsibility. However, a large number of these programs are supported by the Institute in their research efforts and they have been most helpful and cooperative in providing us with their experience as we need it.

Mr. MICHEL. What does the most sophisticated pacer cost?

Dr. COOPER. Approximately $1,000, not counting the cost of implantation.

Mr. MICHEL. How does that compare to 5 years ago?

Dr. COOPER. The general dimension of the cost hasn't changed dramatically during this period of time, although the design and the capabilities of the pacemakers have. I think the important thing here is that they have continually been improved although there is a huge amount of additional sophisticated engineering which, in my opinion, could be applied to this problem.

USE OF ARTIFICIAL OR TRANSPLANTED ARTERIES

Mr. MICHEL. You make mention in your testimony of the artificial arteries that are being implanted in the heart. I am reminded of the father of one of my secretaries who recently underwent an operation. They found, however, that his arteries in the legs, I believe, were such that they couldn't use artificial ones but rather a cleansing, is it, of existing arteries?

Dr. COOPER. The operation is called a coronary by-pass graft, and what they usually do is explore the leg veins in order to find a segment of veins which can be used to hook a new blood supply to the blood vessels of the heart beyond the place where they are occluded.

Sometimes they find the patients have had disease of the veins or occlusion of the veins and therefore these are not useful.

What they use in these circumstances are synthetic vessels. This will work but it is often more acceptable to use a segment of the patient's own blood vessels since he tolerates it much better.

Mr. MICHEL. The trouble was in the legs themselves.

Dr. COOPER. Arteriosclerosis which we talk about a great deal here which affects the blood vessels to the heart muscles can affect the blood vessels throughout the rest of the body.

When the blood vessels to the legs are damaged by arteriosclerosis, and close off by clots as are the vessels in the heart, you can either get gangrene or severe pain in the leg on walking which is called intermittent claudication.

There has been considerable success in reaming out the vessels and opening them up in restoring blood flow through them or providing a bypass around them. The exact same principles are employed in the treatment of disease of the blood vessels to the heart today.

STORAGE OF VEINS FOR TRANSPLANT

Mr. FLOOD. Did you see the story this morning in the Washington Post of the Australian doctor stripping the leg veins and putting them in a bank to be implanted to other patients when needed?

Dr. COOPER. Yes.

Mr. FLOOD. Did you hear of that before?

Dr. COOPER. Yes, sir. This technique is employed worldwide for methods of preserving the graft. Indeed Dr. Hufnagel many years ago initiated some of the studies in this area. Storing and preserving grafts from a variety of patients has been accomplished so that these may be used in other patients.

TABLE ON CARDIOVASCULAR AND PULMONARY DISEASE

Mr. MICHEL. Last year you provided a table on cardiovascular and pulmonary diseases. Will you bring that up to date?

Dr. COOPER. Yes.

(The information follows:)

I. DEATHS FROM CARDIOVASCULAR AND PULMONARY DISEASES DURING 1968[1]

	Under 65	65 and over[2]	Total
MALES AND FEMALES			
Cardiovascular diseases:			
Ischemic heart and hypertensive disease:			
Acute ischemic heart disease (includes "heart attack")	125,101	249,200	374,301
Other ischemic heart and hypertensive disease	57,847	269,360	327,207
Strike	38,353	173,037	211,390
Rheumatic fever and rheumatic heart disease	9,810	6,548	16,358
Congenital heart disease	7,856	165	8,021
Other cardiovascular diseases	27,133	83,903	111,036
Subtotal, cardiovascular diseases	266,100	782,213	1,048,313
Chronic obstructive pulmonary diseases:			
Chronic and unqualified bronchitis	2,093	4,112	6,205
Emphysema	7,592	16,593	24,185
Asthma	1,701	987	2,688
Subtotal, chronic obstructive pulmonary diseases	11,386	21,692	33,078
Total, cardiovascular and pulmonary	277,486	803,905	1,081,391

I. DEATHS FROM CARDIOVASCULAR AND PULMONARY DISEASES DURING 1968[1]—Continued

	Under 65	65 and over[2]	Total
MALES			
Cardiovascular diseases:			
Ischemic heart and hypertensive disease:			
Acute ischemic heart disease (includes "heart attack")	97,108	141,854	238,962
Other ischemic heart and hypertensive disease	39,256	125,112	164,368
Stroke	20,683	76,018	96,701
Rheumatic fever and rheumatic heart disease	4,803	2,720	7,523
Congenital heart disease	4,431	66	4,497
Other cardiovascular diseases	17,003	41,217	58,220
Subtotal, cardiovascular diseases	183,284	386,987	570,271
Chronic obstructive pulmonary diseases:			
Chronic and unqualified bronchitis	1,473	3,121	4,594
Emphysema	6,157	14,277	20,434
Asthma	747	487	1,234
Subtotal, chronic obstructive pulmonary diseases	8,377	17,885	26,262
Total, cardiovascular and pulmonary	191,661	404,872	596,533
FEMALES			
Cardiovascular diseases:			
Ischemic heart and hypertensive disease:			
Acute ischemic heart disease (includes "heart attack")	27,993	107,346	135,339
Other ischemic heart and hypertensive disease	18,591	144,248	162,839
Stroke	17,670	97,019	114,689
Rheumatic fever and rheumatic heart disease	5,007	3,828	8,835
Cogenital heart disease	3,425	99	3,524
Other cardiovascular diseases	10,130	42,686	52,816
Subtotal, cardiovascular diseases	82,816	395,226	478,042
Chronic obstructive pulmonary diseases:			
Chronic and unqualified bronchitis	620	991	1,611
Emphysema	1,435	2,316	3,751
Asthma	954	500	1,454
Subtotal, chronic obstructive pulmonary diseases	3,009	3,807	6,816
Total, cardiovascular and pulmonary	85,825	399,033	484,858

[1] Final 1968 mortality statistics (unpublished).
[2] Includes age not stated.

Source: Division of Vital Statistics, National Center for Health Statistics.

II.—DISABILITIES FROM CARDIOVASCULAR AND PULMONARY DISEASES (UNPUBLISHED FIGURES FROM DIVISION OF HEALTH INTERVIEW STATISTICS, NATIONAL CENTER FOR HEALTH STATISTICS, BASED ON DATA COLLECTED DURING THE PERIOD FROM JULY 1967 TO JUNE 1968).

	Disability category					
	t Restricted activity			Bed disability		
	Total	Under 65	65 and over	Total	Under 65	65 and over
Average annual number of disability-days (in millions):						
Cardiovascular conditions	493	262	231	185	91	94
Heart condition	252	130	122	98	48	50
High blood pressure [1]	69	43	26	22	14	7
Other cardiovascular conditions	172	89	83	65	29	37
Chronic bronchitis and emphysema	172	127	44	66	50	16
Total	665	389	275	251	141	110
Average number of persons (in thousands): [2]						
Cardiovascular conditions	1,351	717	633	506	249	257
Heart conditions	689	355	335	269	132	137
High blood pressure [1]	190	118	71	59	38	20
Other cardiovascular conditions	472	244	228	178	79	100
Chronic bronchitis and emphysema	470	349	121	181	137	43
Total	1,821	1,066	755	687	386	300

[1] Without heart involvement.
[2] Disability days/365.

III.—ESTIMATED NATIONAL HEALTH EXPENDITURES FOR THE CARDIOVASCULAR DISEASES IN 1969 (COMPUTED FROM DATA PUBLISHED BY PHS)

Type of expenditure:	Amount
Hospital care	$2,800,000,000
Nursing home care	1,200,000,000
Physicians' and other professional services	1,800,000,000
Drugs and other health services and supplies	600,000,000
Research and medical facilities construction	600,000,000
Total	7,000,000,000

RELATIONSHIP OF CHOLESTEROL TO HEART DISEASE

Mr. MICHEL. During the last year in a number of publications we have seen many articles on the cholesterol controversy. I remember in the agricultural subcommittee, the Agricultural Research Service are making a big pitch about this. What do we know up to date? Haven't we changed our view with respect to whether it is good or bad to have "X" amount of cholesterol in our blood?

Dr. COOPER. What we have learned is that when we say we have high cholesterol in the blood, we are talking about a family of situations, a spectrum of diseases. We now know high cholesterol for one person may not mean the same thing as for another person.

Mr. MICHEL. But these same two persons, are they undergoing the same analysis?

Dr. COOPER. With the same analysis of their blood they can show a different appearance of the blood, the level can be high, the blood vessels can be considerably different and the extent of disease different. But more important the way to lower the blood cholesterol might be different in the two situations.

We know there are probably at least five types of high blood cholesterol that can be appreciated and dealt with on a selective basis. The

susceptibility of patients with elevated blood cholesterol to vascular diseases, whether of legs or aorta or heart vessels is, in some cases, more related to some type of hypercholesterolemia than to the amount.

But the prevalence and distribution of this abnormality in the general public at large is not appreciated, nor do we know that lowering it will prevent a heart attack. This is a very important question that remains to be resolved.

Mr. MICHEL. In the interval until we really know for sure, if we find it to be somewhat above the normal, it would be to our advantage to eat those kinds of foods that bring it down?

Dr. COOPER. It would be prudent, in my opinion, to try to keep your blood cholesterol within the normal limits for your age and sex range. Therefore, I think it is wise to find out what type of abnormality you have, if you have any, and then treat it appropriately.

CUTS IN NHLI GRANTS AND FELLOWSHIPS

Mr. MICHEL. In your justification you show a proposed decrease in the fellowship program. What is the base for this reduction?

Dr. COOPER. The reduction is a program of curtailment which is applied to this Institute as well as all of the Institutes at NIH which received congressional increases in fellowship programs in 1971. We take our prorated effect on that basis.

Mr. MICHEL. You mention decreases in research grants of $1,618,000 for programs of lesser priority. What are these?

Dr. COOPER. We have analyzed our programs and evaluated them on the basis of six general categories. We have a category devoted to arteriosclerosis and its manifestations, hypertension, blood coagulation, and thrombotic diseases, the other cardiac conditions like heart failure and shock, and lung diseases, and then the special programs which involve artificial organs, transplantation, and the rest.

Obviously all of these are programs of great importance and of considerable opportunity. When one compares one to the other and makes a selection one against the other, I think we would continue to indicate that the top three of those plus the new lung program would be the most important for us to emphasize, that is arteriosclerosis, lung diseases, thrombosis, and hypertension.

LIPIDOSIS

Mr. MICHEL. What does the study of lipidosis involve?

Dr. COOPER. It involves the study of those abnormalities of fat metabolism with which we are concerned.

Mr. MICHEL. That is all.

Mr. FLOOD. Mr. Smith.

RATIONALE FOR MAINTAINING 1971 PROGRAM LEVEL

Mr. SMITH. You have divided your research grant program into six branches. One of them, of course, contains the increase you spoke of. Other than that, it seems that the amount requested for each of these branches is approximately equal to what it was last year.

Why would this be? It seems to me there would be either a need for more emphasis on one of the branches or there might be available those persons or that kind of a team that wasn't available before.

Why would it happen to come out approximately equal except the one particular new emphasis?

Dr. COOPER. Aside from the relevance to the disease missions of the institute, the principal determinant in the selection of the programs for funding is the nature of the various components of the program.

We are now funding programs at a level where we feel that the critical mass of these excellent programs can be maintained at those levels with the exception of those special new initiatives which have been identified. So that when you combine relevance and excellence, we come out with a decision not to modify that spectrum.

Mr. SMITH. Why would the excellence of each one of the branches remain constant by comparison?

Dr. COOPER. Because of the level at which we are funding these—we are paying such a high priority that these are all very good programs of high promise in obviously important areas.

UNFUNDED GRANT APPLICATIONS

Mr. SMITH. This total for research grants is $93.8 million. How many of the approved applications would you say that are not included in this $93.8 million would be of high priority or of excellent standing?

Dr. COOPER. In addition to the ones we are committed to?

Mr. SMITH. Yes.

Dr. COOPER. My estimate for this would be in the neighborhood of about $8 million worth which would be different across those grant lines at that level.

Mr. SMITH. Those would be very excellent and they would not detract from any others?

Dr. COOPER. In my opinion, yes, sir.

Mr. SMITH. That is all I have.

Mr. FLOOD. Mr. Shriver.

PROPER STORAGE AND DISTRIBUTION OF BLOOD

Mr. SHRIVER. Thank you, Mr. Chairman.

Doctor, in this country is there any problem of an adequate supply of blood for transfusions?

Dr. COOPER. There certainly is a question of an adequate distribution of the available supply. What I am trying to say is that there is a loss of blood because it is inappropriately used or because it is not in the right place at the right time.

Mr. SHRIVER. What is being done about that?

Dr. COOPER. We are developing a system by which we hope to utilize the maximum assistance for computerization of typing and transportation systems to maximize the use of the blood. There are pilot studies in various cities going on where the loss of blood due to expired shelf life has been reduced from 25 or 30 percent loss to about 5 or 8 percent loss. How this can be applied to a wide system hasn't yet been studied?

Mr. MICHEL. Will the gentleman yield?

Mr. SHRIVER. Certainly.

Mr. MICHEL. You spoke of breaking down the blood into components and using some for some patients and the residue for other patients. After whole blood has been on the shelf to the point where it has outlived its usefulness as whole blood, is there still time then to break it down?

Dr. COOPER. Some of it can continue to be used for that purpose.

GRANTS AND CONTRACTS TO NONUNIVERSITY INSTITUTIONS

Mr. SHRIVER. On page 1 of your statement you mention grants and contracts to universities, medical schools and other institutions. My question relates to "and other institutions."

Dr. COOPER. These include nonuniversity affiliated hospitals, research foundations, and other research groups. The grants are all for nonprofit institutions. When we deal with profitmakers, we use the contract mechanism.

DEVICE TESTING FACILITIES

Mr. SHRIVER. You mention, "To study the performance of these devices, two test and evaluation centers have been developed for subjecting materials and the devices to bench tests, tests in animals, and, finally, to carefully control clinical trials prior to general use."

Where is that? Here?

Dr. COOPER. No, sir; one is in Chicago and the other is in Salt Lake City, Utah.

Mr. SHRIVER. How large are they?

Dr. COOPER. The one planned for operation this year is approximately $1.5 million, the other for about $900,000.

ESTABLISHMENT OF SPECIALIZED RESEARCH CENTERS

Mr. SHRIVER. On page 83 of the justifications at the bottom you are talking about specialized research centers:

> The Institute was provided a substantial amount, over $16 million, in 1971 to establish specialized centers of research.

Have those been located?

Dr. COOPER. The final decisions on that selection will be made on May 14 at a special meeting of the National Advisory Heart and Lung Council. The technical review of those proposals has been completed and we will make the awards by June.

OPPORTUNITIES FOR ACCELERATED NHLI RESEARCH

Mr. SHRIVER. You mentioned that heart disease kills more Americans each year than cancer. We may be expected to receive inquiries from our constituents as to why we are not instituting a heart disease conquest program. What would be your answer to that?

Dr. COOPER. In my opinion there are additional opportunities available for accelerating progress in conquest of heart disease and chronic lung disease.

PRIVATE HEART DISEASE EFFORT

Mr. SHRIVER. Would you estimate the amount of private efforts in the field of heart disease in prevention and treatment in 1971?

Dr. COOPER. About $45 or $50 million.

Mr. SHRIVER. Where does that come from?

Dr. COOPER. It largely comes from the voluntary agencies, the principal one of which in the field of heart disease is the annual drive of the American Heart Association and its affiliates.

In addition in the field of chronic lung disease there is another $40 million which is raised from public sources for efforts in this regard

CUTS IN LESSER PRIORITY R. AND D. PROGRAMS

Mr. SHRIVER. On page 7 of the justification you mention a decrease of $1.6 million for research grants for programs of lesser priority and a decrease of $3 million for collaborative research and development for the same reason.

Will you tell us what these programs of lesser priority are?

Dr. COOPER. I would hope that the use of the phrase "lesser priority" would not be interpreted as nonproductive programs. But we are emphasizing prevention of arteriosclerosis and heart attack as our principal goal. Then I think I am forced at the current level of resources to try to take best advantage of the best opportunities in the areas of highest possible payoff. The areas that we encompassed in the so-called lesser priorities for the $3 million reduction are, for example, certain facets of engine development for the artificial heart. We have chosen to downplay this while we are awaiting the development of new materials and their testing. Some of the ancilliary activities of the myocardial infarction research units have been deleted. Certain facets of the national blood resource program which have to do with testing of new additives for blood are now completed, and are being used in the expansion of time of shelf life for storage of blood.

CUT IN HEART COOPERATIVE DRUG STUDY

Mr. SHRIVER. I believe you are going to decrease the funds for the heart cooperative drug study?

Dr. COOPER. I mentioned earlier that our anticipated ability to save in this is related to the observation that some of the patients who have heart attacks while they are in this study and for whom we had originally anticipated we might have to provide funds for hospitalization are receiving their hospitalization costs from other sources.

I am not entirely certain we would be able to maintain this activity at that level indefinitely. That is a projection. However, we would make a commitment to maintain the scientific validity of that study by reprograming if necessary.

Mr. SHRIVER. Thank you, doctor.

Mr. FLOOD. Mr. Casey.

SICKLE CELL ANEMIA

Mr. CASEY. Thank you, Mr. Chairman.

I have heard discussion and maybe it has been explained when I wasn't here. What is sickle cell anemia? How does it affect the patient?

Dr. COOPER. The patient's blood is made by the bone marrow, and his ability to make that part of the blood cell that carries the oxygen is called hemoglobin. The hemoglobin is made up of chains of proteins. The way these proteins are made is directed by one gene from the father and one gene from the mother. If the patient has acquired the trait from both his mother and father, because they both carry it, then the patient will make abnormal hemoglobin. When you carry abnormal hemoglobin in the cell and the cell is exposed to certain conditions, like a low oxygen environment, the hemoglobin in the cell will aggregate or clump.

When this happens, the cell is deformed and sometimes it takes instead of a round shape, a form which looks like a sickle. That is where it gets its name, sickle cell.

When these cells take this abnormally long and curved shape, and go through the capillaries they tend to block them. When these cells block off the capillaries to various vital organs like the kidneys or the bone or the brain, or various parts of the body, it deprives them of bloodflow through it, and this makes the organ deficient in oxygen. This is associated with a painful situation which mimics a lot of other painful diseases. This situation is called a crisis—the sickle cell crisis. The repeated exposure and aggregating of those cells and the clumping in the capillaries appears, along perhaps for other reasons as not yet understood, to reduce the life span of that cell.

Therefore, these cells are more likely to be destroyed sooner than they should be. So the patient tends to get a deficiency in blood cells which is anemia. But he suffers mostly from this chronic tendency toward having painful vaso-occlusive crises which are often misunderstood and misdiagnosed. If these involve critical organs in the body, they can cause the shortening of life span. The mechanism as to why some organs are affected in some people, more than in others, is not clearly understood.

Mr. CASEY. Do these particularly affect the heart or lung?

Dr. COOPER. They can affect the heart and can induce a form of heart disease, an involvement of the heart. Any organ can be affected.

NHLI INVOLVEMENT IN RESEARCH ON SICKLE CELL ANEMIA

Mr. CASEY. The reason I ask is you spent quite a bit of time in your statement on sickle cell anemia and you have an increase of $5 million for it. Are you primarily involved in this?

Dr. COOPER. We are principally involved in the study of conditions associated with sickle cell. There are other programs at the National Institutes of Health that are involved in the study of sickle cell disease from their special areas of expertise.

The National Institute of Arthritis and Metabolic Disease, because of their expertise in metabolism of red blood cells in which the hemo-

globin is involved, has a considerable program in this area of about $450,000. The National Institute of General Medical Sciences has some activity in the area as does the National Institute of Child Health and Human Development.

NATIONAL BLOOD RESOURCE PROGRAM

Mr. CASEY. The national blood resource program, is that a joint program or do you have a separate entity designated by that name?

Dr. COOPER. The national blood resource program is a branch of the National Heart and Lung Institute.

Mr. CASEY. It is really under you?

Dr. COOPER. It is really under me, but the planned sickle cell anemia initiative will be coordinated among the other Institutes as well as the Health Services and Mental Health Administration for the public activities that will be needed in the public education sphere and perhaps in the screening part of this problem. This program will be coordinated by Dr. Ringler, the Deputy Director of the Institute.

POTENTIAL BREAKTHROUGHS IN NHLI

Mr. CASEY. Doctor, are you on the verge of any breakthrough in the heart or lung program?

Dr. COOPER. I don't think I could in all candor say we are on the verge of dramatic breakthroughs. On the other hand I think the opportunity for significant reduction in the number of premature deaths from arteriosclerotic heart disease, hypertension, and thrombosis is at hand.

In our promise of detection of causes of chronic lung disease we may be on the upswing as well.

UTILITY OF ADDITIONAL FUNDS FOR NHLI

Mr. CASEY. In other words, if this Congress or somebody, fairy godmother, what have you, dropped you $100 million additional, could you use it advantageously?

Dr. COOPER. The availability of $100 million in——

Mr. CASEY. You are not going to get it necessarily.

Dr. COOPER. I understand. I like to dream.

Mr. CASEY. Assume that we are going to do the same thing for heart, it is a bigger killer, as we did for cancer.

Dr. COOPER. I do think there are opportunities for significant progress beyond the scope of our own budget in both of these disease areas.

Mr. CASEY. That is a pretty diplomatic answer considering you are not here advocating that.

Mr. Smith asked you about the research grants. I believe you told him you knew of at least $8 million worth of grants that could be funded and you thought deserved funding; is that correct?

Dr. COOPER. Yes, sir. I think there are areas of good research that we have assessed and that have promise.

ARTIFICIAL HEARTS

Mr. CASEY. Now you mentioned in your statement that you now have a number of new materials, silicones, polymers, et cetera, which seem not only to work well when made up into mechanical devices for heart and arteries, but they do not cause major damage to blood. That was one of the main problems in the first stages of your mechanical heart; right?

Dr. COOPER. Yes, sir.

Mr. CASEY. Your big problem now, as I gather from your answer to one of the other members of the committee, is the pump itself. Is that right?

Dr. COOPER. It is the determination of whether these materials when fabricated into these shapes and physical characteristics that are needed for the devices will withstand the stress and strain of being in a pumping situation of being flexed over long periods of time while they are implanted in the blood stream. So it has to do with the actual design of the pumps as well as the long-term affects of their implantation. I think we have three or four different types of substances now with improved surfaces which could be tested for this purpose.

Mr. CASEY. They say there are not sufficient human hearts for transplants and mechanical hearts are still out in the future at this point.

Do you think a mechanical device is in the offing at the moment?

Dr. COOPER. I think constructurally, all other things being equal, that the availability of these devices would offer greater hope, but nothing can function as well as the human heart.

EFFECTS OF INFLATION ON NHLI BUDGET

Mr. CASEY. Doesn't your program suffer from inflation just like everything else?

Dr. COOPER. Yes, sir; it does.

Mr. CASEY. Have you enough money in here to hold your own with what you have been doing in the past?

Dr. COOPER. I think as we have indicated in the justification, by holding our own at the dollar level, there will be some loss of what we are supporting in all areas.

Mr. CASEY. What is the rate of inflation in your shop? 15 percent, 20 percent?

Dr. COOPER. I think that ours is consistent with the average in NIH. I would guess it is in the neighborhood of 10 to 15 percent.

Mr. CASEY. Thank you, Mr. Chairman.

RESEARCH ON EARLY-LIFE AND LUNG DISEASES

Mrs. REID. Doctor, I have read some reports which state that some young people are developing a narrowing of their blood vessels which may cause them to have heart attacks early in life. Are you doing anything about this in the way of research?

Dr. COOPER. Yes, we have become increasingly aware of that. This disease of hardening of the arteries may have its incipience early in

life and may have a gestation period or building period of as long as 20 or 30 years.

We were confirmed in that view by the autopsy material that was examined from recent wars in which young men were found to have significant narrowing of their blood vessels to their heart but who died a traumatic death or a war death. We can now detect abnormalities of blood lipids in the young and are able to assess what the natural history of these patterns may be. We are committeed to embarking on a program in which we will advance our investigation to younger age groups in order to determine what the long-term effects might be. Half of our new programs will include segments in which we will begin evaluating this in the youngster.

Mrs. REID. In that same context, then, you have mentioned the Institute's interest in lung disease. Are you going to be concerned there with newborn babies and young children with these diseases, as well as adults, coal miners and so forth?

Dr. COOPER. Yes, we will, Mrs. Reid. I think we have again recognized in certain aspects of chronic lung disease development some of the factors involved may be able to be detected early in life. Some of these are genetic. Some may be related to metabolism of the lung, which may manifest itself in infancy, at a great toll of death, but those that survive may also be at increased risk of chronic lung disease and we must get on with studying these in order to be able to give them advice, if nothing else, about which exposures should be avoided.

RESEARCH ON DISSOLUTION OF LUNG AND HEART CLOTS

Mrs. REID. You mentioned that the Institute has been working successfully with a drug which dissolves blood clots in the lung. What about dissolving clots in the arteries of the heart?

Dr. COOPER. We have completed a study which shows that we can accelerate the dissolution of clots in the lung. At the present time we are beginning a pilot study which will assess the ways in which we should give this to patients who have acute myocardial infarction, occlusion of their coronary arteries, in order to be sure we can give it to them in a safe and effective way. If this proves out to be practical in such acute conditions as the acute heart attack, then we would hope to implement a study on this in the near future.

Mr. REID. That would certainly indicate progress, I would say.

Dr. COOPER. The leads from the European studies in this regard suggest we may be able to effect a considerable saving of life in the hospitalized patient with myocardial infarction, so it is an important avenue of investigation in our view.

CLOT-PRODUCING ASPECTS OF BIRTH CONTROL PILLS

Mrs. REID. I realize that the family planning programs are not in your particular area of concern, but I continue to read about drugs used as birth control pills causing blood clots or high blood pressure. Are you doing any research in this area?

Dr. COOPER. Yes, it is true that our principal responsibility is not in the area of family planning and the development of drugs for that purpose. However, the observation has been made that there seems to be an increased risk of developing blood clots and fatal pulmonary embolism in women who take certain types of birth control pills. In studies supported by the Institute, we have been able to detect that some women seem to increase certain clotting fractions in their blood while on the pill while others do not. This has not developed far enough to anticipate which women might be susceptible, but at least it offers the possibility of advising the ones that do have an abnormal increase that they might best seek their birth control methods by another approach.

So that we are aware that this problem must be further pursued.

HYPERTENSION LINKED TO BIRTH CONTROL PILLS

In the area of hypertension, it has been recently reported that a significant number, in different populations, of women who are on the pill, develop high blood pressure. For example, in the black population some feel that as many as 7 percent of the women will develop high blood pressure.

In another population, 7 percent of the women developed it anyway, that is without taking the pill. So it isn't clear yet because no real systematic study has been done in the nonhypertensive female at an early age, and this is one of the things we have started with the new moneys that have been given to us this year, what the relationship might be.

We also are well aware that a certain number of females, and a high percentage in certain population groups, develop high blood pressure when they become pregnant, so the resolution of this problem remains an important one. We are therefore, giving priority to the study of the natural history of hypertension in the population not only in the severe but also the mild form in the male, in the female and in the young.

OBESITY AND HEALTH

Mr. PATTEN. You hear people say "A lean horse for a long race." If a fellow weighed 128 pounds, he might have a chance to live longer than a fat 300-pound man?

Dr. COOPER. I do subscribe to that, in that form.

Mr. PATTEN. Do you like the rule of thumb that, tell me how long your mother and father lived and I will tell you how long you will live?

Dr. COOPER. Absolutely. I think that is a good bet.

Mr. PATTEN. You say that in the monkey there may be a regression on this fat business, where the polyunsaturated fat diet shows a regression phenomenon that interests you very much because you can apply it to humans and probably there is some hope for some of the fat fellows, is that right?

Dr. COOPER. Yes, sir.

BODY FAT AND CHOLESTEROL LEVEL

Mr. PATTEN. When you say fat, say a fellow weighs 250.

It doesn't necessarily follow that he has a cholesterol problem, does it?

Dr. COOPER. Not necessarily.

Mr. PATTEN. If you look at body fat, do you expect to find fat in the blood too?

Dr. COOPER. If you had to begin applying a rule of thumb, somebody over 20 percent overweight might be expected to have some elevation of certain types of his blood fat but it is true that you could get people who would weigh 250 pounds who would not have a specific abnormality, but it isn't all black and white.

EFFECTS OF LOW BLOOD PRESSURE

Mr. PATTEN. You have made an evil of high blood pressure. What about low blood pressure? Is that an asset?

Dr. COOPER. No, low blood pressure is not an asset, if you mean abnormally low blood pressure. Very often some people who describe low blood pressure refer to a condition of a low blood count. When they say low blood pressure, they really mean they are anemic. In this situation, this is not a good thing.

If by low blood pressure people mean they have a blood pressure which is in the lower range of normal for their age——

Mr. PATTEN. Say 110/120 when you are 65.

Dr. COOPER. I think that is very good, but if it is below normal for their age, then I think it is not very good and may be the herald of some other important disease that needs attention.

HEREDITARY TOLERANCE OF FAT

Mr. PATTEN. Don't you think there is something to be said for all the people who love to eat and can eat anything, even if they are a little overweight, but full of life?

Dr. COOPER. The answer to that again lies in the genetics. If the familial disposition will protect it, I think it is OK, but until you know that you should seek out the important information by which to get the right advice to protect yourself.

Mr. PATTEN. I have taken off hundreds of pounds, 20 pounds at a time, probably 20 times in my lifetime. The weight easily returns. There is something about nature too, isn't there?

Dr. COOPER. There is something about nature that is protective in that respect and it is a very important determinant of the presence or absence of disease.

Mr. PATTEN. I am going to wait until you invent some easy way to lose weight.

Your presentation is very important and I have enjoyed it. I hope you will get the money and will do the most good for the people of this country. It has been a pleasure to be here.

Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Conte?

EFFECTS OF INFLATION ON NHLI BUDGET

Mr. CONTE. Doctor, in answer to Mr. Casey, you said inflation has pushed your costs upward. Do you use the figure 10 or 12 percent?

Dr. COOPER. Yes, sir.

Mr. CONTE. How do you arrive at that? Others have been using six.

Dr. COOPER. I am just adding six and six. If you talk about direct costs, we have to include the inflationary factor that when we pay for a research project we pay for the costs of increasing salaries and fringe benefits of people doing research, increase in animal costs, increases in the costs of supplies, all these factors.

Then we also have experienced in the past several years an increase in the rate of indirect costs which we pay for the support of research. In our institute it has amounted to $8 or $10 million since 1968, increased costs shown as indirect costs percentages.

Mr. SHRIVER. What are you doing about it? This Government is trying to cut down on inflation. If it is 12 percent, it is abnormal.

Dr. COOPER. Perhaps my calculation of 12 is the wrong figure and the right fiscal figure might be 6 percent, but what we are trying to do about it is to make sure that when we review the budgets in association with our consultants that we buy that portion of the activity that is absolutely necessary for the accomplishment of research within the confines of the economy.

COMPETITION FOR GRANT AWARDS

Mr. SHRIVER. Are these absolute costs? Is there any competition?

Dr. COOPER. Yes; there is always competition in all the areas.

Mr. SHRIVER. In the universities?

Dr. COOPER. Yes, sir.

Mr. SHRIVER. Will you explain that?

Dr. COOPER. Where the competition comes? Well, in the grant programs, the grants compete one against the other in the open competition in the given areas for which the grant was submitted.

For example, if it is in the area of heart disease, it might go to a group that is assessing all the programs in heart disease, and the groups would then evaluate whether the right questions are being asked, whether the right procedures are being proposed to answer the question, whether the qualifications of the people that are doing the research are the right qualifications, the number of people is right, whether the equipment that is being asked for is the appropriate equipment, whether it duplicates other equipment that is already available in the institution, whether their requests for supplies are right. Then they make a recommendation as to whether this should be approved or disapproved.

If it is approved, they given it an excellence rating relative to what resources would be available. In that review they compete one against the other about what would be the best questions to ask and how is it best to do the research in the most cost effective way.

CONTRACTING PROCEDURES

Now, in the contract area, we do it by asking for certain things to be done. We evaluate the response again of everybody who applies as to what they propose to do, what are their qualifications to do it, how many people should do it, what their resources are, and so on.

Mr. SHRIVER. It doesn't necessarily go to the lowest responsible bidder?

Dr. COOPER. In the area of contract bidding, if we are seeking out a thing that is comparable in all respects for competition, then it goes to the lowest bidder. But in so many areas of research where you are buying the idea and the approach to the solution of a problem, they are not comparable in the sense of being cost-equated on that basis.

Thus there are both types. When it is applicable we give it to the lowest bidder. When it is not, we buy the most excellent research that would give the most answers in the most cost-effective way.

Mr. SHRIVER. In the judgment of your advisory committees?

Dr. COOPER. And our own experts.

INFLATIONARY FACTORS

Dr. BERLINER. I would like to comment on the figure for the increasing costs. I think it may be a little deceptive to talk about this as simply inflation. Part of it is inflation and I think the figure for inflation costs generally is on the order of 6 percent.

There are two additional factors, however, that impact on our programs. One is the fact that one of the areas in which some of our support money goes is into programs that are involved in the care of patients, with hospitalization and so on, and in the hospital environment the costs have been going up at a much higher rate.

I believe the average rate is of the order of 15 or 16 percent a year. Finally, I think a very important factor is that the costs of doing research have gone up very markedly as a consequence of increased sophistication and the more complicated instrumentation that is required to do the research today than it was several years ago. This is a continuing process. Research costs, I would guess, probably have gone up at least at a rate of 8 to 10 percent and possibly the 12 percent that Dr. Cooper mentioned.

Mr. SHRIVER. Has there been any improvement in the last year?

Dr. BERLINER. It would be very difficult to look at a single year and try to figure out an answer to that question, Mr. Shriver.

Mr. SHRIVER. This is a basic question in the country today, inflation.

Dr. BERLINER. Unquestionably. I realize that.

Mr. SHRIVER. The Government is trying to get a handle on it and that is why I ask what you are doing about it.

Dr. BERLINER. We are dealing in an area where the inflationary pressures are much higher than in most and that is in the medical area.

Mr. SHRIVER. I can see that as it relates to hospital care. I am not convinced from the standpoint that there couldn't be anything done about keeping the costs of research down so there wouldn't be this high

level of increase that has been mentioned just to maintain the same program level.

That is all I have, Mr. Chairman.

DIET AND DRUG REDUCTION OF BLOOD FAT

Mr. CONTE. Could you be more specific and describe what kind of diets and types of drugs have been found effective in reducing blood fat level?

Dr. COOPER. The first type of dietary management which is most effective in all five types of elevated blood lipids is the control of total calories. It is total weight control. What one does then is to try to adjust the level of energy expenditure to the intake of total calories.

Secondly, the composition of the diet ought to be modified, dependent on the specific type of metabolism malady with which you have to deal.

The obvious case is if you were a diabetic and needed to modify your metabolism of sugar. If it is a type of lipid abnormality where the intake of saturated fats is of particular importance, you should reduce the level of intake in your total calories appropriate to your energy level to the amount of saturated fat or total fat in the diet. That would be, say, 30 percent or 35 percent rather than 40 or 45 percent, which you might have been consuming previously.

The same would hold true on the role of polyunsaturated fats to be added to the diet in certain selected types of abnormalities. This is the type of dietary prescription that ought now to be available depending on the selection of the particular type of fat abnormality.

In certain types of these abnormalities, we have learned that some drugs which act by different mechanisms can be helpful in further lowering of the blood fat. Under rigidly controlled conditions in a hospital metabolism ward, you may be able, by strict dietary prescription, to lower blood cholesterol by 25 percent, but in order to take you out of the risk range, you might have to go down 40 or 60 percent. That is why you add your drug.

There are certain drugs that sequester the fats in the bowel, don't allow them to be absorbed from what you eat. An example of this is cholestyramine. This ties up the material in the bowel and it is passed out through the feces; therefore is not absorbed and is therefore not a factor in inducing further elevation of your blood fat.

There are other substances like nicotinic acid, or clofibrate, which are particular drugs.

The mechanisms of these are not entirely clear, but they may act on the pools where the cholesterol is stored or the liver where the fats are metabolized. Their action is not entirely clear, but certain types of abnormalities respond better to certain types of drugs in these various types of action.

VA HYPERTENSION STUDY

Mr. CONTE. Exactly what patients' blood pressure is controlled in the studies conducted in the VA hospitals?

Dr. COOPER. These were a group of male patients with an average age of about 57 years in which they had moderate to marked high blood

pressure. That is, they had definite elevations of their blood pressure. It was not in the labile group. These hypertensives were put on a randomized schedule. Their doctors knew they were under adequate treatment but the specific regimens were randomized for accuracy of reporting and statistical analysis.

What they were able to show in a relatively short period of time—they stopped the trial because it became quite clear that those patients with their blood pressure under control through the use of the drugs seemed to have less complications of hypertension than those that did not.

The main complication that seems to be controlled, or at least prevented, is stroke. The studies were not conclusive about the ability to prevent heart attack or heart disease by controlling the blood pressure.

Second factors might have been involved in this, it might have been that the age group was far enough advanced that they were already preselected out. We feel there is a need to study the mild to moderate hypertensives, the women as well as the men, the blacks as well as the whites. Hypertension in the black population is a very large public health problem. We estimate in this country that there are 22 to 23 million hypertensives only 10 to 15 percent of which may be under treatment.

MONITORING RECOVERY OF HEART ATTACK VICTIMS

Mr. CONTE. What are some of the new measures that have been developed to determine how well a heart attack patient is responding to treatment?

Dr. COOPER. Some of these relate to the newer uses of the electrocardiogram, the electrical signals generated from the heart and their interpretation or resolution. Some relate to the use of a combination of heart motion studies on the X-ray film, which demonstrate the movement of the noninjured and the injured part of the heart.

If the area of involvement seems to become more extensive, and the motions of the heart can be recorded on movie-type film and television tape, then one can draw the conclusion that the disease is extending and the response is not salutary even though the blood and pulse rate may stay the same. Conversely, as the range of motion begins to get more vigorous and smaller, this is a salutary indication.

In addition, there has been some progress made with the use of radioisotopes in identifying so-called hot or cold areas on scattergrams of the front of the chest which could vary in size with the extent of the dead area of muscle, and the response of the patient to treatment may be reduced or expanded depending on what the treatment is or how successful it is.

SUDDEN CARDIAC DEATH

Mr. CONTE. It may be just a lot of hearsay, but you hear about people who dropped dead of a heart attack who had just had an electrocardiogram that gave them a clean bill of health.

Dr. COOPER. The area of so-called sudden cardiac death is a very large public health problem. Perhaps 50 percent of patients who die before they get to the hospital with acute heart attacks under the

age of 65 are involved in this group, but the interesting thing is if you really study these patients' history in retrospect, you will find a significant number of them, even though their last electrocardiogram might be within the range of normal, had some evidence that they were having some difficulty and therefore there might have been a tip-off earlier that they would not walk out of the doctor's office and collapse from a new event.

Mr. CONTE. Have you any statistics indicating how many heart attack victims die under the conditions you mention?

Dr. COOPER. Those in the premature group under 65? It is 80,000 to 100,000 a year. This may not be just 1 hour. We are talking about a time of several minutes to several hours.

BENEFICIARIES OF NEW DEVICES AND SURGICAL PROCEDURES

Mr. CONTE. At page 4 there are 12,000 patients that new surgical experiences are helping. What are the results and how long has this procedure been in general use?

Dr. COOPER. In general use it has been 2 or 3 years. It was proposed many years ago, and tried sporadically, but awaited the development of greater success with cardiopulmonary bypass and general supportive measures during surgery. In the recent 2 or 3 years, the success rate in average followup up to 2 years shows patency of the grafts in about 70 percent. The clinical result of improvement have been somewhat greater than that. If you are willing to accept the absense of pain or the well-being of the patient as improvement, that may be in the neighborhood of 70 to 80 percent.

The overall experience of hospital mortality has varied depending on how you select the patients, from less than 5 percent up to 17 percent. For this particular disease at this particular time in its evaulation, this is a very encouraging set of statistics, but it does indicate that we need to evaluate this very critically before it is promulgated to wide varieties of patients because I think it should be noted that since the turn of the century there have been 17 other operations proposed for the relief of pain in the chest due to heart disease or myocardial infarction and none of them up until this one have stood the test of critical evaluation.

BREAKTHROUGH IN BLOOD STORAGE

Mr. CONTE. What breakthroughs have you had in regard to storing blood?

Dr. COOPER. It is recognized that the addition of some other products that are currently approved for licensing might have the ability to prolong the shelf-life of blood by about 50 percent. These are substances such as adenosine. But it is recognized that there are other substances, perhaps adenosine with another substance called inosine, that might provide more extended survival time. This was set back for a period for needed evaluation because the suggestion was made that these substances might induce a lesion in the kidney if you got several transfusions, such as massive transfusions for trauma. This has required re-evaluation.

The other method that has undergone recent experimentation was freezing of blood, or the blood fractions and there has been some considerable success in this area of blood freezing which would offer the possibility of rather indefinite preservation.

SHORTAGE OF LUNG DOCTORS

Mr. CONTE. You mentioned the shortage of lung doctors. What is that shortage? Do you know?

Dr. COOPER. Yes. We called together a group of specialists after we received our new mandate and we had 150 people together representing all the major medical centers in the country and we made a survey at that time and we estimated that there are at least 48 major medical centers in which there is not a full-time lung specialist available for either continuous service to the sick or for teaching in the medical centers. Upon making this survey, it was clear that the community, both the pulmonary and the nonpulmonary community, identified this absence of manpower as the most critical need in the development of the lung program.

ANIMAL MODELS IN EMPHYSEMA STUDY

Mr. CONTE. Could you tell us a little bit about why animals haven't worked out so well in your studies and research in emphysema?

Dr. COOPER. The ability to produce a suitable animal model is difficult. Some may be related to the anatomy of the lung, some of it to the susceptibility of the species to the affecting agent, and our understanding of what the mechanism of affectation might be. There has been some small animal success in the hamster and for many years the people who have studied black lung disease have noted the ability of the horse and the pony to develop a certain type of emphysema very akin to the human one, but these animals are difficult to come by and are expensive and difficult to maintain. There have been repeated attempts over the past several years to induce obstructive lung disease by the implantation of various foreign bodies in the lung. This is always fraught with the induction of an overwhelming infection, the mechanism of which is not entirely understood, but which is very poorly tolerated in most animals that are subjected to this type of thing in the chest.

It has been proposed recently that these valuable animals be evaluated critically and there have been two reports in the last couple of years on the lung function and the circulatory function in these animals that have been exposed to this problem.

REDUCTIONS IN FELLOWSHIP AWARDS

Mr. CONTE. Doctor, at page 86 of your justifications what accounts for the planned reduction in fellowship awards for the coming fiscal year?

Dr. COOPER. This is a plan that is common to all the institutions in which we are partaking of our prorated share.

Mr. FLOOD. I might say we developed information on this earlier.

Mr. CONTE. Did you ask what this is going to mean, this reduction?

Mr. FLOOD. And the inconsistencies in the budget cuts in the program, at some length.

Mr. CONTE. I don't agree with it.

Mr. FLOOD. I don't either.

Mr. CONTE. Doctor, I wish we had more time. I want to compliment you. You have a wonderful background. I read it with great interest. You come from a great school and you really have done a great deal in your young life. We are certainly proud of you and we think you have handled this very well today.

Mr. PATTEN. Another contribution from the great State of New Jersey.

Mr. FLOOD. Thank you, Doctor.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

Amounts Available for Obligation

	1971	1972
Appropriation	$193,479,000	$195,492,000
Real transfer to:		
"Departmental management"	-24,000	---
Real transfer from:		
"National Institute of General Medical Sciences" (Proposed transfer for increased pay costs)	1,446,000	---
Comparative transfers to:		
"National Institute of General Medical Sciences"	-144,000	---
"National Institute of Child Health and Human Development"	-36,000	---
"Health Manpower"	-4,332,000	---
"Office of the Director"	-71,000	---
Comparative transfers from:		
"National Institute of Arthritis and Metabolic Diseases"	78,000	---
"National Institute of Allergy and Infectious Diseases"	802,000	---
"National Institute of General Medical Sciences"	429,000	---
Total, obligations	191,627,000	195,492,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
79	Research		$118,083,000		$120,981,000		+$2,898,000
	General research support grants		(8,127,000)		(7,267,000)		(-860,000)
	Scientific evaluation and planning		(163,000)		(163,000)		---
	Heart cooperative drug study		(4,579,000)		(3,255,000)		(-1,324,000)
	Specialized research centers		(16,442,000)		(16,442,000)		---
86	Fellowships		6,871,000		6,195,000		-676,000
87	Training		13,592,000		13,592,000		---
	Direct operations:						
88	Laboratory and clinical research	358	16,361,000	369	17,137,000	+11	+776,000
89	Collaborative research and development	40	30,612,000	46	31,166,000	+6	+554,000
92	Biometry, epidemiology and field studies	64	1,990,000	64	2,048,000	---	+58,000
92	Review and approval of grants	72	2,669,000	72	2,886,000	---	+217,000
93	Program direction	56	1,449,000	56	1,487,000	---	+38,000
	Total obligations	590	191,627,000	607	195,492,000	+17	+3,865,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions..	590	607	+17
Full-time equivalent of all other positions.....	63	63	--
Average number of all employees.....	645	658	+13
Personnel compensation:			
Permanent positions.....	$8,341,000	$8,937,000	+$596,000
Positions other than permanent.....	423,000	515,000	+92,000
Other personnel compensation.....	68,000	68,000	---
Subtotal, personnel compensation.	8,832,000	9,520,000	+688,000
Personnel benefits.....	871,000	912,000	+41,000
Travel and transportation of persons.....	375,000	383,000	+8,000
Transportation of things.....	75,000	84,000	+9,000
Rent, communications, and utilities..	325,000	325,000	---
Printing and reproduction.....	200,000	200,000	---
Other services:			
Project contracts.....	29,728,000	30,122,000	+394,000
NIH Management Fund.....	7,965,000	8,403,000	+438,000
Other.....	1,510,000	1,525,000	+15,000
Supplies and materials.....	2,200,000	2,230,000	+30,000
Equipment.....	1,000,000	1,020,000	+20,000
Grants, subsidies, and contributions.	138,546,000	140,768,000	+2,222,000
Total obligations by object.....	191,627,000	195,492,000	+3,865,000

Summary of Changes

1971 estimated obligations	$191,627,000
1972 estimated obligations	195,492,000
Net change	+3,865,000

	Base		Change from Base	
	Positions	Amount	Positions	Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase costs	---	---	---	$407,000
2. One additional day of pay in 1972	---	---	---	27,000
3. Within grade pay increase.				153,000
4. Noncompeting continuation of research grants	---	---	---	2,499,000
B. Program:				
1. Research grants	---	$118,083,000	---	399,000
2. Laboratory and clinical research	358	9,946,000	11	118,000
3. Collaborative research and development	40	30,483,000	6	500,000
C. Payment to "National Institutes of Health management fund" for centrally-furnished services	---	7,965,000	---	438,000
Total, increases	---	---	17	4,541,000
Decreases:				
A. Program:				
1. Fellowships	---	6,871,000	---	-676,000
Total, net change	---	---	+17	+3,865,000

Explanation of Changes

Built-in increases--The increases will provide: $407,000 for annualization of 1971 pay increase costs; $27,000 for one additional day of pay in 1972; $153,000 for within grade pay increases in 1972; $2,499,000 for changes in the amounts required to fund in 1972 those project grants which were funded in 1971 and are being continued in 1972 as a part of a commitment made prior to 1972.

Research grants--The net increase of $399,000 includes: increases of $701,000 for new initiatives of high priority in research on arteriosclerotic and pulmonary diseases and $3,500,000 for basic and clinical research on Sickle

Explanation of Changes (continued)

Cell Anemia; as well as decreases of $1,618,000 for programs of lesser priority, $1,324,000 for the Heart Cooperative Drug Study, and $860,000 for general research support grants, a program included in each NIH appropriation containing research grant projects, but administered separately by the Division of Research Resources.

Fellowships--The request includes a decrease of $676,000 and an estimated decrease of 84 fellowship awards.

Laboratory and clinical research--The program increase of $118,000 and 11 positions will permit full implementation of the new Pulmonary Function Laboratory and for increased activity in the study of lipidosis and in coronary artery disease in conjunction with the Collaborative Research and Development program.

Collaborative research and development--The net program increase of $500,000 and 6 positions reflects increases of $1,500,000 for research on Sickle Cell disease and $2,000,000 for a detection, prevention, and evlauation program in the fields of respiratory disorders, lipidosis, and coronary artery disease; drug usage in patients with mild hypertension; and for research in blood storage, blood clots, and inherited blood disorders. These increases are partially offset by a $3,000,000 decrease of other Collaborative Research and Development programs of lesser priority.

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1971 House Report	
1. The Committee noted again the rising incidence of lung diseases and suggested that greater emphasis be placed on these disorders in the Institute's research and training programs. (Page 19)	1. The Institute now has on board an Associate Director for Pulmonary Programs who has moved rapidly ahead with scientists and doctors in the community to identify critical pulmonary problems, including those in chronic respiratory ailments such as emphysema. One such known problem is the need for more doctors well-trained to treat lung disease. The Institute is establishing a Pulmonary Academic Award Program in response. In specialized research centers pulmonary research has been identified as one of four targeted areas in which such centers will make an important contribution to many unsolved problems. There is being established a Pulmonary Function Laboratory intramurally for basic investigations and collaborative clinical studies are being initiated. It is estimated that there will be an increase in funding in pulmonary research and training of over $10,000,000 between 1970 and 1972 by this Institute.
2. The Committee again noted that arteriosclerosis represents one of this Institute's major research efforts, yet remains the most critical national health problem. The Committee found it disturbing that funds provided in the budget estimate for this program and related work on coronary artery disease are not even sufficient to maintain the 1970 program level. (Page 19,20)	2. The Congress appropriated substantial additional sums for 1971 and the administration provides continued support in 1972 for arteriosclerosis as a new initiative. A more concerted research effort against arteriosclerosis and its complications is being mounted through specialized research centers and the collaborative studies programs. Mainly through these two mechanisms, an additional $10,000,000 is being funded on arteriosclerosis from 1970 to 1972.

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1971 House Report (Continued)	
3. The Committee noted that there may be a correlation between premature arteriosclerosis and elevated blood lipids and that the Institute will attempt to determine appropriate diet and drug treatment to reduce that risk. (Page 19)	3. While it is expected that the reduction of blood lipid levels will reduce the risk of heart disease, this fact remains to be proven. The Institute is establishing new Lipid Research Clinics in 1971 to investigate this problem.
4. The Report noted that the Committee has for the past six years listened to plans that described the desirability of establishing special cardiovascular research centers. The Committee hoped that the budget request of $7,000,000 increase for this item will enable these centers to begin operation. (Page 20)	4. The appropriation for 1971 included a $16,000,000 increase for specialized centers of research (SCOR). The Institute announced to the community plans for centers in arteriosclerosis, thrombosis, hypertension, and pulmonary diseases. Applications are currently being intensively reviewed, with a final review planned at a special National Advisory Heart and Lung Council meeting in May 1971.
1971 Senate Report	
1. It was clear to the committee that there is an urgent need to train clinicians and investigators in the treatment and prevention of lung disease. To that end the Committee directed that some portion of the 1971 appropriation increase be used to launch a suitable training program. The Committee also recommended that part of this increase be used to accelerate and intensify research on the treatment of acute respiratory disease such as emphysema. (Page 35)	1. See item (1) in the 1971 House Report (above).

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action Taken or to be Taken
1971 Senate Report (Continued)	
2. In reviewing the arteriosclerosis program the Committee noted that the Institute was trying to develop new techniques and instrumentation to measure the severity of arteriosclerotic lesions, and to identify and manage patients susceptible to elevated blood lipids which may cause arteriosclerosis. (Page 35, 36)	2. The Institute through its medical devices applications programs is accelerating research and testing of both circulatory and respiratory assist devices. In the area of lipid metabolism new Lipid Research Clinics are being established. (Also see items (2) and (3) in the 1971 House Report (above).
3. The Committee noted that there has been a substantial decline in the mortality rate from hypertension over the past decade. While drugs are credited for the control of moderate to severe hypertension, little is known of their value to mild hypertension, which is also suspect in its role with coronary artery disease. (Page 36)	3. The Institute has planned a program aimed at preventing heart disease by controlling blood pressure. Hypertension clinical trials are schedueled to commence during 1971.
4. The Committee noted that the need for blood has continued to rise, and in as much as human blood is a limited resource, it is important that it be used as efficiently as possible. To this end the Committee urged increased research for the improvement of transfusion methods, blood storage, and the prevention of blood clots which are a central factor in many cardiovascular diseases. (Page 37)	4. The National Blood Resource Program is very active in these areas. Just completed is a clinical trial on pulmonary embolism using a substance called urokinase, which does dissolve blood clots. The results of this trial have been so promising that a sequential phase is being prepared to compare urokinase with another clot-dissolving product, streptokinase.
5. The Report noted that while there was considerable testimony as to the desirability of establishing cardiovascular research centers, not a single center has been established. The Committee therefore proposes the establishment of such centers. (Page 37)	5. See item (4) of the 1971 House Report (above).

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation requested
Public Health Service Act Section 301--Research and Investigation, in General.....	Indefinite	$195,492,000
Title IV, Part B--National Heart Institute.....	Indefinite	195,492,000

PUBLIC HEALTH SERVICE ACT

Title IV--National Research Institutes, Part B,
National Heart Institute

Section 411. There is hereby established in the Public Health Service a National Heart Institute (hereafter in this part referred to as the "Institute").

Section 412. In carrying out the purposes of section 301 with respect to heart diseases the Surgeon General, through the Institute and in cooperation with the National Advisory Heart Council (hereafter in this part referred to as the "Council"), shall--

(a) conduct, assist, and foster researches, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of heart diseases;

(d) make grants-in-aid to universities, hospitals, laboratories, and other public or private agencies and institutions, and to individuals for such research projects relating to heart diseases as are recommended by the Council... 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... 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....

Explanation of Transfers

Real transfer to:	1971 Estimate	Purpose
Department Management	-$24,000	To establish the Facilities Engineering and Construction Agency.
Real transfer from:		
National Institute of General Medical Sciences	1,446,000	Proposed transfer for increased pay costs.
Comparative transfer to:		
National Institute of General Medical Sciences	-144,000	To provide an equitable distribution of the Management Fund in 1972.
National Institute of Child Health and Human Development	-36,000	id.
Health Manpower	281,000	id.
Health Manpower	-4,051,000	Transfer of institutional support funds to Health Manpower.
Office of the Director	-71,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director
Comparative transfer from:		
National Institute of Arthritis and Metabolic Diseases	78,000	Transfer of regular research grants for the pulmonary research program.
National Institute of Allergy and Infectious Diseases	802,000	id.
National Institute of General Medical Sciences	429,000	id.

National Heart and Lung Institute

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$97,073,000	$105,723,000	$160,100,000	$132,912,000
1963	126,898,000	143,398,000	149,398,000	147,398,000
1964	130,108,000	129,325,000	130,545,000	129,325,000
1965	125,640,000	124,521,000	125,171,000	125,171,000
1966	141,412,000	146,212,000	143,462,000	141,462,000
1967	148,407,000	154,770,000	164,770,000	164,770,000
1968	167,954,000	167,954,000	177,954,000	167,954,000
1969	169,735,000	164,120,000	172,120,000	166,927,500
1970	160,513,000	160,513,000	182,000,000	171,377,500
1971	171,747,000	178,479,000	203,479,000	193,479,000
1972	195,492,000			

Justification

National Heart and Lung Institute

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	590	$9,703,000	607	$10,432,000	+17	+$729,000
Other expenses	--	181,924,000	--	185,060,000	--	+3,136,000
Total	590	191,627,000	607	195,492,000	+17	+3,865,000

General Statement

A start has been made on a coordinated attack upon the many different pulmonary disorders which presently cause so much disability and death throughout the country. An associate director for pulmonary programs has been engaged, who is not only outstanding as a physician and medical researcher in the field of pulmonary disease but who is competent in evaluating the needs and potentials in the field and able to initiate and direct new programs aimed at conquering these diseases. Since a dearth of well qualified teachers was identified as the primary obstacle to improving the care and treatment of patients with lung disease as well as uncovering, through research, new ways of treating and preventing these disorders, a new program entitled the Pulmonary Academic Award Program has been initiated to create improved respiratory disease curriculae, to assure that students will receive superior teaching in respiratory diseases, and to encourage, foster, and support the development of respiratory diseases as a sub-specialty, both in areas of research and in patient care. These awards are to be self-limiting in the sense that within five years of a school's receiving such an award the school is expected to underwrite the program for its own merits. $200,000 has been earmarked for this program in 1971. It is expected that this amount may double in 1972.

In the pulmonary area, as well as in the areas of arteriosclerosis, thrombosis, and hypertension, special grants in aid for specialized centers of research are being established, responses have been obtained and are being reviewed with the best to be funded in 1971. Most of these centers are multidisciplinary in nature which means that the talent of various investigators are brought to bear upon problems in the four disease areas identified above. By means of this new mechanism the best trained and most imaginative investigators in the country will be encouraged to direct their efforts to research endeavors which may be expected to provide new preventive measures or new therapies as well as to prototype ways of taking these research findings to the patients who need them. One of the hallmarks of these specialized centers of research will be close cooperation and interaction between the centers and the Institute staff as well as among the centers themselves. Clearly this will demand that the Institute have on its staff a sufficient number of suitably qualified professionals to interact with the investigators in the four different areas, to help keep the programs "on target".

The collaborative programs of the Institute which are funded through research contracts also require close cooperation between the research institutes and the National Heart and Lung Institute. While not new initiatives as such, the emphasis within the Myocardial Infarction Branch upon the prevention of sudden cardiac deaths and the attention of the Medical Devices Applications Program to Test and Evaluation Centers merit emphasis. The question of sudden cardiac death is a particularly difficult and pressing one. Some of these deaths are undoubtedly due to myocardial infarction, others are due to arrhythmias, and still others have a quite unknown etiology. It is obvious that without an understanding of the etiology prevention is impossible. It is also obvious, since many deaths occur within one hour of the onset of symptoms, if not within a very few minutes of the onset of the symptoms, that prevention is the only possible hope.

The Test and Evaluation Centers, while not a new initiative, are something of a new concept in medical research and therefore have required a good deal of managerial development for their implementation. Two of these are now operational and they bear every indication that this particular method of taking the research to the people, of making sure that all reasonable safeguards have been implemented prior to the mass use of new therapies and new devices, will be highly successful.

The clinical applications program has a number of ongoing studies which are detailed in the body of the justification. Clinical trials are a very necessary activity in the spectrum of research, prevention, and patient care. Inevitably they take a number of years to complete and hence there is rarely a breakthrough to report. There is, however, a new program being started in the ascertainment of the beneficial effects of drug therapy for patients living ordinary lives in the community who have high blood pressure. Several centers are to be involved in this trial. They will follow a common protocol, the results will be pooled, and the knowledge gained will be of very practical value to the many thousands of persons who suffer from high blood pressure. Many of those who suffer from early manifestations of the disease, that is to say, who become disabled in their twenties and thirties, are black and these persons particularly should benefit from this trial.

The National Blood Resource Program has recently initiated plans for cooperative studies in the clinical management of sickle cell disease. This disease is almost totally discriminatory on a racial basis, being confined to the black population. It not only markedly foreshortens the life of the sufferer but it imposes unpredictable, repeated crises of pain for which a definitive therapy has yet to evolve. There are some promising therapeutic leads and these are to be explored in the clinical management studies.

Also requiring close collaboration between the Institute staff, specifically the members of the new Lipid Metabolism Branch, and the scientific community is that portion of the new initiative in arteriosclerosis which will establish lipid clinics to bring to the people the benefits of some of our intramural work establishing five different types of blood fat disorders. Each of these abnormalities, two of which are known to precipitate premature heart disease, requires special diets and sometimes special drugs as well. Through these clinics, with new diet booklets and by prevalence studies, the Institute is working closely with the medical community to see that research which is ready to be used to help prevent heart disease is promptly made available to those who need it most.

Similarly, to develop new knowledge and to establish a basis for taking it to the people, a Respiratory Diseases Branch has been established within the Collaborative program. While this is too new to have made any progress as of this date, much is expected of it, particularly in those disease entities which constitute a significant public health problem.

While the initiatives and new findings are important and exciting, they are only one part of the Institute's overall program. A very real effort is being made to maintain a balance in the research directed toward the various diseases which affect the cardiovascular and pulmonary systems and between the various mechanisms used to encourage, foster, and support these activities.

Extramural Programs

The National Heart and Lung Institute administers cardiovascular and pulmonary research and training grant programs of great scope and diversity. Research projects supported range from epidemiological studies of large human population groups to studies of individual cells and cellular components and the biochemical reactions that occur within them. The diversity of this research is dictated by the complexity of the problems posed by the cardiovascular-pulmonary diseases. For the most part, however, their causes are not known with certainty. In many instances a host of complex factors--genetic, environmental, and physiological--seem to operate in their development and in their protean clinical manifestations. The largest percentage of NHLI funds, a requested $140,768,000 is devoted to this effort.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Research projects.....	$88,772,000	$93,854,000	+$5,082,000
Special programs.....	29,311,000	27,127,000	-2,184,000
Total, research grants.....	118,083,000	120,981,000	+2,898,000

1,515 regular research grants were supported in 1970 for $82,338,356, approximately 1,488 will be supported in 1971 for $88,772,000, and $93,854,000 is requested for 1972 to support 1,440 grants. These include individual projects, large multidepartmental or multidisciplinary program projects, or parts of large scale cooperative studies and clinical trials. The regular program encompasses six major disease areas toward which program activities are directed and which represent organizational alignment: arteriosclerosis; cardiac diseases; hypertension and kidney diseases; pulmonary diseases; thrombosis and hemorrhagic diseases; and grant programs of a special nature, which include artificial heart and transplantation studies. In addition, in Special Programs, we support a prorated portion of General Research Support Grants, the Cooperative Drug Study, and Specialized Research Centers.

Program Plans for 1971 and 1972

Arteriosclerosis

The support of research in arteriosclerosis continues to be the major orientation of the National Heart and Lung Institute. This includes research into the etiology and pathogenesis, prevention, diagnosis, and treatment of arteriosclerosis, coronary artery disease, peripheral vascular disease, cerebrovascular disease, aging, and disorders of connective tissue of vessels.

It may be of interest to refer to some selected areas of research. Progress on many fronts continues to be made on the elucidation of the hereditary, environmental, dietary, endocrine, hemostatic and local intimal factors concerned in the pathogenesis of atherosclerosis. As new knowledge is obtained, new questions arise.

The thesis that dietary fats are in some manner involved in the pathogenesis of atherosclerosis--which was proposed more than two decades ago--is an assumption underlying much research on atherosclerosis today. While the original hypothesis incriminated the level of fat in the diet, this was subsequently changed to include the chemical nature of the fat: solid, staurated fats were believed to be harmful; liquid, polyunsaturated fats beneficial. Implicit in this concept was the well-documented relationship between the amount and type of dietary fat on the one hand and the blood level of cholesterol and other lipids on the other. And, although not susceptible to direct proof in man, there was strong inferential evidence that high blood levels of cholesterol were concerned with the initiation or progression of atheromatous lesions. Although there have been those skeptical of the validity of these assumptions, it is clear that the dietary fat--hypercholesterolemia--atherosclerosis concept remains the major influence in the planning of research projects in this area.

It has recently been demonstrated in the monkey (Rhesus) that fatty plaques of atherosclerosis induced by dietary cholesterol undergo regression and maturation when the animals are placed on low cholesterol, polyunsaturated fat diets. While the regression phenomenon has thus been demonstrated in a subhuman primate, its nature, mechanisms and limitations remain to be elucidated. The finding has very important implications for the reversal of at least some kinds of atherosclerotic lesions in man.

A large institutionalized human population is under study to ascertain if dietary modification can prevent the occurrence of heart attacks. The study, however, has several years to run and will probably have to be increased in size

before a clear answer can be obtained. A study of the effect of several hypocholesteremic drugs is also under test in the Heart Cooperative Drug Study (see Special Programs).

In the area of diagnosis, technical progress has been made with a device which consists of a minute magnet that can be controlled in its passage through the blood vessels, air passages, or intestine. The small, traveling magnet can carry catheters and similar devices into suprisingly small passages and allow special diagnostic measurements to be made from restricted regions of the body. It has been successfully used in the lung and is being developed for use in the cerebral circulation. A second area of diagnostic interest is that of computer recognition and analysis of electrocardiographic data in coronary heart disease. The field is developing a useful degree of sophistication, although practical application is somewhat limited as yet.

In addition to the therapeutic research related to diet and drugs referred to above, the more direct approach of surgical removal or bypass of arteriosclerotic lesions in blood vessels continues to be an active area of research. These techniques, which are successful in the larger blood vessels of the body and legs, continue to be extensively explored in relation to the coronary arteries and the amelioration of coronary heart disease. Technical progress now permits work with vessels with a diameter in the range of 2 millimeters.

The mass of information resulting from projects relating to arteriosclerotic diseases and supported by the NHLI is large. In both fundamental and applied areas, progress toward their prevention and amelioration has been made during the past year.

Cardiac Diseases

This area of research includes cardiac diseases and cardiac arrhythmias, cardiovascular dynamics, heart failure and shock, and congenital and rheumatic heart disease.

Cardiac disease is a rather general category among which studies currently being supported are those dealing with biochemistry and metabolism of heart muscle, electrophysiology of myocardial tissue, effects of anesthetics and trace metals on the heart, and heart sounds and murmurs. In cardiac arrhythmias many of the investigations concern therapeutic approaches, particularly pacemakers and drugs. There is a growing interest in attempting to clarify underlying mechanisms; a number of active grants deal with electrocardiography and vectorcardiography and applications of the computer in this field.

The problems of congestive heart failure and shock are of major clinical importance to the medical community. These are not discrete disease entities but rather symptom-complexes that are the products of severe underlying cardiovascular disease of several etiologies. Circulatory failure may be either acute or chronic in nature. The acute form includes cardiovascular shock, fainting, and often sudden death --due to profound disturbances of heart rhythm and blood pressure. The chronic form of circulatory failure is generally known as congestive heart failure and denotes prolong impairment of the ability of the heart to maintain an adequate flow to the tissues. Most of the Heart and Lung Institute's research grant support in this disease category is concerned with causation. It is not yet known whether heart failure represents a "weakness" of the heart muscle cells or if it is the result of defective energy production or utilization. The answer may be found in intensive studies on the ultrastructure and arrangement of the heart muscle fibers and contractile proteins, or it may lie somewhere in the complex biochemical mechanisms by which the heart generates chemical energy and then harnesses that energy to drive the contractile process.

Despite the many diagnostic and therapeutic advances which have been made in the past 15-20 years, some 35% of babies born with congenital heart disease still succumb to their malformation. A number of these could be saved if they received therapy early enough and the Institute's training programs are attempting to fulfill this need by underwriting the cost of training doctors in the very special techniques which those infants require. However, even when this goal is reached, there will still be a sizeable number of children whose defects are not correctable by surgery and for these understanding of the etiology that prevention may be initiated is the only hope. Accordingly, it is essential that work which is classed as basic research proceeds to uncover the mysteries which now almost completely surround the causes of these malformations.

Hypertension and Kidney Diseases

High blood pressure is the most commonly diagnosed form of cardiovascular disease in the United States. Approximately 22 million adult Americans have hypertension and about 13 million have heart disease as a result of this underlying condition. It is a contributor to the more rapid development of atherosclerosis--a predominant factor in heart attacks, strokes, and diseases of deficient blood supply to other organs.

Great advances in the diagnosis and therapy of hypertension have been made. A wide variety of effective drugs are now being utilized in everyday clinical practice.

Projects in 1971-1972 are devoted to searches for new therapeutic agents, the role of endocrine disturbances in hypertension, more precise chemical and immunologic techniques for the diagnosis of certain types of hypertension, and better understanding of neural factors in the control of blood pressure. Renin-angiotensin mechanisms are under intensive study as are fluid and electrolyte aspects.

Adequate treatment of moderately severe hypertension has been shown to be of striking benefit in terms of mortality and morbidity. Whether the treatment of mild hypertension will result in similar benefits is not known: this is to be the focus of clinical trials to be conducted through the Collaborative R & D activity, 1971-1972.

Pulmonary Diseases

The incidence of respiratory illness, especially chronic obstructive diseases such as emphysema and bronchitis is, unfortunately, increasing in the American population. These diseases are complex and intimately involved with other circulatory and organ systems. Patients usually become chronically sick and debilitated. Specific etiology is obscure in many cases, although environment, heredity, smoking habits, allergy, infection, and metabolic factors are variously involved. Research efforts are diverse and multidisciplinary. The Institute's respiratory disease research program has several foci: chronic obstructive disease, pulmonary vascular disease, lung mechanics and pulmonary physiology.

The Institute's pulmonary research program has centered primarily on chronic lung diseases, pulmonary vascular diseases, pulmonary physiology and, in recent years, lung transplantation.

A good animal model for emphysema studies is needed; those that have been developed to date have a number of shortcomings. One grant recipient is developing a new animal model of experimental emphysema in hamsters.

The study of the role of alpha$_1$ antitrypsin deficiency in the etiology of pulmonary emphysema gives promise of leading to more significant advances in this field than any other approach that has been tried in recent years. As a result of this, an Institute directed program is to be initiated in 1971 through the contract mechanism in Collaborative Research and Development.

Pulmonary embolism is a serious unsolved problem. Some comparative therapeutic studies are underway to evaluate the efficacy of venous interruption as against the use of anticoagulants.

Several lung transplantation studies are underway. Numerous physiological, neurological, surgical and immunological problems need to be solved. Much additional study will be needed in this field before it will be determined if transplantation can become a practical surgical procedure.

These diseases are considered a vital program area requiring increased national attention and greater research and training support. Since this Institute became the National Heart and Lung Institute, it has, as outlined in the General Statement, brought on board an excellently qualified associate director for pulmonary programs, who is activiating new programs responsible for identifying and improving methods of care for respiratory patients, developing specialized pulmonary centers of research, establishing an intramural pulmonary laboratory, and increasing the number of teachers into this field. Within the past year the number of research grant requests coming to the Institute has increased three-fold. Concurrent with this, the Institute's National Advisory Council has been increased by four additional members representative of the lung community. Accumulation of new knowledge about the respiratory system, both in health and disease, is expected to accelerate in the future with the increased interest in, and the special emphasis on this program.

A problem of critical importance is the need for more doctors well-trained to treat lung diseases. Accordingly, we have established a Pulmonary Academic Award Program which will enable young physicians who have already had training in lung diseases to pursue the solution of these problems and to teach others how to deal with patients who suffer from them.

Thrombosis and Hemorrhagic Diseases

This research area constitutes major health problems in this country. If viewed in an isolated fashion, it could well exceed any other group of pathogenetic mechanisms causing or contributing to morbidity in our population. These disease mechanisms are particularly important in the cardiovascular disease area; their estimated prevalence (potentially or actually) related to coronary-myocardial disease in the population at any one time being over 3,000,000 people. It is estimated that thromboembolic disease accounts for 80% of the stroke population, thrombosis being vastly more important than embolism. Thrombosis is also tremendously important in the field of trauma. Venous thrombosis and embolism is one of the most important causes of death in automobile accidents in patients who survive the initial crash. The extent of the overall problem of hemorrhagic diseases has never been accurately estimated.

The Institute has ear-marked $3,500,000 in its grants' programs in 1972 for research on Sickle Cell Disease. In spite of the large amount of refined molecular knowledge about hemoglobin S, the mechanisms which cause and sustain the painful blood vessel occlusive crisis of this disease are little understood and no treatment of proved efficacy is available for crisis. Estimates of the prevalence of sickle cell trait (gene frequency) range from 8 to 13% of the black population of the United States. Sickle cell disease (homozygous S) occurs in approximately one in 400 of the U.S. black population. This represents a total of some 50,000 sickle cell disease patients in the U.S. today, all of whom have shortened life expectancy

and many of whom are plagued by recurrent attacks of painful crisis. Emphasis is now being placed on developing effective treatment methods and preventatives for crisis, on better diagnostic screening methods for both sickle cell disease and trait, and on genetic counseling.

Also in applied research, studies of urokinase, started in 1964 as a basic research project, have culminated in a controlled field trial of pulmonary embolism supported by the National Blood Resource Program. The purpose is to test the efficacy of urokinase in dissolving emboli critically located in the lung vasculature.

Other Programs

The greater part of these programs concern about 30 large multi-categorical program project grants. These are some of the most important programs supported by the NHLI. By virtue of their broad foci on the cardiovascular and pulmonary problems, these programs are not readily identified within the more discrete research areas viewed above.

The transplantation of organs, valves, and vascular segments is practiced widely under a variety of clinical situations. Immunologic rejection remains the most critical factor in this area of clinical application, particularly in the case of heart and lung transplantation. One of the great needs currently is for a more sensitive method of detecting early signs of rejection clinically. Several groups are studying these problems from a basic immunological and physiological approach. Other, larger groups are attacking these problems as part of a continuum of research extending from fundamental studies of prevention to clinical evaluations of transplanted patients, including therapeutic aspects. Solution of the complex picture of cardiac transplantation must be accomplished before this procedure can be expected to realize its potential clinical contribution. Much more effort is required.

Heart Cooperative Drug Study

This study aims primarily to determine whether certain drugs which reduce the concentration of blood lipids are capable of improving survival among patients with overt coronary heart disease. A second objective is to determine whether the degree to which these drugs lower serum lipids is correlated with their effect on mortality and subsequent heart attack rates. Furthermore, the equally intensive study of individuals in the study who do not receive lipid-lowering agents is already providing valuable data on the outlook for men who have recovered from an initial myocardial infarction but are not on lipid-lowering drugs.

The study is underway at 53 participating clinics. Patient recruitment was completed in June of 1969 (over 8,300 patients are enrolled), and the clinical phase of the project will be completed in 1974, by which date all patients will have completed a five-year period of carefully supervised study under one of the described regimens.

Specialized Research Centers

The Institute was provided a substantial amount, over $16,000,000, in 1971 to establish specialized centers of research (SCOR). The Institute has announced to the community its intent to establish a limited number of such centers devoted to the solution of specific, identified, high priority problems in certain disease areas. These four important areas are--arteriosclerosis, hypertension, thrombosis and pulmonary diseases. Applications for these awards are currently under intensive review.

The objective of the establishment of these centers is to focus resources, facilities, and manpower on particular problems and to expedite the development and application of new knowledge essential for improved diagnosis, treatment, and prevention of diseases in these target areas. It is anticipated that these centers will make an important contribution to many of the unsolved problems in these areas.

Changes in 1972

The net increase of $2,898,000 for research grant programs includes a $2,499,000 "built-in" increase for changes in the amounts required to fund in 1972 those project grants which were funded in 1971 and are being continued in 1972 as a part of a commitment made prior to 1972 and program increases of $701,000 for new initiatives of high priority in research on arteriosclerotic and pulmonary diseases and $3,500,000 for basic and clinical research on Sickle Cell disease. There are also reflected decreases of $1,618,000 for programs of lesser priority, $1,324,000 for the Heart Cooperative Drug Study, and $860,000 for general research support grants.

Research Grants Program Analysis
(Based on Estimated Assignment to Program Branches)

	1971 Estimate	1972 Estimate	Increase or Decrease
Arteriosclerosis	$15,358,000	$16,492,000	+$1,134,000
Cardiac diseases	21,039,000	21,126,000	+87,000
Pulmonary diseases	6,036,000	6,373,000	+337,000
Hypertension & kidney diseases	11,985,000	11,867,000	-118,000
Thrombosis & hemorrhagic diseases	12,339,000	15,890,000	+3,551,000
Other cardiovascular and pulmonary programs	22,015,000	22,106,000	+91,000
Subtotal	88,772,000	93,854,000	+5,082,000
General research support grants	8,127,000	7,267,000	-860,000
Scientific evaluation	163,000	163,000	---
Heart cooperative drug study	4,579,000	3,255,000	-1,324,000
Specialized research centers	16,442,000	16,442,000	---
Total, research grants	118,083,000	120,981,000	+2,898,000

Distribution of Research Grants
(Amounts in thousands)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Noncompeting continuations	1,065	$63,935	1,000	$66,434	-65	+$2,499
Competing projects	423	23,192	440	25,775	+17	+2,583
Supplementals	(146)	1,645	(146)	1,645	---	---
Subtotal, regular program	1,488	88,772	1,440	93,854	-48	+5,082
General research support grants		8,127		7,267		-860
Scientific evaluation and planning		163		163		---
Heart cooperative drug study		4,579		3,255		-1,324
Specialized research centers		16,442		16,442		---
Total, research grants		118,083		120,981		+2,898

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Total Fellowships.....	$6,871,000	$6,195,000	-$676,000

Introduction

The primary objective of the fellowship program is to increase the number of scientists qualified to carry on independent cardiovascular and pulmonary research. The fellowship programs are an integral part of the Institute's training effort.

Program Plans in 1971 and 1972

The above objective is carried out through four means: (1) the postdoctoral fellowships are awarded in a wide variety of cardiovascular disciplines to encourage young physicians and scientists to obtain research training and experience so that the country's research potential can be maintained; (2) special fellowships are awarded to more mature individuals, often faculty members, who find it highly productive to spend a year or two in research laboratories other than their own in which they can improve current skills or acquire new ones; (3) the highly successful research career development program supports the younger investigator of demonstrated ability and provides the means whereby the grantee institutions can expand their cardiovascular potential; (4) the research career award provides stable support for the senior investigator.

Funds requested for 1972 will provide for 255 awards, compared to 339 in 1971, a decrease of 84.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Continuations:						
Noncompeting.....	214	$4,973,000	200	$5,031,000	-14	+$58,000
Competing.....	23	508,000	22	546,000	-1	+38,000
Supplementals.....	(15)	30,000	(10)	20,000	(-5)	-10,000
New.....	102	1,360,000	33	598,000	-69	-762,000
Total, fellowships.....	339	6,871,000	255	6,195,000	-84	-676,000

Fellowships (By Type of Program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Postdoctoral.....	64	$537,000	27	$238,000	-37	-$299,000
Special.....	91	1,220,000	45	687,000	-46	-533,000
Research career development.	157	4,291,000	157	4,451,000	0	+160,000
Research career.....	27	823,000	26	819,000	-1	-4,000
Total, fellowships.....	339	6,871,000	255	6,195,000	-84	-676,000

Fellowships Program Analysis

	1971 Estimate Amount	1972 Estimate Amount	Increase or Decrease Amount
Arteriosclerosis.....	$1,320,000	$1,189,000	-$131,000
Cardiac diseases.....	2,459,000	2,218,000	-241,000
Pulmonary diseases.....	1,031,000	929,000	-102,000
Hypertension and kidney diseases.....	948,000	855,000	-93,000
Thrombosis and hemorrhagic diseases..	831,000	750,000	-81,000
Other cardiovascular programs.....	282,000	254,000	-28,000
Total, fellowships.....	6,871,000	6,195,000	-676,000

Training Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Total training grants.....	$13,592,000	$13,592,000	---

Program Plans in 1971 and 1972

During the Institute's 22 years, some 17,000 postdoctoral investigators have been trained in all different facets of cardiovascular and pulmonary diseases. Initially, the emphasis was mainly upon teaching fundamental research; more recently a special emphasis has been put upon the development of physicians oriented toward clinical research. In total some 75% of the trainees have been physicians.

In judging the "success" of a training program, there is a natural and perhaps unavoidable tendency to assess the number of people who actually pass through the program and by the proportion of these who subsequently become renowned investigators. Certainly these are two measures which can be used, but the real hallmark of the success of the training programs is the new knowledge which skilled cardiologists and cardiac surgeons daily apply in the treatment of the cardiac ills of patients throughout the country. This new knowledge and these new skills have been many. But a well-trained investigator and clinician is not the final, completed end-product of the training program. As these men and women practice their skills they enlighten and train those with whom they work, whether or not they are engaged in a formal teaching program. Just as yeast must continually be allowed to regenerate itself, so it is essential to keep replenishing the corps of highly trained cardiovascular and pulmonary physician-researchers that new drugs, new diagnostic and therapeutic tools, new methods of prevention may, like loaves of bread, be available for distribution to those with or at risk of heart disease. Furthermore, by their presence in the scientific and medical community, the well-trained cardiologist, cardiac surgeon, and cardiac researcher help maintain standards of excellence in medical care which the American people have come to, and have a right to, expect.

Distribution of Training Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Continuations:						
Noncompeting.....	315	$10,735,000	314	$11,292,000	-1	+$557,000
Competing.....	42	2,082,000	40	2,000,000	-2	-82,000
Supplementals.....	(17)	150,000	(16)	100,000	(-1)	-50,000
New.....	14	625,000	5	200,000	-9	-425,000
Total, training grants.....	371	13,592,000	359	13,592,000	-12	---

Laboratory and Clinical Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	358	$5,841,000	369	$6,225,000	+11	+$384,000
Other expenses	--	10,520,000	--	10,912,000	--	+392,000
Total	358	16,361,000	369	17,137,000	+11	+776,000

Experience has taught that in studying a complex problem there is danger in directing a total program toward the solution of specific questions because of the danger of having asked the wrong questions. As a corollary, the big discoveries are repeatedly found in unanticipated places. Therefore the Institute has deployed part of its resources to provide the environment to attract and hold the kind of mind that provides such discoveries. Within the framework of seeking fundamental knowledge of disease process, basic studies comprise a significant portion of the Intramural program. Such studies range from study of the subtle biochemical mechanisms controlling the central and autonomic nervous systems to a study of the basic functioning of the primitive cell. The balance and major portion of Intramural Research is directed specifically toward a solution to the various forms of cardiovascular distress. Because of the recognized excellence of its programs, the Institute also attracts many trainees, who, after accelerated and intensive training, return far better equipped for research in the medical and scientific communities.

One hundred hospital beds are at the disposal of the clinical program and support studies involving diagnosis, surgical repair, metabolic investigations related to studies of arteriosclerosis, other circulatory diseases and studies of hypertension. Support is given also by a vigorous out-patient program with approximately 5,000 visits by patients (within the above and related categories) to clinics related to the studies of staff members of five of the intramural branches.

Pulmonary diseases are a matter of growing concern. Relatively little is known about the visceral functions of the lung; how the lung metabolizes the important peptides, amines and other chemicals in the blood and the importance of this to diseases of lung circulation and to emphysema and other mechanical defects. There is an increasing interest in the lung in the Intramural program where a new type of artificial lung has been developed. When fully developed, its use will be particularly applicable to treat hyaline membrane disease which kills approximately 20,000 American infants a year.

The total increase of $776,000 includes a program increase of $118,000 and 11 positions for full implementation of an intramural pulmonary laboratory and for increased activity in the study of lipidosis and in coronary artery disease in conjunction with the Collaborative Research and Development program.

There are also increases of $207,000 for annualization of 1971 pay increase costs, $98,000 for within grade pay increases, $16,000 for one additional day of pay in 1972, and $337,000 for payment to the National Institutes of Health management fund for centrally furnished services.

Collaborative Research and Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	40	$783,000	46	$911,000	+6	+$128,000
Other expenses		29,829,000	--	30,255,000	--	+426,000
Total	40	30,612,000	46	31,166,000	+6	+554,000

This activity was expanded in 1971 and will continue in 1972 to include programs in (1) medical devices applications, (2) myocardial infarction, (3) blood resources, (4) clinical applications, (5) lipid metabolism, and (6) respiratory diseases.

Medical Devices Applications Program

The mandate of what was formerly called the Artificial Heart Program has been broadened to include the development of devices needed to support patients with chronic lung disease and the name of the program has been changed to the Medical Devices Applications Program.

In planning the work needed from research and development groups, the program uses a modified systems development approach rather than the sequential step-by-step approach which is customary in the medical field. As opposed to sequential development, systems development is an approach whereby all sub-systems are considered concurrently and their design, development, testing and assemblage into complete, workable systems is achieved by the coordinated and directed efforts of various individuals and institutions, each concentrating on specific problems lying within a particular area of expertise. By thus bringing together the biomedical skills in medical schools and hospitals and the talents of university physical and engineering scientists, the chemical industry, engineering and actuarial firms,and other groups from private industry--and coordinating the efforts of these participants--the program expects to produce the most reliable and beneficial types of circulatory assist and cardiac replacement systems, as well as respiratory assist devices including oxygenators, at minimal cost in time and money.

In 1971 directed and goal-oriented research and development has been continued under contract in the following areas: development of circulatory assist devices, physiologic effects of devices in animals, development and evaluation of materials for use in circulatory assist devices, effects of additional endogenous heat, cardiac control parameters, blood flow studies, development and testing oxygenators, instrumentation, biological fuel cells, and energy systems.

There are now a number of new materials developed for artificial organs which seem to work well when made up into these devices and possess that most critical property, not causing damage to the blood. The next hurdle to be met with these materials is to determine how well they stand up under use and how well the body responds after having had them implanted.

Another important program development has been the establishment of two test and evaluation facilities to ensure that materials, components, and devices developed by the program are adequately and systematically tested before they are considered for clinical use. The central purpose of the test and evaluation effort is to assure both the scientific community and the Government that the product is safe, effective, and reliable. This will also provide physicians with the basic information they need about the device and its application. By thus accelerating acceptance of a device or system, adequate testing and evaluation will speed the results of research to the patient and shield him from the hazards of inadequately tested modes of therapy.

Myocardial Infarction

The Myocardial Infarction Branch has the responsibility for the design and administration of a national research program leading to the reduction of death and disability from heart attack. The program is fostering the development of new knowledge and the translation of results into methods which will have wide clinical application.

To achieve these goals, the program has sought to focus the attention of the scientific community upon heart attack, and it has attracted new people and new disciplines to work upon the problem. Broad multi-disciplinary research programs have been established, as well as projects of limited scope and short-term goals. Special resources to facilitate research upon heart attack are being developed. Cooperation and communication have been fostered among participants. Effective techniques for targeting and structuring research are evolving.

To study the acute illness in the hospitalized patient, nine Myocardial Infarction Research Units are now active. Each has a multi-disciplinary program emphasizing clinical investigation, supported by more fundamental studies. They are designed to answer specific questions about the disease process and its therapy; at the same time, they are to nurture creative research upon the problem of heart attack. The basic measurements and historical information which characterize the patients coming into the studies and during the investigations have been standardized; however, the specific research projects of each MIRU are varied since they are designed to capitalize upon the unique resources and interests at each institution and thus provide a broad and balanced total program.

These units are continuing to provide new knowledge as to how best to care for patients who arrive at a hospital having had a heart attack. New methods have been developed for determining the size of the infarct, new ways of measuring changes in the patient's blood pressure, his cardiac output and the amount of oxygen carried in his blood, as well as new methods of determining how well the patient is responding to treatment.

Sudden death within minutes of the onset of symptoms accounts for a very substantial fraction of the deaths from heart attack; indeed, more than half of the deaths occur before hospitalization. A number of programs are being supported which directly concern those patients who do not live long enough to get to a hospital to have their heart attack cared for.

National Blood Resource Program

This program was established in response to a critical problem relative to the national supply of transfusion blood and blood components. Specifically, a rapid acquisition of scientific information regarding fractionation techniques resulted in an increasing identification of the cellular and protein components of blood as therapeutically useful. However, there was at that time and there remains today a serious technological lag which prevents the large-scale application of this knowledge. The problem is made more acute because requirements for blood have increased significantly during the past few years and will continue to rise. As human blood is a limited resource, it is most important that it be used as efficiently and effectively as possible. The program is working actively on the improvement of transfusion methods, on blood storage and preservation, and on ways of breaking blood up into its component parts so that patients who do not need whole blood but who need only one fraction can receive only the required fraction, leaving the rest for other patients who need other fractions.

There has been an acceleration of research on the prevention of blood clots which are a central factor in many cardiovascular diseases, as well as in lung diseases. The program has just completed a clinical trial in pulmonary embolism

using a substance called urokinase, which dissolves blood clots. The results of this trial have been so promising, that a sequential phase is being prepared to compare urokinase, which is a product isolated from human urine, with another clot-dissolving drug streptokinase, which is made from a particular species of bacteria. Streptokinase is much easier to manufacture and hence, would be much less expensive. Attempts are also being made to reduce the cost of urokinase.

The National Blood Resource Program has also contributed to the multifaceted attack on the problem of hepatitis, a serious liver disease, which can be acquired from blood transfusions. New tests are being refined which will detect the presence of hepatitis virus in blood so that contaminated blood will not be used for transfusions.

One particular group of individuals who often need large numbers of transfusions of whole blood are patients with sickle cell disease. This disease is limited to black people and may affect as many as 1,000 babies born each year. A number of new leads for treating these patients have recently emerged. The National Blood Resource Program plans to initiate tightly controlled and experimentally and statistically well designed clinical investigations to determine which of these is best.

Clinical Applications

Hypertension, by itself, constitutes a major health problem. However, it also appears to enhance the risk in coronary heart disease. Thus, control and prevention of hypertension offers another potential path for the prevention of coronary heart disease. Studies conducted in Veterans Administration hospitals have provided strong indications that under the particular conditions of the VA study, blood pressure can be controlled and the complications of high blood pressure prevented. Proof that controlling blood pressure will reduce heart attacks has yet to be established as has the feasibility and the efficacy of giving the drugs to patients who are living in different parts of the country, working at many different types of jobs, being of different ages, and, perhaps most importantly of all, not being under the strict management of a controlled clinical trial as was the case in the VA study. The Institute plans to continue clinical trials in hypertension in 1971-1972.

Lipid Metabolism

Within the purview of the new Lipid Metabolism Branch, lipid research clinics will be established throughout the country to develop the most practical means of mass ascertainment of the patients with lipid disorders that presage heart attacks while attempting to determine just how many people there are at such risk in the country.

Respiratory Diseases

A study will be initiated in 1971 to determine how many people there are in the community who have a genetic predisposition to lung disease by virtue of the fact that they lack a particular enzyme called alpha$_1$ antitrypsin. It is known that patients who inherited this abnormality from both parents have more lung disease than other people in the community but it has not been yet determined how many people there are who inherited it from only one parent, and why only some of them have lung disease. It appears that certain factors in the environment, particularly certain kinds of work, may be especially harmful for these individuals.

Changes in 1972

The net increase of $554,000 and 6 positions reflects increases of $1,500,000 for research on sickle cell disease and $2,000,000 for a detection, prevention, and evaluation program in the fields of lipidosis, coronary artery and pulmonary disorders; drug usage in patients with mild hypertension; and for research in blood disorders and blood clotting. These increases are partially offset by a $3,000,000 decrease of other Collaborative Research and Development programs of lesser priority.

There are also increases of $38,000 for annualization of 1971 pay increase costs, $9,000 for with-in grade pay increases, $2,000 for one additional day of pay in 1972, and $5,000 for payment to the National Institutes of Health management fund for centrally furnished services.

Biometry, Epidemiology, and Field Studies

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	64	$1,081,000	64	$1,126,000	--	+$45,000
Other expenses	--	909,000	--	922,000	--	+13,000
Total	64	1,990,000	64	2,048,000	--	+58,000

This activity undertakes research into the etiological factors relating to cardiovascular disease in general population groups and evaluates the therapeutic effectiveness of new drugs, products, or measures which may have promise for the prevention or treatment of cardiovascular disease. A very important responsibility is for conducting or cooperating in clinical trials or controlled therapeutic evaluations of new agents or measures for the prevention or treatment of cardiovascular disease. These studies are funded by both grant and contract mechanisms, so that full range of program capability is available. This activity consists of three branches: Therapeutic Evaluations, Epidemiology, and Biometrics Research.

The Institute's responsibilities for liaison and monitoring of the Coronary Drug Project and other grant-supported cooperative clinical trials are implemented by the Therapeutic Evaluations Branch. Further knowledge of risk factors as well as of protective factors in coronary disease are being gained from population studies conducted by the Epidemiology Branch.

The increase of $58,000 includes $27,000 for annualization of 1971 pay increase costs, $15,000 for within-grade pay increases, $3,000 for one additional day of pay in 1972, and $13,000 for payment to the National Institutes of Health management fund for centrally furnished services.

Review and Approval of Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	72	$1,010,000	72	$1,149,000	--	+$139,000
Other expenses	--	1,659,000		1,737,000	--	+78,000
Total	72	2,669,000	72	2,886,000	--	+217,000

This activity provides professional direction for the scientific review and administration of most grant supported cardiovascular and pulmonary research and training programs, including the necessary operational and technical support activities and scientific and financial analysis of such programs.

The increase of $217,000 includes $112,000 for annualization of 1971 pay increase costs, $23,000 for within-grade pay increases, $4,000 for one additional day of pay in 1972, and $78,000 for payment to the National Institutes of Health management fund for centrally furnished services.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	56	$988,000	56	$1,021,000	--	+$33,000
Other expenses	--	461,000	--	466,000	--	+5,000
Total	56	1,449,000	56	1,487,000	--	+38,000

This activity provides support for the Institute Director and his immediate staff, the Office of Administrative Mangement, the Office of Program Planning and Evaluation, and the Office of Heart and Lung Information. Funds support the over-all administration, coordination, and direction of the varied programs and activities of the Institute. The Director and his 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.

The increase of $38,000 includes $23,000 for annualization of 1971 pay increase costs, $8,000 for within-grade pay increases, $2,000 for one additional day of pay in 1972, and $5,000 for payment to the National Institutes of Health management fund for centrally furnished services.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Research Grants. (Public Health Service Act, Section 301, Title IV, Part B)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$118,083,000	Indefinite	--	$120,981,000

Purpose: This activity funds project grants to assist public and other non-profit research institutions to establish, expand, and improve research activities related to diseases of the cardiovascular and pulmonary systems.

Explanation: Research projects supported range from epidemiological studies of large human population groups to studies of individual cells and cellular components and the biochemical reactions that occur within them. The diversity of this research is dictated by the complexity of the problems posed by the cardiovascular-pulmonary diseases.

Accomplishments in 1971: In 1971 an estimated 1,488 regular research grants will be awarded to increase scientific knowledge and find more effective means of prevention, diagnosis, and treatment in such areas as arteriosclerosis, cardiac diseases, pulmonary diseases, hypertension and kidney diseases, and thrombosis and hemorrhagic diseases.

Objectives for 1972: Recent in-depth surveys of where the Nation stands now in its cardiovascular research accomplishments show the time is ripe to reap the benefits of research accomplishments engendered over the past 20 years, particularly in the field of arteriosclerosis and the diseases it causes. In 1971-1972 increases of $16,000,000 have been provided for the operation of specialized centers of research in arteriosclerosis, thrombosis, hypertension, and pulmonary diseases. It is anticipated that these centers will make an important contribution to many of the unsolved problems in arteriosclerosis and related diseases. An estimated 1,440 research grants will be supported in 1972.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Fellowships. (Public Health Service Act, Section 301, Title IV, Part B)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$6,871,000	Indefinite	--	$6,195,000

Purpose: This program supports advanced research training of qualified scholars for research and academic careers in the basic and clinical sciences related to the cardiovascular and pulmonary areas; and thereby increases the number of trained research investigators and teachers in these fields.

Explanation: The program sponsors advanced research training for individuals whose career development extends from the immediate post-doctoral period through the advanced stages of research attainment. Fellowship awards are made directly to individuals, not to institutions, and consist of stipends, dependency allowance, tuition and fees, and travel costs.

Accomplishments in 1971: An estimated 339 fellowships will be awarded (64 post-doctoral, 91 special, 157 research career development, 27 research career). The Institute recently undertook a follow-up study of 12,000 individuals who have received research training support through fellowships and graduate training grant programs. A preliminary evaluation of the accumulating data reveals that the majority of individuals supported are now in academic positions. A significant number have competed successfully for their own research grant support and are directors of their own research training programs.

Objectives for 1972: Under the reduced budget an estimated 255 fellows will be supported. A continuing priority will be improving the research capability of investigators in arteriosclerosis and cardiac diseases, and other cardiovascular and pulmonary areas.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Training Grants. (Public Health Service Act, Section 301, Title IV, Part B)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$13,592,000	Indefinite	--	$13,592,000

Purpose: Training grants provide support for the establishment, improvement, or expansion of training programs to prepare scientists for research and academic careers in the cardiovascular and pulmonary fields.

Explanation: Graduate training grants are intended to suppport the direct costs of a formalized training program (including stipendiary support to named post-baccalaureate trainees), plus indirect costs, currently limited to 8% of direct costs.

Accomplishments in 1971: During the Institute's 22 years, some 17,000 post-doctoral investigators have been trained in all different facets of cardiovascular and pulmonary disease. Initially, the emphasis was mainly upon teaching fundamental research; more recently a special emphasis has been put upon the development of clinically oriented physicians. In total some 75% of the trainees have been physicians. In 1971 some 1,020 trainees will be supported through 371 grants.

Objectives for 1972: In 1972 an estimated 972 trainees will be supported through the graduate research and clinical training programs.

62-645 O - 71 - pt. 3 - 29

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Laboracory and Clinical Research. (Public Health Service Act, Section 301, Title IV, Part B)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
358	$16,361,000	Indefinite	369	$17,137,000

Purpose: This is a directed research program within the facilities of the NIH at Bethesda. Within the framework of seeking fundamental knowledge of disease process, basic studies comprise a significant portion of the program. Such studies range from study of the subtle biochemical mechanisms controlling the central and autonomic nervous systems to a study of the basic functioning of the primitive cell. The balance and major portion of research is directed specifically toward a solution to the various forms of cardiovascular distress. Because of the recognized excellence of its programs, the Institute also attracts many trainees, who, after accelerated and intensive training, return far better equipped for service in the medical and scientific communities.

Explanation: The Institute has 358 positions for this activity, of which about half are for scientists and physicians and the remainder for technical personnel. Basic and clinical research is carried on in 13 major laboratories and branches. One hundred hospital beds are at the disposal of the clinical program. Support is given also to a vigorous out-patient program with approximately 5,000 patient visits annually.

Accomplishments in 1971: The findings of intramural scientists have exerted profound effects in major areas of cardiovascular research. Current efforts include the study of blood lipids directed toward an understanding and control of arteriosclerosis; continuing efforts in the use of enzyme inhibitors and drugs in the treatment of hypertension; continuing contributions to the understanding of nerve and hormonal factors in heart performance, and the mechanisms by which the autonomic nervous system and various cardiac stimulants provide support to a failing circulation; developing important new techniques for the detection and clinical evaluation of various types of congenital and acquired heart disease (an enviable record of success has been compiled in the surgical treatment of these disorders); and continuing definition of the complex processes involved in the synthesis, transport, and metabolism of cholesterol and other fats.

Objectives for 1972: A continuing priority will be maintained in the excellence of the research projects described above. There is requested a program increase of 11 positions and $118,000 for full implementation of an intramural pulmonary laboratory and for increased activity in the study of lipidosis and in coronary artery disease in conjunction with the Collaborative Research and Development program.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Collaborative Research and Development. (Public Health Service Act, Section 301, Title IV, Part B)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
40	$30,612,000	Indefinite	46	$31,166,000

Purpose: This activity supports research and development in (1) medical devices applications, (2) myocardial infarction, (3) blood resources, (4) clinical applications, (5) lipid metabolism, and (6) respiratory diseases.

Explanation: These projects are supported through contracts performed in collaboration with other Federal agencies, university and medical school research centers and industrial research organizations. All funds are used to support scientific research into the causes, prevention, diagnosis and treatment of cardiovascular and lung diseases.

Accomplishments in 1971: Mecical devices applications broadened to include the development of devices needed to support patients with chronic lung disease, specifically in oxygenator fabrication, new and improved oxygenators, and analysis of respiratory assist program. New programs initiated in myocardial infarction include interventions to minimize infarct size and enhance repair, methods of quantifying infarct size in the clinical setting, and programs on sudden cardiac death and the onset of myocardial infarction. The blood program will expand or initiate work in the study of blood banking and hematherapy, in the identification and control of hepatitis, for MI and platelet antiaggregating agents in thrombosis, in hereditory blood disorders, in urokinase production, and in white cell transfusions. There will be a major hypertension clinical trial initiated in clinical applications, as well as lipid research clinics. The respiratory disease area will initiate a study of alpha$_1$ antitrypsin deficiency.

Objectives for 1972: The new programs initiated in 1971 and itemized above will be continued as need and new programs begun in sickle cell disease and new iniatives in arteriosclerosis.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Biometry, Epidemiology, and Field Studies. (Public Health Service Act, Section 301, Title IV, Part B)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
64	$1,990,000	Indefinite	64	$2,048,000

Purpose: This activity undertakes research into the etiological factors relating to cardiovascular disease in general population groups and evaluates the therapeutic effectiveness of new drugs, products, or measures which may have promise for the prevention or treatment of cardiovascular disease.

Explanation: This research is conducted partly by in-house staff scientists (and includes a biometrical group) and partly through contract to other research organizations. Organizationally, it now has responsibility for liaison and monitoring of the Heart Cooperative Drug Study and other grant-supported cooperative clinical trials.

Accomplishments in 1971: This activity will continue research as described under "Purpose".

Objectives for 1972: The high level of research will be maintained. Additional emphasis will be focused on clinical trials or controlled therapeutic evaluations of new agents or measures for the prevention or treatment of cardiovascular disease.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Review and Approval of Grants. (Public Health Service Act, Section 301, Title IV, Part B)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
72	$2,669,000	Indefinite	72	$2,886,000

Purpose: This activity provides professional direction for the scientific review and administration of most grant-supported cardiovascular and pulmonary research and training programs, including the necessary operational and technical support activities and scientific and financial analysis of such programs.

Explanation: Funds are made available to the Associate Director for Extramural Programs to provide scientific and administrative direction of grant programs. This includes scientific evaluation, administrative grants' management, and grants' processing activities.

Accomplishments in 1971: This activity handles the processing of all NHLI grants following the primary review process. In addition, it provides important aspects of program stimulation and formulation. If we can view this activity as "overhead", its funds were about 2% of the entire grant program. The staff of this activity reviewed some 1,500 new and competing renewal research grant, training grant, and fellowship applications for scientific merit and program relevance and maintained surveillance over some 2,250 research and training projects which are to be funded in 1971.

Objectives for 1972: The activities of 1971 will be continued.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Program Direction. (Public Health Service Act, Section 301, Title IV, Part B)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
56	$1,449,000	Indefinite	56	$1,487,000

Purpose: This activity provides support for the Institute Director and his immediate staff, the Office of Administrative Management, the Office of Program Planning and Evaluation, and the Office of Heart and Lung Information.

Explanation: Funds support 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.

Accomplishments in 1971: This year is seeing a greatly accelerated research program throughout the Institute on lung diseases. Within the Office of the Director there has been recruited an Associate Director for Pulmonary Programs who has moved ahead rapidly with scientists and doctors in the community to identify critical problems in this area.

Objectives for 1972: Continued leadership will be provided for: the establishment of the new specialized centers of research; the varied range of research endeavor in the pulmonary field, including the new Pulmonary Academic Award Program to help provide the need for more doctors well-trained to treat lung disease; a coordinated effort for therapy in sickle cell disease; new programs in clinical applications in lipid metabolism and in hypertension; as well as the continuing cross section of quality research and training supported by the Institute.

New Positions Requested

Fiscal Year 1972

	Grade	Number	Annual Salary
LABORATORY AND CLINICAL RESEARCH			
Scientist	Full	3	$34,668
Scientist	GS-15	1	24,411
Scientist	GS-14	1	22,918
Scientist	GS-12	1	18,449
Scientist	GS-9	1	11,526
Scientist	GS-7	2	20,516
Clerical assistant	GS-6	1	7,294
Animal caretaker	WB-3	1	5,212
		11	144,994
COLLABORATIVE RESEARCH AND DEVELOPMENT			
Scientist	GS-15	1	24,411
Scientist	GS-13	2	42,464
Public health program specialist	GS-12	2	28,384
Scientist	GS-7	1	10,282
		6	105,541
Total new positions, all activities		17	250,535

WEDNESDAY, MAY 5, 1971.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. SEYMOUR J. KRESHOVER, DIRECTOR
DR. ROBERT Q. MARSTON, 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
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
GERALD F. MEYER, CHIEF, HEALTH BRANCH, DIVISION OF BUDGET

Object Classification (in thousands of dollars)

Identification code 09-30-0873-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	3,693	4,082	4,508
11.3	Positions other than permanent	124	129	129
11.5	Other personnel compensation	37	52	52
	Total personnel compensation	3,854	4,263	4,689
12.1	Personnel benefits: Civilian employees	408	494	529
21.0	Travel and transportation of persons	152	178	233
22.0	Transportation of things	28	46	54
23.0	Rent, communications, and utilities	121	120	156
24.0	Printing and reproduction	34	67	76
25.0	Other services	2,413	6,778	7,253
26.0	Supplies and materials	347	540	568
31.0	Equipment	110	216	307
41.0	Grants, subsidies, and contributions	21,251	22,932	24,538
42.0	Insurance claims and indemnities	1	---	---
	Subtotal	28,719	35,634	38,403
95.0	Quarters and subsistence charges	−3	−3	−3
99.0	Total obligations	28,716	35,631	38,400

Personnel Summary

	1970 actual	1971 est.	1972 est.
Total number of permanent positions	290	304	312
Full-time equivalent of other positions	16	16	16
Average number of all employees	300	310	319
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0873-0-1-651	1970 actual	1971 est.	1972 est.
Program by activities:			
1. Grants:			
(a) Research	15,401	16,125	18,886
(b) Fellowships	1,614	1,601	1,367
(c) Training	5,355	5,206	4,285
Total grants	22,370	22,932	24,538
2. Direct operations:			
(a) Laboratory and clinical research	5,034	6,095	6,265
(b) Collaborative research and development	1,057	4,353	5,384
(c) Biometry, epidemiology, and field studies	472	700	909
(d) Review and approval of grants	738	766	861
(e) Program direction	367	396	443
Total direct operations	7,668	12,310	13,862

Program and Financing (in thousands of dollars)—**Continued**

Identification code 09-30-0873-0-1-651		1970 actual	1971 est.	1972 est.
	Total program costs, funded [1]	30,038	35,242	38,400
	Change in selected resources [2]	−1,322	----------	----------
10	Total obligations	28,716	35,242	38,400
	Financing:			
25	Unobligated balance lapsing	28	389	----------
	Budget authority	**28,744**	**35,631**	**38,400**
	Budget authority:			
40	Appropriation	30,644	35,257	38,400
40	Portion withdrawn (Public Law 91-204, sec. 410)	−2,054	----------	----------
40	Pay increase (Public Law 91-305)	164	----------	----------
41	Transferred to other accounts	−11	−10	----------
43	**Appropriation (adjusted)**	**28,744**	**35,247**	**38,400**
46.10	**Proposed transfer for wage-board increases**	----------	**17**	----------
46.20	**Proposed transfer for civilian pay act increases**	----------	**281**	----------
46.30	**Proposed transfer for military pay act increases**	----------	**86**	----------
	Relation of obligations to outlays:			
71	Obligations incurred, net	28,716	35,242	38,400
72	Obligated balance, start of year	19,442	19,986	22,534
74	Obligated balance, end of year	−19,986	−22,534	−24,383
77	Adjustments in expired accounts	−759	----------	----------
90	Outlays, excluding pay increase supplemental	27,413	32,329	36,532
91.10	Outlays from wage board supplemental	----------	16	1
91.20	Outlays from civilian pay act supplemental	----------	263	18
91.30	Outlays from military pay act supplemental	----------	86	----------

[1] Includes capital outlay as follows: 1970, $126 thousand; 1971, $216 thousand; 1972, $307 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $9,394 thousand; 1970, $8,072 thousand; 1971, $10,000 thousand; 1972, $10,000 thousand.

NOTES

Excludes $32 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	*1971*
Office of the Director	29	31
National Eye Institute	88	81
National Library of Medicine	--	112

Includes $282 thousand in 1971 and $282 thousand in 1972 for activities previously financed from: Research resources, 1970, $281 thousand.

Includes $401 thousand in 1972 for activities previously furnished from Health manpower (in thousands): Health manpower, 1970, $401 thousand; 1971, $401 thousand.

Excludes $985 thousand in 1972 for activities transferred to: Health manpower, 1970, $985 thousand; 1971, $985 thousand.

INTRODUCTION OF DR. KRESHOVER AND ASSOCIATES

Mr. NATCHER. The committee will come to order.

We take up at this time the National Institute of Dental Research of the National Institutes of Health. We have before the committee Dr. Seymour J. Kreshover, the Director, and you have with you a number of your associates.

Will you identify them at this time?

Dr. KRESHOVER. On my immediate left is Mr. Christoferson, executive officer, and to his left is Mrs. Pettinato who is our budget officer.

DR. KRESHOVER'S OPENING STATEMENT

Mr. NATCHER. We are delighted to have you again before the committee. You have with your statement, Doctor, a biographical sketch which will be incorporated in the record at this point and we will be pleased to hear from you.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH OF DR. SEYMOUR J. KRESHOVER

Position:
Assistant Surgeon General.
Director, National Institute of Dental Research, NIH.
Date and place of birth: June 22, 1912, New York, N.Y.
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.
Professional and work experience:
1938–39—University fellow, University of Illinois Graduate School.
1942–43—Assistant in oral surgery, Yale University School of Medicine.
1942–46—Military service, U.S. Army.
1946–48—Teaching fellow in histoanatomy, New York University.
1949–56—Professor of oral pathology, director of dental research, director of graduate and postgraduate studies, the Medical College of Virginia, Richmond.
1956–60—Associate trustee, board of medical education and research, University of Pennsylvania.
1956–66—Scientific Director, National Institute of Dental Research, NIH.
1966– —Director, National Institute of Dental Research, NIH.
Association memberships:
American Dental Association.
American Medical Association.
American Association for the Advancement of Science (fellow).
American Public Health Association (fellow).
Diplomate, American Board of Oral Medicine.
1961–67—Chairman, Commission on Dental Research, Federation Dentaire Internationale.
1962—President, International Association for Dental Research.
1963–66—Secretary, Section Nd (Dentistry), AAAS.
1968—Regent, American College of Dentists.
Honors, awards:
1961—D. Sc. (honorary), University of Buffalo.
1965—Public Health Service Meritorius Service Medal.
1967—D. Sc. (honorary), University of Pennsylvania.
1969—D. Sc. (honorary), Boston University.
Author of some 50 publications.

GENERAL STATEMENT

Dr. KRESHOVER. Mr. Chairman and members of the committee, it is a privilege to testify before you today on behalf of the National Institute of Dental Research.

As you may recall, the recent White House Conference on Children and Youth identified health as one of its overriding concerns. From various past surveys we know that dental diseases are especially pervasive in children. It is particularly gratifying to report that a great part of the work of the National Institute of Dental Research is devoted to these afflictions, many of which continue into, and plague, the adult years.

THE DENTAL INSTITUTE'S GOALS

The Dental Institute conducts and supports a broad range of laboratory, clinical, field, and epidemiologic studies directed toward improved therapy, control, and ultimate prevention of oral problems through application of advancing and new knowledge. Prevention is of crucial importance in dentistry because, unlike medicine's brilliant successes with cures, oral health problems are largely irreversible. Major program activities are concerned with dental caries, or tooth decay; periodontal (gum) disease; problems of growth and development, especially cleft lip and palate and malocclusion; and a variety of oral lesions affecting the tongue, cheeks, and lips.

The magnitude and impact of the major oral-facial diseases and disorders, as well as the current state of the art and the potential for significantly advancing knowledge in the next 5 years, have been described in the report, "Oral Disease: Target for the 70's," which I was privileged to provide at the request of this committee. I should like to allude briefly to these areas in terms of recent accomplishments and where we stand today.

POTENTIAL BREAKTHROUGHS AGAINST TOOTH DECAY

The area of knowledge where we stand closest to the point of application is in tooth decay or dental caries. The inclusion of an increment of $5 million in the NIDR budget for fiscal year 1971 for a targeted, concerted effort has enabled us to launch in deed as well as in spirit the national caries program.

In addition to work conducted by NIDR and grant-supported scientists, we have initiated a number of collaborative projects to pursue promising leads. Unlike most diseases of infectious origin, where there is only a single causative agent, caries is a very complex disease depending for its initiation and progression on three factors operating at one and the same time. These, you will recall, are susceptible teeth; a diet rich in refined carbohydrates, particularly sucrose—table sugar—and specific caries-inducing bacteria. It is unlikely, therefore, that there will ever be one solution to the problem of tooth decay. For this reason, we must seek approaches that will depress to a minimum the three interacting factors that cause the disease.

On the basis of what we have learned about caries to date, we have reason to believe that an accelerated research effort over this decade

will pay off in new agents and methods to make this universal affliction almost completely preventable. The solutions we seek will hopefully be less demanding of scarce professional manpower, and well within the capabilities of auxiliary personnel to administer, as well as more practical for the individual patient to follow.

One research pathway that we plan to follow intensively is the study of agents that will alter the metabolic byproducts or inhibit the growth of caries-inducing bacteria incorporated in plaque deposits. Since such bacterial film seems to be a vital link in dental infections, it is promising to note in preliminary research findings that enzymes may help in dispersing or inhibiting the production of plaque.

Another approach focuses on bactericidal agents to keep the population of caries-inducing organisms within threshold limits. For example, recent animal studies have shown that the antibiotic Vancomycin, applied to the teeth, can eliminate a highly cariogenic bacterium—streptococcus mutans—which had been inoculated previously. Significantly, this effect, in turn, caused a marked reduction in plaque accumulation and appreciably less caries. In test tube studies, other antibacterial agents, including Chlorhexidine, proved equally effective in combating the suspected microorganisms.

The decay-inhibiting effect of phosphates, when added to caries-inducing foods, has also been assessed in animal experiments. These studies continue promising.

NIDR scientists are also examining whether a high level of fluoride can be built up in the tooth enamel in a relatively short period of time through intensive local applications; and, if so, whether such levels provide a significant and lasting degree of protection against decay.

Illustrative of a different approach, data collected by a grantee in Colombia, South America over the past 4 years suggest that table salt may be a useful vehicle for providing fluoride to populations when public water supplies are not available.

The most conspicuous research progress made recently, however, involves an adhesive sealant. A 2-year study, in which the grinding surfaces of children's teeth have been painted with a clear plastic, has shown an outstanding degree of protection against decay in their vulnerable pits and fissures.

Should current large-scale clinical studies, with hundreds of human subjects, prove equally successful, a most valuable prophylactic measure will be available for widespread public health application.

Further research accomplishments in the field of caries are outlined in the research highlights, which also encompass other areas of study.

In 1972, we plan to spend $9,100,000 for caries, an increase of $2,900,000 over the 1971 operating level.

RESEARCH ON IMPROVED ORAL RESTORATIONS

Research leading to improved restorations will also be strengthened as a result of the increased funding for caries. Since the specialized tissues of the mouth cannot replace themselves when they are lost, repairing the damage from dental diseases today depends upon the effective use of available synthetic materials. At present, the most

widely used product—believed to account for 80 percent of all fillings—is amalgam, made chiefly of silver, tin, and mercury. A logical research emphasis, therefore, is to try to lengthen the lifespan of amalgam fillings by altering the alloy's structure and composition.

At the same time the search for new materials and techniques continues. A new binder developed recently holds great promise for improving the physical properties of composite materials, particularly for front teeth, where esthetic requirements are greater. Another highly significant advance of the past year is the development of a coupling agent which bonds the entire composite filling to the tooth enamel or dentin. Clinical trials are now underway to verify its effectiveness.

Another major target in the restorative area is to develop biologically acceptable implants to directly replace lost teeth. Continuing studies in subhuman primates have shown that single tooth implants made of a plastic can be maintained for as long as 9 years. Recent research suggests that greater stability of the implant in the jaw may be achieved by making the roots of the plastic tooth porous. Ceramic implants are now also under study.

PERIODONTAL DISEASE RESEARCH

Periodontal disease is an insidious disease because, without warning, it undermines the gums and other tooth-supporting tissues, eventually causing sound teeth to loosen and fall out. As the main cause of tooth loss after age 35, it represents a major health problem.

Since there is more than one kind of periodontal disease, the term is used in a collective sense. The most common form is characterized in its onset by a reddening and swelling of normally pink gums. While reversible at this point, the inflammation progresses if ignored. Current studies suggest that some of the inflammation which leads to tissue damage may be an allergic response to bacterial products. The organisms themselves do not appear to penetrate into gingival tissue to any substantial degree. Experimental studies have shown, however, that the enzymes, toxins, and metabolic products released by the bacteria are capable of injuring both the surface lining and deeper tissues of the gums. Products of certain bacteria isolated from plaque deposits on the teeth are particularly suspect.

Plaque, too, is a collective term, for different organisms form different kinds of plaque. As this area of study unfolds, we hope to gain new insights into the different types of plaque-forming organisms, their mode of action, pathogenic effects, and methods of control. One of our targets is the development of a realistic preventive measure which would inhibit or repeatedly interfere with microbial colonization on the teeth and gingival tissues, without making unreasonable demands on the individual.

An important facet of research relates to factors responsible for formation and loss of bone. In another approach, Institute-supported scientists are examining the ability of the surface cells of gum tissue to reattach themselves to the tooth structure after separation due to mechanical or chemical irritation. This ability may well constitute a major line of defense against periodontal disease.

DENTAL AND ORAL-FACIAL ANOMALIES

Facial disfigurement is probably the most tragic of all disabilities. Whereas an abnormal hand may be placed in a pocket, malformed faces and associated speech defects cannot be hidden.

A large number of oral and facial clefts appear to be caused by the combined effects of many genetic and environmental factors. Adverse effects accumulate to a critical point or threshold beyond which normal development of the unborn child is not possible, and a cleft results. Slight modification of any one of these factors may reduce the accumulation of influences below this critical point and hence prevent the defect.

More research emphasis needs to be placed on determining these causative factors. The special report indicates that a clearer picture is now emerging as a consequence of past studies, thereby pointing the way to more productive efforts in this mystifying field. Concurrent research will continue to improve rehabilitative techniques to achieve the greatest degree of normalcy for victims of cleft lip and palate.

Another area in which initial emphasis necessarily had to be placed on treating symptoms is malocclusion, or bad bite. In this country, about one-third of school-age children suffer from malocclusion severe enough to require orthodontic treatment. Greater attention must now be directed to studies of growth and development, both to improve diagnostic and treatment procedures and to prevent malformation from occurring.

Since recent research has revealed that many forms of malocclusion seen in the human can be produced in the moneky through changes in the oral environment, the prospects for unraveling their causes appear brighter. Recent interest in maxillo-mandibular surgery for the treatment of certain types of malocclusion has resulted in an increased number of such procedures being performed. Since sound biological data are required to support these approaches, the animal studies will hopefully provide firmer foundations for therapy.

PAIN CONTROL

For the first time this year, and not appearing before in our justification, is a field we call pain control, a highly important, long neglected area of research. As emphasized in the 5-year plan, this problem is of central concern to dentistry. Urgent needs include study of the administration of anxiety-reducing agents and general anesthesia to the ambulatory dental patient, as well as investigations of the causes and modes of action of oral-facial pain.

During the past year, an advisory committee of experts recommended that pain control be given special program focus because of its serious dimensions. Reflecting the scope of the problem is the statistic of some 5 million persons a year receiving general anesthesia on an ambulatory basis, largely in dental offices, to say nothing of the tens of millions of dental patients who receive local anesthetics to counter or eliminate pain.

ULCERS OF LIPS AND MOUTH

The 5-year plan also includes another area that is ripe for a targeted research and development program. This is the area of viral diseases of the mouth, in particular the herpes simplex virus. This virus not only manifests itself as bothersome cold sores or fever blisters, but it has also been implicated in nonepidemic viral encephalitis, certain skin diseases, and genital and eye infections.

DENTAL RESEARCH INSTITUTES MOMENTUM

I am happy to report that the five dental research institutes and centers, operating in university environments under NIDR grant support, have gained remarkable momentum in their development. The quality of research in these institutes and the broad range of disciplines represented by their investigators have stimulated a new interest in dental problems.

This program represents one of the brightest hopes of overcoming the traditional deficit of research in the dental sciences. The fledgling institutes have clearly demonstrated a potential for serving as national resources to help solve the Nation's mounting oral health problems. The amount requested for this program for fiscal year 1972 is $6.2 million, which includes $1.5 million over the operating level for 1971.

Mr. Chairman, the scope of this brief presentation is necessarily limited. A more detailed report on accomplishments of the past year will be found in our research highlights.

BUDGET REQUEST

Our budget request for 1972 is $38,829,000, an increase of $4,126,000 over the 1971 operating level of $34,703,000. It reflects an increase of $2,900,000 for the national caries program and $1,500,000 for dental research institutes.

Now it would be my privilege to respond to any questions or other points you might care to make at this time, Mr. Chairman.

Mr. NATCHER. Thank you, Dr. Kreshover, for your statement.

The budget gives you somewhat preferential treatment, Doctor, compared with most of the institutes. You have what appears to be a real program increase of about $4 million. What sets you aside and places you in this right good position?

OPPORTUNITIES TO MOVE FORWARD

Dr. KRESHOVER. The one thing that is most important is that we recognize the opportunity to move forward in two critical areas because of what I would elect to describe as the science base.

For a long time, even today, dentistry as a health profession has lagged rather seriously behind medicine, I think largely because of its great emphasis in earlier years on the manual skills and because it has been viewed as an art rather than, as it is today, as a science.

Accordingly, as we face the critical problems of oral ills, both of the

hard and soft tissues, we recognize how deficient we have been in establishing this science base.

By science base, I refer to an understanding through fundamental science of the basic mechanisms that go into what happens in disease; the fact that we have been able through basic science to learn much about the mechanisms of tooth decay, or dental caries.

For example, largely through the efforts of scientists working in the National Institute of Dental Research as well as grant-supported investigators, we have learned that dental caries is truly an infectious disease and is transmissible. This is demonstrated in the animal model system.

We also know that this factor of infectivity, of a microbial component, must be present at one and the same time with two other factors for the lesion to develop. They must have a certain kind of diet upon which the bacterial flora can harvest and we also must have a susceptible tooth and a susceptible host for the disease to occur.

With the science base we have established, we were able to describe to the leadership of the National Institutes of Health and through the leadership of the NIH to the Department, and thence to the Congress, the Appropriations Subcommittees for the House and Senate, the fact that we are now able and ready to move forward to bring much of the new knowledge to the point of application.

We were then favored with the increase that we have described in our budget presentation.

AIM OF THE DENTAL RESEARCH AWARD PROGRAM

Mr. NATCHER. Doctor, on page 115 you say you have a new mechanism of research support, the special dental research award program. Tell us what this new program is and what it will accomplish that would not be accomplished by your old programs.

Dr. KRESHOVER. Over a period of recent years we have recognized that our training and fellowship programs were necessarily going to the more experienced, mature scientists, operating in either a dental school setting, a medical school setting, or an affiliated teaching hospital or some other, like institution.

We found, because of the austerity that is upon all of us, that it became increasingly difficult to provide adequate support to the young man or woman just out of dental or graduate school.

Accordingly, we made the recommendation to our National Advisory Dental Research Council that it endorse a new program whereby a certain amount of dollars contained within our own apportionment in training and fellowships could possibly be set aside for the award of research grants to these people.

I must correct what I said. The allocation of dollars that we identified was not out of training and fellowship money, it came out of the research grants money.

It ostensibly was to support people in the conduct of research, but as they pursued their research they would gain experience of the same character as in a training or a fellowship program.

The amount of money set aside for these awards was quite modest, in the range of some $200,000. The award of grants in individual cases is not to exceed $10,000.

We have had a remarkable response by applicants for this award, and we have great hopes that it will give a new sense of opportunity to young investigators in the field of dental science.

TRAINING NEEDS AND TRAINING GRANT LEVEL

Mr. NATCHER. On page 125, Doctor, you say, "As public demand for dental care increases, the need for dental research training becomes even more compelling." Then you go on to tell us about the critical lack of competent clinical investigators.

Then the table that follows shows you are cutting back the number of training grants from 85 to 81. Is this being consistent?

Dr. KRESHOVER. In the sense, Mr. Natcher, that the totality of training programs and fellowship programs at the National Institutes of Health is under study, and Dr. Marston and his staff are watching their progress with a very careful eye, we as an Institute become a part of the total priority system at NIH insofar as support is concerned.

We, therefore, are taking our measure of curtailment along with the other categorical institutes. We are seeking to move forward, nevertheless, on selected fronts of highest priority, and this is why we identify specifically the clinical area for emphasis in training.

Quite obviously, other programs will have to suffer some curtailment for the time being, but we are part of the total apparatus and we take our part with it.

CLEFT LIP AND PALATE

Mr. NATCHER. Doctor, what new do you have to report to the committee concerning cleft lip and cleft palate? Is there anything new from last year?

Dr. KRESHOVER. The most important things I could point to are not of a specific nature. They again recall my comment earlier on the need for broadening the base with respect to a better understanding of what constitutes oral and facial anomalies.

At the present time our principal emphasis is on better understanding, culling out the contributing factors of genetics on the one hand and environment on the other hand. We recognize also, as I don't think we emphasized adequately at our last appearance before you, Mr. Chairman, that cleft lip, with or without cleft palate, is a distinct anomaly, as distinguished from cleft palate alone.

While both of these characteristic deformities have a composite of hereditary and environmental factors, we recognize that they are different insofar as specific etiologies are concerned.

We also recognize that both in connection with cleft lip and palate we must develop further our experimental animal model systems to better understand the respective contributing roles of genetics and heredity.

For example, we understand that, in the experimental animal model system, the physical interplay of positioning of the fetus, amniotic pressures, and the possible pressure of the fetal chin area upon the thorax, may cause a consequent interposition of the tongue into the roof of the mouth and therefore prevent the rotation and medial migration of the palatine shells and adequate fusion.

We recognize also, from the standpoint of heredity, unusually different characteristics in different population groups, pointing again to ethnic considerations. For example, in the Japanese, we find that cleft palate is quite common, appearing in one out of every 370 to 375 live births. Next frequency would be the American Indian, and then the Caucasian. The least prevalent is the Negro. So there are very specific genetic components that we are seeking to understand better.

TOOTH TRANSPLANTS

Mr. NATCHER. What additional information can you give to the committee concerning tooth transplants, Doctor.

Dr. KRESHOVER. Not a great deal more than what I described at the last hearings. Specifically in the area of replacement of lost teeth and other parts in the oral environment, we, like other fields of biology and medicine, understand the importance of immune response, the rejection phenomenon. Accordingly, we have sought in our dental investigations to go to synthetically fabricated implants; a plastic replica, as it were, of the lost tooth that could then be introduced into the boney socket.

The results of limited clinical trials have been notably successful and we trust, that in a reasonably short time we might be able to move forward with more widespread utilization in dental practice.

RESEARCH ON PREVENTATION OF TOOTH DECAY

Mr. NATCHER. What additional information would you like to give concerning prevention of dental decay, Doctor?

Dr. KRESHOVER. Insofar as our dental caries program is concerned we have now, as a part of our special national effort, invested heavily in the opportunities available through collaborative research.

We described in a publication recently distributed to investigators in a variety of research settings, including industry, the challenges in studies of dental caries and the response has been almost staggering, to say the least.

We now have received from prospective contractors, proposals in the magnitude of approximately $4¼ million. This is in addition to the sum of $1¼ million that has already been programed for studies in the dental caries area.

By and large, our approach to the study of dental caries as a part of the national program, falls into three general categories. First, are the opportunities for new advances in protecting the susceptible tooth, either through adhesive sealants, as I mentioned earlier; by alternative measures of fluoridation application; and by making the tooth substance more resistant to the encroachment of bacteria and their acid-producing properties.

A second direction of effort, has been the area of diet. Here, opportunities exist to better explore sugar substitutes since, as I indicated earlier, sucrose seems to be the principal culprit.

We would also move forward to gain a better understanding of the role of phosphates as a diet additive; and we would also wish to understand better the contribution, or the role of trace elements, in addition to fluoride, which is an element that we have long recognized contributes to caries resistance.

We know, for example, that manganese and molybdenum and vanadium, as trace elements, can significantly reduce carries in certain population groups. But these are only small signs at the moment, and the body of evidence is not yet adequate to recognize these as very real contributions.

We know, too, that other trace elements by their presence in the diet can also increase dental caries, as, for example, selenium.

A third approach, of course, is that of combating the bacteria themselves. You have heard so much of late about the enzyme dextranase developed in 1966 by National Institute of Dental Research scientists in collaboration with investigators in the Merck laboratories in Rahway, N.J.

INCREASED FUNDS TO EXPLOIT POTENTIAL DECAY CURE

Dr. MARSTON. Mr. Chairman, I would like to go a little further in answer to your question about what information the Dental Institute and NIH would have for the committee about this problem of tooth decay. Dr. Kreshover has covered the substantive progress which was accelerated very markedly last year. In the light of advances in the state of the art and the fact that tooth decay is a common problem for the people of this Nation and the world, a decision was made to markedly accelerate the program.

If you put the 2 years together—1970 and 1971—we are talking about three or four times the effort. Although the amount is not large, there are significant increases in effort over a short period of time as the result of an evaluation both within the Dental Institute and the NIH and the Department of how rapidly one can expand a program of this type when the leads are good.

A year is a short time when one is talking about a goal of having a major impact on a disease that has almost a 100-percent prevalence. But the first year, working on the changes needed for a major expansion of this program, has been very reassuring. Indeed, I think all of us have reason to feel that we have gone a long way toward initiating this program.

There is substantive justification for increasing the effort, but also reassurance that this was a wise sense of timing a year ago. We do feel things are going well from the standpoint of progress, from the standpoint of the management of the program. This has considerable implications for a disease which, while not killing people, affects so many in all age groups in the population.

Mr. NATCHER. Thank you, Dr. Marston.

Mr. Michel?

LOCATION OF THE DENTAL INSTITUTES

Mr. MICHEL. Doctor, turning to your testimony here, where are the five dental research institutes?

Dr. KRESHOVER. They are at the following univerities: University of Alabama, University of North Carolina, University of Pennsylvania, University of Michigan, University of Washington in Seattle, Wash.

Mr. MICHEL. We are funding them out of the Dental Institute to what extent in each case? Are they all pretty much the same?

Dr. KRESHOVER. They are approximtaely the same.

Mr. MICHEL. Will you put that in the record?

Dr. KRESHOVER. Yes, sir.

(The information follows:)

Funding of dental research institutes

Institution	*Amount*
University of Alabama	$1,057,577
University of Michigan	822,035
University of North Carolina	1,017,047
University of Pennsylvania	739,622
University of Washington	[1] 379,787

[1] The original grant to Washington was a planning grant. This institute is about 2 years behind the others.

RESEARCH DONE AT THE INSTITUTES

Mr. MICHEL. Are all of these five institutes doing the same thing?

Dr. KRESHOVER. No, sir; they are not.

Mr. MICHEL. They are pursuing what areas?

Dr. KRESHOVER. For example, the University of Alabama is primarily involved in fundamental and applied programs relating to the etiology, treatment, and prevention of all oral diseases with special emphasis on hard tissues, calcification studies, and dental caries.

At the University of North Carolina——

Mr. MICHEL. That program has been underway how long?

Dr. KRESHOVER. Slightly over 3 years.

Mr. MICHEL. Do you have any results from that yet?

Dr. KRESHOVER. The results of the center programs are not spectacular and dramatic in terms of pointing to particular achievements. Rather, there is the sense of an increasing resource of talented investigators utilizing total university strengths to apply a concerted effort along the broader base of science, and ultimately related to more targeted objectives.

For example, at the present time there are really very few established research centers in the United States, indeed the world, that are applying a broad front of better understanding and attack on the oral facial anomalies.

At the University of North Carolina, the focus is on the important area of growth and development of the craniofacial complex.

At Pennsylvania, the principal areas of emphasis are concerned with the periodontal diseases and what we call herpetic lesions of the mouth, tissue ulcerations.

At the University of Washington the principal studies are directed also to the periodontal diseases but, in addition, to salivary gland physiology. The rather regrettable dearth of adequate study in the salivary gland field, that we recognize is part and parcel of the oral environment, has quite obvious relationships not only to oral disease but also as a mirror possibly of more general manifestations of diseases of a systemic nature.

At Michigan, the program is one that I don't think we could identify with any specific field at this time. It is one that is largely limiting its efforts to a broad sweep of basic sciences.

The dean of the School of Medicine at Michigan at the time the award was made, Dr. Hubbard, was keenly interested in broadening the base for dental studies and accordingly moved vigorously to attempt to get basic sciences and medicine more and more aware of needs in the dental field.

Mr. MICHEL. All of these five you list here are State universities are they not?

Dr. KRESHOVER. Pennsylvania is kind of a border institution. I would say they still consider themselves to be a private institution as contrasted with the other institutions named.

PARTICIPATION OF OTHER DENTISTRY SCHOOLS

Mr. MICHEL. If some other school of dentistry would like to get in the act, how do they compete with the ones already established? Will these five be through eternity?

Dr. KRESHOVER. With the amount of money requested, Mr. Michel, in our proposed 1972 budget, we would anticipate that no additional Institutes would be supported. The Institutes are now at a point where they are moving forward and exploiting unique opportunities, having assembled critical masses of scientists.

Accordingly, they all have been feeling a pinch for funds and will welcome opportunity now to resume progress as represented in the increase in the President's budget for 1972.

On the other hand, there are universities that have described at considerable length keen interest in moving forward in the Dental Research Institute area, and we would hope at some future time to be able to provide funding for them.

Mr. MICHEL. If a young, budding dentist wanted to get involved more in the research field here and in the problem areas you have described, would he tend to naturally gravitate toward one of these five centers if he has set for himself a goal in that field as a specialty?

Dr. KRESHOVER. Whereas training and opportunity for experience in research are very unique, and I would say challenging, in the five centers, I must remind the committee that we have some 90-plus training programs already underway in a variety of other settings throughout the country. These represent a variety of disciplines.

I would suspect that in many of the training opportunities that young men and women would seek today as a followup to their undergraduate dental education, they undoubtedly would focus down on a specific field.

DENTAL SCHOOLS IN THE UNITED STATES

Mr. MICHEL. How many schools of dentistry do we have in the country?

Dr. KRESHOVER. There are 53 dental schools currently operating. Of that number currently operating, two have already indicated they will be closing their doors. The two that will be closing are St. Louis University in St. Louis, and Loyola University Dental School in New Orleans, which will leave 51.

Then we must add to the then operating 51, six new dental schools that are currently planning to open.

Mr. MICHEL. Where are those?

Dr. KRESHOVER. The six new dental schools are at Oklahoma, Colorado, Stoneybrook, Florida, Southern Illinois, and San Antonio, Tex.

NIDR DENTAL SCHOOL SUPPORT

Mr. MICHEL. Of those 51 existing dental schools, how many receive any kind of grant or assist from the National Institute of Dental Research?

Dr. KRESHOVER. My last assessment of support programs for schools of dentistry in this country shows that all of them, in some degree, receive support from the National Institute of Dental Research. There is not one school that does not.

Mr. MICHEL. Would you supply for the record a list of the dental schools and how much they each get in some form?

Dr. KRESHOVER. Yes, sir.

TOTAL NIH SUPPORT FOR DENTAL SCHOOLS

Dr. MARSTON. As you understand I am sure, there are other components of NIH that also have programs that affect dental schools particularly the Division of Dental Health, and under the manpower legislation.

Are you interested in the full support?

Mr. MICHEL. Yes. Let's fill out the record and show the total amount from NIH.

Dr. MARSTON. Yes.

(The information follows:)

NIH obligations to dental schools

(*In thousands*)

School of dentistry	*1970 total obligations*
University of Alabama School of Dentistry	$2,114
Loma Linda University School of Dentistry	780
University of California, Los Angeles, School of Dentistry	727
University of California, San Francisco, School of Dentistry	929
University of Southern California School of Dentistry	1,177
University Pacific School of Dentistry	1,105
University of Colorado School of Dentistry	2
University of Connecticut School of Dentistry	460
Georgetown University School of Dentistry	792
Howard University School of Dentistry	931
University of Florida School of Dentistry	12,513

Emory University School of Dentistry	1,156
Medical College of Georgia School of Dentistry	505
Loyola University School of Dentistry	1,344
Northwestern University Dental School	451
University of Illinois College of Dentistry	789
Indiana University School of Dentistry	737
University of Iowa School of Dentistry	1,257
University of Kentucky School of Dentistry	808
University of Louisville School of Dentistry	1,087
Louisiana State University School of Dentistry	145
Loyola University Louisiana School of Dentistry	39
University of Maryland School of Dentistry	704
Harvard University School of Dentistry	1,520
Tufts University School of Dentistry	8,484
University of Detroit School of Dentistry	744
University of Michigan Dental School	1,854
University of Minnesota School of Dentistry	1,251
St. Louis University School of Dentistry	14
University of Missouri School of Dentistry	893
Washington University School of Dentistry	1,131
Creighton University School of Dentistry	699
University of Nebraska School of Dentistry	682
New Jersey College of Medicine and Dentistry, Newark	240
Fairleigh-Dickinson University School of Dentistry	191
Columbia University School of Dentistry	944
New York University School of Dentistry	1,263
State University of New York at Buffalo, School of Dentistry	997
University of North Carolina School of Dentistry	2,114
Case Western Reserve School of Dentistry	947
Ohio State University School of Dentistry	3,994
University of Oklahoma School of Dentistry	45
University of Oregon Dental School	638
Temple University School of Dentistry	835
University of Pennsylvania School of Dentistry	1,624
University of Pittsburgh School of Dentistry	1,038
Medical College of South Carolina School of Dentistry	77
Meharry Medical College School of Dentistry	1,455
University of Tennessee School of Dentistry	638
Baylor University College of Dentistry	765
University of Texas Dental Branch	853
Virginia Commonwealth University, Medical College of Virginia School of Dentistry	291
University of Washington School of Dentistry	5,753
West Virginia University School of Dentistry	435
Marquette University School of Dentistry	590
University of Puerto Rico School of Dentistry	294
Total	73,845

STATISTICS ON DENTURES AND FALSE TEETH

Mr. MICHEL. Do you have any idea how large a percentage of our people have dentures or false teeth?

Dr. KRESHOVER. I don't know that I have the specific answer to that. All I can say is at the present time there are some 20 million adults in this country who are completely toothless. I would say by far the vast majority of these would be wearing full dentures.

Over the age of 35 years, approximately two out of three people in this country have one or more teeth lost as a consequence mostly of periodontal disease.

Mr. PATTEN. What age?

Dr. KRESHOVER. From age thirty-five years on up, approximately two out of every three people have at least one tooth lost as a consequence of disease.

The way the teeth are replaced by dentistry is either by what is called a fixed prosthesis or a removable prosthesis. Usually, if only few teeth are lost and they are in the same segment of the mouth, the replacement would be by what is called a fixed bridge. On the other hand if more teeth are lost at the same time, and particularly if they are in different parts of the mouth, a movable denture would be placed.

I think from these kinds of data, that is, two out of three Americans over the age of 35 with at least one tooth missing and 20 million Americans with no teeth at all, we can see the staggering dimensions of the number of people who have dentures.

MERITS OF GOLD FILLING

Mr. MICHEL. Why is gold preferable to amalgam filling, or is it?

Dr. KRESHOVER. Insofar as the ideal is concerned, gold is recognized to be a superior restorative material to amalgam. Gold can be condensed much more effectively than can amalgam. The most noticeable characteristic of gold in contrast to amalgam that appeals to the practicing dentist is what happens at the margin, the interface between the restoration and the natural tooth.

In the case of amalgam, the properties of amalgam, its structural tendency to change with age causes defects at this marginal juncture, with a rather frequent occurrence of what is called secondary caries. On the other hand, when gold with a good margin is attained through skillful manipulation and placement, this does not occur.

There are other characteristics needless to say of any metallic restoration that are unfavorable as, for example, conduct of heat; that is, thermal changes which both gold and amalgam would, of course, have.

ELEMENTARY LESSON ON TOOTH CARE

Mr. MICHEL. If you had an opportunity to address a school audience and you only had a couple minutes to talk to them and wanted to make the most of that time to do something constructive to remedy the problems you are addressing yourself to here today, what would you tell those children?

Their parents tell them to brush their teeth regularly and don't chew ice and drink a lot of milk and don't drink a lot of sweet drinks or eat too much sweet food. This comes from a simple layman.

What other things do we tell them?

Dr. KRESHOVER. The kind of a speech I would try to give an audience like this is, number one, to dramatize the field of dentistry to the point where they would recognize its importance. As far as health priorities are concerned the children, as well regrettably as their parents, should not give it short shrift, and should not delay seeking dental care long after they would seek other kinds of attention.

Accordingly, Mr. Michel, I would try to describe the mouth and what the mouth contains as a kind of vital organ system. I would

emphasize the fact when they think of their mouths they not think of their teeth alone, and that they think of it as a vital organ and apparatus.

I would try to tell them that if they didn't have a mouth, they would be unable to communicate with their fellow man so speech is vital at the outset. I would try to tell them that without a mouth they would be able to take no nourishment whatever and accordingly would not survive very long.

I would try to tell them that without a mouth they would have great difficulty in respiration and that their breathing would suffer significantly. I would tell them that without a mouth, just as without a heart or liver or lungs, they wouldn't live.

I think that having dramatized it this way. I would call upon them to seek attention for the ills of the mouth, whether they are of the teeth, the tongue or other parts. I would attempt to tell them about the incidence of oral cancer as a dramatic example of what could go wrong with the oral tissues. I would tell them that perhaps 5 percent of all cancers occur in the mouth. I would try to tell them about some of the other lesions of the mouth, the soft tissue ulcerations and also the manifestations of systemtic diseases that find expression in the mouth so that a physician couldn't even practice his profession without being aware of the mouth and what he sees in the mouth.

PUBLIC INFORMATION EFFORTS ABOUT THE MOUTH

Mr. MICHEL. Now I am going to make it a little more difficult. A lot of these things you talk about are fine and good and I wish we had the time to tell everyone about them. But to get wide dissemination of information on this problem we go to the television tube and the most we get under public service maybe is a 30-second or 1-minute shot.

Are we doing anything in the public information field to alert the public to the problem of dental caries and what can be done quickly or easily?

Dr. KRESHOVER. Yes; we are particularly in connection with the activities of our information office.

I have one figure here that struck me as being a very exciting one, and that is that in calendar year 1970 our own information office in the Dental Institute received about 9,500 requests for information about dental diseases. The information office also, in conjunction with the American Dental Association, produced a film about a year ago entitled the "Laboratory of the Body." As of December 31 of this past calendar year 1970, I was surprised to learn, Mr. Michel, that 1,057,000 people had seen it exclusive of the television audience where the film also was shown.

The film won two awards, the gold medal from the Atlanta International Film Festival and the Golden Eagle award from the Council on Nontheatrical Events.

As far as the national caries program is concerned, we have had a flurry of newspaper and magazine articles throughout the past year. We also have had many news reporters visit us at the Institute. We welcome them cordially.

We also had a series of five 28-minute colorcasts this past year which described some of the research conducted and supported by the Dental Institute. These were produced by our information office in cooperation with the National Broadcasting Co. TV in Washington. These were shown in five major cities during the last year, as well as shown at the U.S. Naval Academy and other institutions that hopefully will now have a new kind of image of dentistry.

I think we have been doing a reasonably good job, Mr. Michel, in the area of public information.

PROGRESS IN EXPANDING DENTAL RESEARCH

Mr. MICHEL. Last year we discussed how dental research has lagged behind the broad base of medical research.

Dr. KRESHOVER. Yes, sir.

Mr. MICHEL. Have we gained any ground during the past year and will the proposed budget for 1972 provide a further push forward?

Dr. KRESHOVER. Yes, sir. I think we are gaining ground steadily. I won't say rapidly. I think added to the opportunity described in the programs of the National Institute of Dental Research are the research institutes that you asked about earlier.

I think all of these are contributing notably to a broadening of the base for the dental sciences.

While it is regrettable, I can provide you with only one example where this kind of adequate base has been established upon which to launch a program of application, and that is in the area of dental caries. I do feel very sincerely, however, that we are at the point now when we might be able to launch similar programs in other areas as, for example, in the field of pain control; a new field that we recognize is very vital to our public. Also in the area of soft tissue ulcerations of the mouth. Herpes, for example.

RATIO OF RESEARCHERS TO ACTIVE DENTISTS

Mr. MICHEL. In the hearing last year I mentioned some figures in a 1968 report you provided me showing there was one biomedical research worker for every seven active physicians, one Ph. D. scientist in health research for every 9½ physicians. The figures show in contrast there was only one dental researcher for every 44 active non-Federal dentists.

Dr. KRESHOVER. That is correct.

Mr. MICHEL. Do you know if those ratios have changed any since that report?

Dr. KRESHOVER. I would say not.

Mr. MICHEL. That should be cause for some concern, shouldn't it?

Dr. KRESHOVER. I think, by and large, the time has been too short really between when I provided those figures for you when you discussed the broad problem of the dental sciences before the American Dental Association, and today.

Our training programs and fellowship programs, needless to say, are moving forward, but I think it will take another 3 years before we can provide you with statistics that show improvement.

PRIVATE FUNDS FOR DENTAL RESEARCH

Mr. MICHEL. I think a problem we are also confronted with here is we have a large amount of money contributed from sources in the private sector for cancer research and for the heart fund, and for a number of these other maladies, but is there anything in the private sector that contributes any substantial sums of money for dental research?

Dr. KRESHOVER. No, sir, there is not. Regretably, the dental profession, the dental sciences, do not have this kind of constituency, this kind of association to look to.

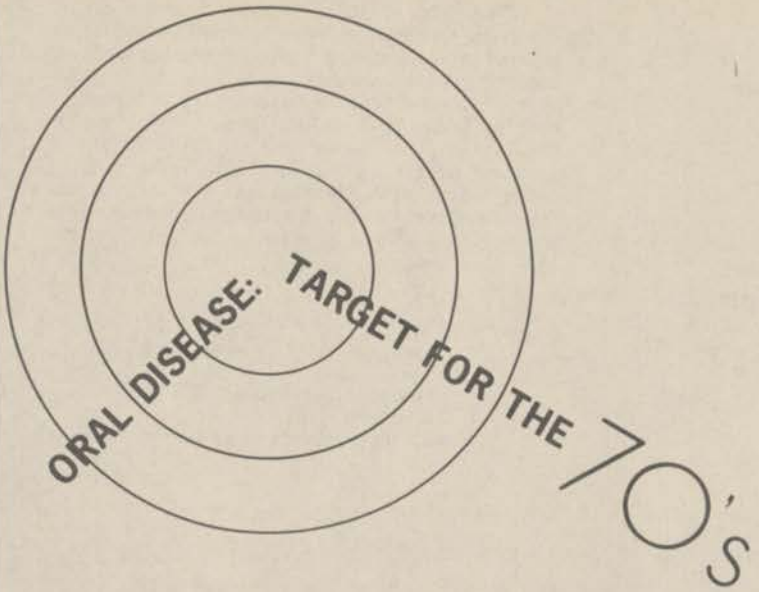
I believe again it is principally an expression of the failure of the public to adequately understand and appreciate the importance of dental problems. It relates to the rather serious economic impact of dental education on total university structure where, most regrettably again, the demand for financial support coming from schools of dentistry for a contribution from the capital resources of the university is not in keeping with perhaps what other components of the university would receive.

FIVE-YEAR PLAN OF THE NATIONAL INSTITUTE OF DENTAL RESEARCH

Mr. MICHEL. Mr. Chairman, I have gone through the report that we asked the Institute to prepare when we issued our report last year on the 1971 appropriation bill. I think it is well done and that we and others will find it valuable to refer to from time to time during the next few years. With your permission I would like to place it in the record.

Mr. NATCHER. I think that is a good idea.

(The report follows:)



Five-year Plan of the National Institute of Dental Research for Optimum Development of the Nation's Dental Research Effort

Pain Control ---- 479
Dental Caries ---- 483
Periodontal Disease ---- 488
Ulcers of the Lips and Mouth ---- 492
Deformities of Face and Mouth ---- 495
The Science of Materials and Restoration of the Mouth ---- 500
Broad Front of Research on Oral Disease
Summary ---- 502
Appendix ---- 508

The program plans described herein are in response to requests made by the Committees on Appropriations of the House of Representatives and the Senate in their reports on the 1971 appropriations for the Departments of Labor, and Health, Education, and Welfare. They present a "realistic plan" based on the professional judgment of the Dental Institute leadership, in consultation with the National Advisory Dental Research Council, for the optimum development of the Nation's dental research effort during the next five years.



Seymour J. Kreshover, D.D.S., M.D.
Director
National Institute of Dental Research

December 30, 1970

PREAMBLE

As the crisis in the delivery and cost of health care deepens, all threats to individual well-being require more critical examination and evaluation. Among these, diseases and disorders of the mouth are unique problems. They are universal. They vary widely in form, severity, and duration. They are largely irreversible, for the body lacks the inherent power to repair most of the damage they inflict. Despite continuous improvements in treatment and control, the major problems of tooth decay and periodontal (gum) disease cannot be adequately overcome with corrective measures. Thus, unlike medicine's brilliant successes with cures, dentistry must stress prevention.

Further, the mouth is a complex system of organs and tissues that affects not only our general health but behavior and personality as well. No other part of the body is so versatile in such vital behavioral and emotional functions as nourishment, appearance, and self-image; the communication of feeling and ideas through speech and facial expression; and the sensual enjoyments of flavor, texture, and temperature. Oral diseases impair nutrition, especially in older people, mar appearance, and impede communication. The individual thereby suffers biologically, psychologically, and socially.

The state of the mouth affects the whole body, and conversely the mouth mirrors the health of the total system.

Of vital medical importance, the mouth also serves as the most accessible site for the study of basic life processes and of various factors--such as inflammations, infections, lesions, tumors, trauma, genetic anomalies, and degradation of tissues--that affect many organ systems and parts of the body.

Today, only a small fraction of the people in the United States get reasonably complete dental care. Almost half receive no care at all. Economic barriers to requests for treatment will drop as private dental insurance and aid programs expand. As health expectations of the American public rise, demand is expected to skyrocket, overwhelming professional and auxiliary manpower, despite any realistic increases in their numbers. The solution, in the final analysis, is to devise simpler, more effective means of control, treatment, and, ultimately, prevention. Because they are so pervasively destructive, a relatively small investment in the prevention of oral diseases would substantially enhance the quality of life.

The following plan for the optimum development of the Nation's dental research effort in the next five years is a vital step toward the achievement of preventive care. The plan exploits those areas with the greatest opportunity for success on the basis of current scientific knowledge. In particular, it stresses five fields: (1) pain control, a neglected area of central concern to dentistry; (2) dental caries (tooth decay), the focus of

a newly launched, national program; (3) periodontal (gum) disease, for which recent advances in immunology present exciting prospects for future pay-offs; (4) herpetic virus infections (affecting not only the mouth--fever blisters, but also eyes, brain, and skin), for which the state of knowledge is ripe for a targeted program of prevention; and (5) problems of oral-facial growth and development, on which more basic study is required to ultimately prevent malocclusion and cleft lip and palate, and related speech disorders.

This report does not dwell on past accomplishments. However, it should be noted that studies by the intramural staff of the National Institute of Dental Research,coupled with grant-supported contributions from other institutions, have played a major role in opening these new pathways of productive research. The unique setting of the Institute in the diverse complex of the National Institutes of Health has enabled scientists in many allied fields to collaborate in clinical and basic research. This fruitful interchange benefits both the dental and general medical sciences. The five-year plan draws heavily on these various resources in its approach to the practical application of these leads.

PAIN CONTROL

"Pain is perfect misery, the worst
of all evils;
And, excessive, overturns all patience."
Milton

Since scarcely anyone escapes its ravages, pain has exerted a powerful malefic influence on man throughout history. Its understanding and control, therefore, are essential requirements not only for increasing individual comfort but also for positively influencing the future of mankind.

Throughout history, facial and dental pain have served as classic examples of distress. The image of dentistry traditionally has been associated with pain. Thus, even before the epochal discovery by a dentist of general anesthesia, the study and control of pain has been an overriding concern of dentistry.

Pain is a central issue in the practice of dentistry for two reasons. First, members of the profession are called on to treat the painful symptoms localized in the facial region, such as facial neuralgia, glossodynia (burning tongue), dysfunction of the temporomandibular joint, oral cancer, recurrent stomatitis (canker sores), and other conditions. Second, as a problem unique to dentistry, pain is intimately associated with almost all dental corrective, surgical, and restorative procedures, so that even the anticipation of such treatment creates major difficulties for the patient and the dentist.

Public demand for relief from pain related to dental procedures is reflected in the growing use of both local and general anesthesia. Each year, in the United States alone, some 50 million dental carpules (2 cc doses) are used to produce local anesthesia. About 5 million persons a year receive general anesthesia on an ambulatory basis, the great majority in private dental offices. In fact, over one-fifth of all general anesthetics administered in the United States are used in conjunction with dental treatment.

TREATING PAIN SYMPTOMS

"Perhaps no other clinical research presents such problems as research in the nature and control of pain; its staggering difficulties have discouraged scientists." This statement by Dr. John J. Bonica, University of Washington at Seattle, the most noted American authority on pain, partly explains the dearth of research in this area.

62-645 O - 71 - pt. 3 - 31

Since the etiology and mechanism of action of oral-facial pain is largely unknown, treatment is empirical and usually inadequate.

> * *Because this area has been so grossly neglected, a substantial amount of clinical study and research in relevant basic sciences will be required before hope for improved care and relief can be held out to afflicted persons.*

CONTROLLING PAIN AND FEAR IN DENTAL PROCEDURES

To alleviate the fear, dread, and anxiety with which many patients approach dental care, a number of promising agents are available. Newer physiologic concepts and techniques have established nitrous oxide, long used in general anesthesia, as one of the more promising anti-anxiety agents in dental practice. In addition, newer drugs are being developed for intravenous administration along with the local anesthetic. However, because of lack of adequate knowledge and clinical data, the conscientious dentist cannot fully utilize these anxiety-reducing agents and drugs with complete safety to the patient.

> * *There is urgent need for studies on safety and on acceptable techniques for administration of anxiety-reducing agents.*

The great interest of the profession in these agents is evident in the current oversubscription of the few continuing education courses offered on this subject in the United States. Indeed, many dental practitioners have sought attendance at special pain control courses in Britain, where basic and applied research is considerably further advanced in the clinical administration of amnesic and sedative agents than in this country.

> * *There is a parallel need for the clinical study of problems related to general anesthesia in dentistry as more and more dental patients are demanding general anesthesia on an ambulatory basis.*

A recent NIDR survey disclosed that general anesthesia is used and preferred by 60 percent of oral surgeons, despite the fact that many more physiologic and technical problems are involved in patient management compared to local anesthesia.

In ideal ambulatory practice, the patient should be unconscious for only a short period of time, should recover quickly and completely, and

should be able to return home within an hour or two. He does not have the hospitalized patient's advantage of 24 hours' rest, careful surveillance of diet and water intake, and premedication to reduce anxiety. Because of the nature of general anesthesia for ambulatory patients, the oral surgeon frequently cannot follow the almost universal hospital practice of nasotracheal intubation, thereby assuring respiratory efficiency and an adequate oxygen intake.

Thus, for many reasons, research findings obtained in studies of general anesthesia administered in the hospital are not readily applicable to general anesthesia administered to the ambulatory dental patient.

> * *The use of almost every drug and technique must be reinvestigated under actual dental treatment conditions before it can be safely adapted to ambulatory patients.*

There exists an almost total lack of the necessary basic and clinical research information relevant to both local and general anesthesia for dentistry. Pharmaceutical companies have supported a small amount of clinical research in local anesthesia, such as drug evaluation, but practically nothing in general anesthesia.

In May 1970 an ad hoc advisory committee of experts, convened by NIDR to study the problem of pain control in dentistry, recommended that it be given a special NIDR program focus with substantially increased support for research and training of both investigators and dental faculty. Some of the specific recommendations of the committee are reflected in the following section.

RESOURCES

The problem of symptomatic facial pain can best be solved in special centers of research. However, establishment of oral pain centers would not be feasible at this time because of the almost total lack of trained personnel in the basic and clinical areas to conduct research in this complex field. A practical alternative would be to support "Oral Sections" in the two existing pain control centers, located at the University of Washington at Seattle and at Harvard Medical School in Boston, if it can be administratively arranged. This would require additional funding as noted in the appendix. Within the course of the next five years, should fiscal resources be available, it is reasonable to assume that the first totally independent oral pain control units could be established within existing Dental Research Institutes.

Similarly, the problem of controlling pain associated with dental procedures must be attacked systematically, starting with model units for research and training (including faculty training) in qualified institutions. It is recommended that a minimum of five geographically distributed units be identified and activated in the first year of the projection, so that critically needed research programs could move forward without delay. Several such centers already have adequate facilities and staff, but lack the financial capability. Individual research projects and training grants in the fields of behavioral science, neuroanatomy, neurophysiology, pharmacology, and other relevant basic sciences must also be supported, both to add new knowledge to the field of anesthesiology, and to develop critically needed manpower.

The NIDR has over the past 12 years supported a cooperative intramural study with the Anesthesiology Department of the Clinical Center, NIH, on the physiological effects of general anesthetic agents used by oral surgeons. There is need to expand the NIDR intramural investigations both in size and in scope so that the very promising studies on local anesthesia and intravenous sedation can be further explored. However, because of the magnitude of the overall anesthesia-analgesia problems and the critical need for almost immediate solutions, the NIDR extramural and collaborative areas must be utilized to the fullest possible degree.

The required levels of support appear in the appendix.

DENTAL CARIES

Dental caries affects ninety-eight percent of the population and is the most prevalent affliction of children. By the time the average child reaches school age, he has three decayed teeth, and the average fifteen-year-old has eleven decayed teeth. Yet, potentially, tooth decay is one of the most preventable of diseases.

Approximately two billion dollars is spent each year for its treatment by the forty percent of the population who seek or are in a position to receive dental care. If all cavities incurred each year could be filled, the annual cost would reach about ten billion dollars.

A NATIONAL CARIES PROGRAM FOR PREVENTION

Sufficient scientific knowledge now exists on which a targeted research and development program to make caries largely preventable has been structured. This program is based on growing evidence that caries results from three groups of factors. Like three interlocking circles, all of these must interact at one and the same time for the disease to develop and progress. First, the mouth must harbor certain types of caries-producing microorganisms. Second, the diet must contain refined carbohydrates, particularly sucrose (table sugar), which enable the bacteria to stick to the teeth as they ferment the sugar to acid that dissolves the calcified structure of the tooth. Third, the teeth must be susceptible to the locally destructive action. Caries, therefore, is the result of dental infection caused by characteristic groups of bacteria that reside on the teeth and ferment carbohydrates in the diet to produce destructive acids and enzymes.

The purpose of the Institute's program is to reduce the incidence of caries and to extend the capabilities of the dentist, the hygienist, and others on the dental team to prevent decay. Because of the complex nature of caries, it is unlikely that any one approach will completely solve the problems of its prevention and control. Efforts are therefore directed to depressing the effects of all factors to a minimum and utilizing a combination of techniques instead of concentrating on one.

Several promising leads, as described below, will be pursued through an appropriate sequence of studies: laboratory research, clinical studies, field trials and field demonstrations. When they reach the point of readiness, they will be applied widely in personal oral health programs and/or in community health services. Various lines of inquiry will be added as further leads develop during the course of investigation. To speed these studies:

* *It is essential to develop caries-susceptibility tests and procedures for shortening the present two-to-three year time needed for evaluation of anti-caries measures.*

* *Basic studies on tooth structure also are needed. It is necessary, for example, to know more about posteruptive changes in enamel, and the capability of the tooth surface to remineralize.*

Protecting the Teeth

Fluoride....Many years of study and practical application have conclusively demonstrated that fluoride is an effective anti-caries agent when administered in the community water supply. Its value in increasing the resistance of the tooth to destructive acids will be expanded by developing other effective vehicles to provide fluoride for the more than 40,000,000 Americans who do not have access to community water supplies.

Alternate means of administering fluoride include direct topical application, tablets, or addition to salt.

* *It is imperative to undertake a series of clinical studies to provide answers to the questions: (1) What level of fluoride in the enamel itself provides optimum protection against caries; (2) What is the best method for achieving the optimum fluoride level in enamel; (3) What supplemental applications are required to maintain the optimum fluoride level in teeth.*

* *More knowledge also is required to fully understand the action of fluorides on solubility of tooth enamel, on remineralization of the tooth surface, and on bacteria and their products. Decay-causing organisms and their metabolic by-products must be investigated further in order to obtain clues for developing methods of reducing their cariogenicity.*

Sealants....Pits and fissures of the chewing surfaces of the teeth are vulnerable sites for trapping food and decay-producing bacteria. Research has already demonstrated that these anatomical sites do not benefit as much

by topical fluoride treatment as do the smooth surfaces of the teeth. Many dentists have therefore believed that the best method for preventing caries in this region is to fill the pits and fissures, generally with an amalgam restorative. This time-consuming procedure necessitates cutting away otherwise healthy tooth material. In a new, highly promising, experimental approach, a plastic adhesive sealant covers these vulnerable anatomical regions without altering the tooth surface. Success of the initial clinical trial points to the desirability of more extensive studies of sealant materials.

* *Continuing laboratory and clinical studies are needed to develop optimally effective adhesive sealants which offer protection against decay for prolonged periods of time.*

* *The feasibility of correcting caries-vulnerable surface defects of enamel by means of structural fusion induced by lasers should be ascertained.*

Modifying the Diet

Sugar substitutes....An abundance of evidence shows that the frequent consumption of sucrose, particularly between meals, favors the induction of caries.

* *There is need to determine whether replacement of sucrose in the diet by other types of sugars would reduce caries effectively. If so, these studies may point to the possibility of a less harmful ingredient in the manufacture of confections, baked goods and mixes, and commercially available dessert preparations.*

Dietary additives....The addition of phosphates to caries-inducing diets is known to reduce tooth decay in animals. No unequivocal data are available, however, as to whether the incorporation of phosphates or other dietary additives in different vehicles, such as flour, salt, milk, and snack foods, will reduce caries in humans.

* *An investigation of the efficacy of these additives is urgent. Their use would represent a more immediately practical approach than changing eating habits.*

Trace elements....There are indications of a correlation between low caries experience and increased concentrations of certain elements other than fluorine in the diet.

> * *To further pursue this question, it will be necessary to study the effects of elements that are found in such small quantities in the drinking water and soil that they are known as trace elements. Among these, for example, are molybdenum, titanium, lithium, and boron.*

Combating Bacteria

Mechanical cleansing....The microbial factor is a chief target in the prevention and control of caries, since it is the active agent of decay. Mechanical dispersion of bacterial deposits, or plaque, from the teeth by oral hygiene methods is beneficial in control of the disease.

> * *Although the effectiveness of the toothbrush cannot be disregarded, it is important to develop other cleansing agents and techniques that can be applied simply and with a minimum of time.*

Preventing adhesion....It is known that caries-causing bacteria utilize sucrose to secrete a sticky material (plaque) which enables them to attach themselves to the teeth where they produce acid by fermenting carbohydrates.

The enzyme dextranase, which dissolves the sticky material, has successfully reduced caries in animal experiments. Following limited clinical tests, which have shown some favorable indication of plaque control with topically applied dextranase, more extensive trials are now underway.

> * *Laboratory work, concurrent with the dextranase trials, should be extended to identify other substances which will dissolve or alter the composition of plaque.*

Inhibiting growth....Another research approach focuses on inhibiting the growth of the major caries-inducing bacteria through the topical use of antimicrobial agents. A coordinated program is planned for screening various agents as potential preventives of caries.

* *Studies will be conducted on the effectiveness of different antiseptics in mouth rinses, as well as the use of antibiotics applied in the form of gels in mouth appliances. The feasibility of using antimetabolites to alter the metabolic by-products of oral bacteria will also be investigated.*

Immunization....Long-term studies at the Great Lakes Naval Training Center and Columbia University indicate that about one person in 750 in the United States develops no caries, seemingly regardless of diet and exposure to bacteria. The basis for this immunity has not been ascertained--whether it is innate or acquired, whether it depends on antibodies or nonspecific constitutional factors, whether or not it can be developed by artificial means. Because of the great paucity of supporting data, the feasibility of preventing caries by immunization against cariogenic bacteria and their antigenic products merits vigorous exploitation.

* *A prime target of investigation should be the particular mechanisms of local immunity in the oral cavity, such as antibody production by salivary glands and other regional tissues.*

(This type of immunologic study is directed to caries, as contrasted with that discussed in the section on periodontal disease.)

Resources

NIDR-supported research has developed the major scientific evidence for a targeted program against caries. The unique cadre of scientists active in this field needs to be strengthened, both to extend intramural and extramural research and to supervise a greatly expanded program of collaborative research with investigators in academic, industrial, and other research institutions. The requested increases are reflected in the appendix.

PERIODONTAL DISEASE

Periodontal disease has been called a sneak thief because, without warning, it undermines the gums and other tooth-supporting tissues, eventually causing sound teeth to loosen and fall out. As the main cause of tooth loss after age 35, it represents a major health problem. Periodontal disease is, in general, poorly controlled, and methods of tooth replacement are often unsatisfactory. Since only a small proportion of people know and demand the benefits of present control measures, the true needs for care remain essentially untouched. Furthermore, as demand increases, the capabilities of the profession to cope with the problem will be far outstripped. Hence, there is an urgent need to expand research on the disease so that more effective and less expensive programs of control and prevention can be developed. Sufficient information has now accumulated from past research to warrant an intensive effort to better understand, control, and ultimately prevent this widespread disease.

THE DISEASE PROCESS

It is now widely accepted that bacteria which live in the mouth are a major contributing factor to periodontal disease. These microorganisms grow in a plaque, or film, on the tooth surface next to the gum tissue and release toxins and other substances which then enter the tissues and cause inflammation. Eventually, this process destroys the bone and the connective tissue fibers which hold teeth firm. As a result, the teeth loosen and finally are lost.

Clinical and animal studies indicate that certain types of oral bacteria are more important in the disease than others. Other evidence suggests that plaque bacteria produce substances which directly damage the surface epithelium. Bacterial endotoxins, enzymes, chemotactic agents, and yet unknown antigens and toxins can cross the damaged layer and penetrate the deeper periodontal tissues where they trigger a local reaction called inflammation.

Inflammation

Long-continued (chronic) inflammation frequently leads to destruction of local tissues through mechanisms which are just beginning to be explored by immunopathologists and cell biologists. Mechanisms implicated in periodontal disease are similar to those in other inflammatory conditions, such as rheumatoid arthritis and certain kidney disease. Indeed, knowledge of factors responsible for inflammatory periodontal disease may well enlarge understanding of inflammatory conditions in other parts of the body. Moreover, periodontal tissues are far more accessible for study than bone joints or kidneys. With increased emphasis upon research on molecular mechanisms of inflammation, it should be possible to develop specific inhibitors and anti-inflammatory agents to treat these diseases.

Tissue Loss

In the periodontal disease process, inflammation in the gums is soon followed by deterioration of the collagen fibers that fasten the gums and teeth to the jawbone. Eventually, part of the jawbone itself is irreversibly destroyed. However, the exact relationships of local inflammation to collagen fiber destruction and to bone resorption are not yet clear. A promising lead on one of these questions was recently obtained when an enzyme believed to initiate the breakdown of collagen was found in inflammatory cells, in bone and in periodontal tissues. This enzyme, called collagenase, is a normal constituent of these tissues, but its level rises in disease.

Throughout life, bone, which is made up largely of mineralized collagen, undergoes a continuous, balanced resorption (breakdown) and repair. In the disease state, however, the destructive mechanisms proceed at a faster rate, so there is a net loss of the bone which supports the teeth. A possible relationship between bone destruction and inflammation is indicated by the recent finding that inflamed gingival tissue contains a substance that enhances bone resorption.

Future Research

Current information indicates that promising areas for future research include:

* *Expanded studies, using both human and animal model systems, to identify specific bacteria which cause disease and to show their mode of action.*

* *Intensive study of the inflammatory process, including the development of new animal and tissue culture models to facilitate such research. Specific substances involved in inflammation should be sought and measured in the diseased tissues themselves, and their relationship to structure-destroying host enzymes determined. How certain white cells of the body's infection-fighting system, such as neutrophils and lymphocytes, may participate in the disease process should be examined. Humans who lack known molecular parts of the immune system should also be studied to help assess certain aspects of the important role of immunology in periodontal disease.*

* *Expansion of studies to understand and control the factors responsible for degradation of connective tissue and bone.*

* *Initiation of multidisciplinary study on responses of connective tissue to inflammation, particularly factors controlling production of collagenase and other enzymes which degrade connective tissues. Appropriate model systems are critically needed, since these processes are difficult to study in the living animal.*

PREVENTION

Recent studies indicate that, in the major type of periodontal disease, which is characterized by inflammation, the whole chain of events begins with bacterial plaque deposition on the teeth. Therefore, one approach is to prevent plaque formation. Since plaque also plays a key role in tooth decay, measures for preventing periodontal disease will coincide in many ways with those described under Dental Caries.

Anti-microbial Agents

Although, in theory, tooth brushing and other mechanical measures can control the formation of dental plaque, these procedures have not been generally successful. They require regular, assiduous, and tedious efforts which most people are unwilling to make. The need clearly is for less time-consuming solutions. A realistic preventive measure should inhibit or repeatedly interfere with microbial colonization on the teeth and gingival tissues, without making unreasonable demands on the individual. Achievement of such measures would require:

* *Expansion of studies to determine how bacteria stick to teeth and gums; more intensive pursuit of current findings that bacteria can stick to oral tissues by producing adhesive substances and and also by interacting with saliva, soft tissue surfaces, dietary components, and with other species of bacteria.*

* *Development of better laboratory and clinical tests so that new preventive chemical agents designed to inhibit specific adhesive mechanisms can be developed more rapidly.*

* *Testing of antibacterial chemicals for ability to suppress growth of specific plaque-forming bacteria without causing undesirable side effects.*

Immunization

Important approaches to immunotherapy merit intensive research:

* *Development of safe ways to stimulate salivary glands to produce antibodies for preventing plaque formation or protecting against harmful microorganisms. If feasible, this new kind of vaccination could become a public health measure.*

* *Development of ways to counteract allergic reactions of tissues to particular antigens from plaque bacteria. (Antigens are agents that stimulate the production of specific antibodies.)*

* *Supporting studies to identify the key antigens in periodontal destruction, and the processes by which immune reactions to foreign substances become self-destructive.*

RESOURCES

Bringing these research plans to fruition will require trained researchers in pathology, microbiology, immunology, biochemistry, and physiology, as well as in clinical investigation. Special programs are needed to train clinical researchers and to orient basic scientists to the problem of periodontal disease.

Research efforts can be expanded at several centers where periodontal disease programs already exist. Prominent among these sites are the National Institute of Dental Research itself and those Dental Research Institutes established and supported by NIDR in university settings. Three of the latter are already emphasizing studies of periodontal disease.

This proposed program will require substantial increases in funding, as reflected in the appendix.

ULCERS OF THE LIPS AND MOUTH

Few of the common illnesses of man are as baffling to medical science as oral ulcerations. Despite their common occurrence, little is known of their causes. Equally distressing to patient, dentist, and physician is the lack of effective treatment or preventive measures.

These diseases of the soft tissues of the mouth affect, at any given time, 20 percent of the population. About 70 percent of these persons endure recurrent discomfort. Millions of Americans are thus affected in varying degree. Effects range from annoyance through severe pain to possible death in newborn infants, young children, and certain adults.

Of all these complex disorders, only the cause of herpetic infections is well established.

HERPES SIMPLEX

Although other viruses may cause oral infections, the herpes simplex virus is by far the most common. It is estimated that 90 percent of the population carries the virus in a latent form.

The first exposure to this virus, usually in early childhood, produces a primary herpetic infection that can be quite severe. Following this initial attack, the individual becomes a carrier and may suffer repeated, secondary herpetic infections about the nose, lips, and oral tissues. These recurrences, commonly known as cold sores or fever blisters, frequently follow lowered physical resistance, illness, trauma, or emotional stress.

The herpes simplex virus has also been implicated in non-epidemic viral encephalitis, skin disease, and genital and eye infections.

At present, there is no cure for these viral infections, and methods available to control the severity of the infections and discomfort they cause are at best unsatisfactory.

Initiating a Targeted Program for Treatment and Prevention

The oral cavity, with its highly visible structures, presents an ideal workshop for the clinical study of the herpes virus, which affects so many other less accessible vital organs, such as the brain and the eye. In view of recent strides in virology and immunology, it is probable that a major organized research effort in the area of viral diseases of the mouth could lead to early treatment and prevention of not only oral herpes but other general herpetic infections as well as similar virus infections. Recent findings pertaining to the structure, chemical composition, and biosynthesis

of herpes simplex virus, and new information about virally-induced pathology and the immune response to this infection offer promising leads for the development of methods to treat and to prevent it.

An organized program would move along three main lines:

* *Research on development of an effective vaccine to prevent the infection.*

* *Testing and clinical evaluation of anti-viral drugs for effectiveness in treating patients with acute viral infections.*

* *Concurrent studies in human and animal systems to uncover the factors responsible for the occurrence and persistence of these infections.*

Resources

Except for the laboratories and clinics in the National Institute of Dental Research, very few institutions in the United States have established a virus research program concerned with oral diseases. In view of the opportunities to develop more effective treatment and ultimate preventive measures in a relatively few years, a concerted collaborative effort with non-governmental scientists should be launched through expanded grants and contracts. Such a program would require only small increases in the Institute's intramural staff.

APHTHOUS ULCERS

Like herpes simplex, aphthous ulcers, known as canker sores, are a common affliction. However, no specific viral or bacterial agent has yet been found, although one bacterial strain has been suspected as a cause. These lesions usually first appear in the first or second decade of life, develop inside the mouth, and affect between 20 and 50 percent of the population. Frequently, the severe pain they cause makes eating or drinking extremely difficult.

Finding the Cause of the Disease

There is an association between the frequency and severity of the lesions and a number of environmental factors, such as overexposure to sunlight. Abrasions from hard food or from bristles on a toothbrush, allergies to foods,

and endocrine disturbances also sometimes seem to trigger attacks. Another predisposing factor is emotional stress. For example, the disease is more likely to develop in college students during examination periods than during vacation.

As indicated previously, the specific cause of aphthous ulcers remains elusive, and its determination will require an expanded program of research by virologists, bacteriologists, and immunologists. Once the etiologic agent has been identified, steps can be taken to devise more effective treatment procedures and ultimately preventive measures.

Resources

To permit a more intensive focus on this disease, an expanded program of intramural, collaborative, and extramural research will be required. Requested increases are reflected in the appendix.

DEFORMITIES OF FACE AND MOUTH

Facial disfigurement is probably the most tragic of all disabilities. Whereas an abnormal hand may be placed in a pocket, malformed faces and associated speech defects cannot be hidden.

As the fetus develops and grows, genetic and environmental influences determine the degree of "normalcy" of the individual. During this period, the basis is laid for any deformities that will be apparent immediately at birth or in later stages of growth. Thus, cleft lip/cleft palate are evident at the outset, in contrast to malaligned teeth which emerge later.

CLEFT LIP AND PALATE

Of the common oral-facial anomalies, clefts of the lip and palate cause the most severe deformity and impairment of function. Malformed teeth and jaws often accompany the deformed noses and lips characteristic of clefts. A defective palate makes it difficult to speak, breathe, and swallow properly. It also increases susceptibility to upper respiratory infections and hearing problems. Furthermore, psychological counseling for the patient and his family is often necessary for therapy and rehabilitation.

Each year, 6,000 to 7,000 babies join the ranks of over one-quarter million persons in the United States with this deformity. Cleft lip/palate constitutes thirteen percent of all reported birth anomalies. Rehabilitation of a cleft patient involves the coordinated efforts of many specialists and costs around $14,000 through the 18th year. The annual expenditure for those receiving treatment and rehabilitative services is estimated at $100 million.

Improving Treatment

Support for interdisciplinary research in corrective treatment has been well rewarded by development of procedures to enable the affected individual to take a useful and productive position in society. However, further study, necessarily extending over a period of time, is required to determine the best surgical and rehabilitative procedures, and the best timing of treatment. The final evidence of success must depend on the ability of the person with a cleft to eat and breathe properly, speak intelligibly, and fit comfortably into society. Unfortunately, the end results of treatment are still somewhat less than perfect for many reasons. In addition to defects in appearance and speech, patients frequently are ill-prepared for adult life from a psychological and social standpoint.

* *There is need for long-term studies both to evaluate the physical restoration of clefts and to determine the nature and magnitude of the psychosocial problem among late adolescents and young adults.*

* *Further study is also required to better understand, correct, and prevent related speech disorders.*

Preventing Deformity

A large number of oral and facial clefts appear to be caused by the combined effects of many genetic and environmental factors. Adverse effects accumulate to a critical point or threshold beyond which normal development of the unborn child is not possible and an oral cleft results. Slight modification of any one of these factors may reduce the accumulation of influences below this critical point and hence prevent the defect.

Only a bare beginning has been made in research to determine causative factors so that steps may be taken to reduce the incidence of these malformations. To develop the base of knowledge on which preventive efforts can be built, the following types of studies are essential:

* *The factors which predispose a child to develop oral clefts must be differentiated from the environmental hazards which act on the unborn infant. Preliminary studies suggest that families of cleft victims have certain oral-facial deviations that are related to the defect. A thorough analysis of these characteristics would enlarge understanding of the predisposition of clefts, identify high-risk pregnancies, and improve the quality of genetic counseling.*

* *Pregnancy studies of high-risk mothers should be supported to identify hormonal or other metabolic defects which contribute to cleft production.*

* *Studies of afflicted twins and of genealogies, or family trees, in which clefts occur are needed to make better distinctions between hereditary and environmental factors and to examine the nature and relative importance of these factors in different types of clefts.*

* *There is need for comprehensive studies relating incidence and prevalence of oral clefts to various suspected environmental agents. Such epidemiologic studies seem to be the best way to detect and monitor the possible adverse effects of drugs, disease epidemics, environmental pollutants, such as pesticides, and other agents suspected of contributing to birth defects. Some may already have contributed to the apparent increase in oral clefts reported from European centers. No adequate comparable data exist for the United States.*

* *More animal research is needed to show how normal sequences in fetal growth are altered in the formation of various kinds of clefts, and to develop and test preventive therapy.*

Resources

The team approach to clefts requires cooperation between physicians, surgeons, pediatricians, dentists, speech pathologists, psychologists, and others with highly specialized training. Clinical and basic research training for proper study of the cleft patient can be obtained by these specialists at cleft palate centers, many of which are supported by NIDR. However, increased fiscal support for fellowships is required by these centers in order to attract specialists for such training. Additional funds are also needed for new and important research programs at these centers in the vital areas of surgery, speech, and rehabilitation. Other increases would be urgently required to accelerate programmed research efforts in etiology, with special attention to collaboration with bolstered intramural projects, including epidemiologic studies.

One of the existing university-based Dental Research Institutes has ongoing studies in growth and development, and two others have strong resources in this area and should be encouraged to develop active programs. Additional support for individual research grants would be required for this purpose.

OTHER FACIAL MALFORMATIONS

The total number of individuals with severe non-cleft malformations is appreciable. They include a variety of deformities related to more generalized birth defects, as well as those affecting only the facial region. In addition, numerous individuals each year suffer mutilation of the face as a result of injuries or disease, such as cancer, requiring radical surgery. The prosthetic needs of these patients are not being met adequately because suitably

durable materials do not exist and fabrication is time consuming and costly.

* *Further study is required for a better understanding of these birth defects to permit efforts to reduce their incidence.*

* *More emphasis should be placed on the improvement of materials and techniques for prosthetic devices for victims of oral-facial injury or disease.*

The trend for larger cleft lip and palate centers to broaden their research scope to include other facial malformations should be encouraged.

MALALIGNMENT OF TEETH AND JAWS

Most of the people of the world suffer from malocclusion, or bad bite, of varying severity. In addition to varying degrees of disfigurement and associated psychological problems, malocclusion may lead to faulty chewing and speech, as well as predisposing to periodontal disease.

In the United States, about one-third of school-age children suffer from malocclusion severe enough to require orthodontic treatment. Thus, in 1968, some 14 million constituted the group in need of such care. However, the 4,000 orthodontists in practice in that year could treat less than 10 percent of this group. It is estimated that at present over $500 million is spent a year for orthodontic treatment for this small number of patients. Those that receive care are generally in favorable economic circumstances.

Improving and Extending Treatment

Improved methods to predict future facial growth are needed to diagnose and treat malocclusion at the earliest possible time. Today's research is largely biomechanical and only helps to treat the symptoms of this complex disorder. There are practically no studies of its causes. A greater understanding of the growth and developmental process is essential to prevent malformation from occurring in the individual. The development of simpler ways to prevent crowding and to straighten teeth would enable the practitioner to more efficiently treat most types of malocclusion, thus bringing care within the reach of millions now untouched.

The following basic work is needed before clinical studies can be developed to meet the need for early diagnosis and improved therapy:

* *Epidemiological research to measure functional and morphological traits of malocclusion in relation to a variety of biological and psychological parameters. Treated and untreated populations must be compared to determine biological benefits and undesirable side effects of orthodontic therapy. To further these important directions of research, methods are now available to weigh the effects of facial disfigurement on such factors as personality, self-image, attitudes, family background, and education.*

* *Studies of the complex interaction of genetic and environmental influences on pre- and post-natal growth and development of the face to discover what initiates the malformation and how it develops.*

* *Studies of basic biological controls of muscle and jaw growth for potential application in intercepting malocclusion.*

Resources

There is need for more investigators with competence in the clinical area and basic sciences. To produce this manpower will require new training programs in universities and special fellowships to attract scientists, such as biometricians, developmental biologists, epidemiologists, psychologists, and biochemists, to studies relevant to this area of malformation.

Additional funds and staff are needed to fully exploit currently available university resources for the study of malocclusion. Similarly, additional funds, for both direct programs and collaborative research, would enable NIDR, which has unique capabilities in the clinical and basic science fields, to develop coordinated research programs in deformities of the face and dentition. Requested increases are reflected in the appendix.

THE SCIENCE OF MATERIALS AND RESTORATION OF THE MOUTH

Until oral diseases can be completely eradicated, practically every person, during his lifetime, will need some type of restorative material to repair damaged tissues, to preserve the integrity of the mouth, and to restore both function and esthetic appearance. Whether the need arises from tooth loss, congenital malformation, oral cancer, or oral-facial injury, research continues to develop longer lasting, more easily applied materials and improved techniques for such restorations.

It is believed that, if promising research approaches to dental materials problems are vigorously pursued in the next five years, the everday practice of dentistry will advance significantly. Strong emphasis should be placed on the development of adhesive and composite fillings and on the study of artificial implants.

ADHESIVES

The first workshop of experts on biomaterials, convened by NIDR in 1961, called attention to the importance of developing adhesives for such dental purposes as protecting against decay in occlusal (biting) surfaces, serving as a binder in composite filling materials, serving as a liner for fillings, and eliminating the need for orthodontic bands. While attention has been given to all these prospects, the most notable success has been achieved in protecting the biting surfaces of the teeth against decay. This promising development of a sealant is discussed in the section on Dental Caries.

Composite Fillings

Because of the shortcomings of silicates and acrylics, dental scientists over the past 15 years have sought an improved filling for anterior teeth. Development, under NIDR support, of a plastic binder represented an important step forward. This binder serves not only as the basic ingredient of the highly promising plastic sealant currently being tested against tooth decay, but also as the basis for all the composite materials on the market today. Disadvantages inherent in this binder appear to have been largely overcome by a new formulation recently developed by one investigator. A coupling agent which bonds the entire composite filling to tooth enamel or dentin has also been developed. Following successful laboratory tests, clinical trials are now underway.

* *Studies of this type must expand so that new tailor-made composites can be developed both for anterior and posterior teeth. The need continues for easily workable materials that match ideal specifications much more closely than those now available.*

Marine Adhesives

There is a continuous search for suitable adhesive materials for dental purposes. It is believed that adhesive secretions from barnacles, mussels, and other common marine animals might be effective because they stick to a variety of surfaces under water, and remain adherent for many years. While the idea of studying a natural adhesive to learn how to synthesize a tailor-made one for dental use has intrigued many scientists, the possibilities have barely been explored because the chemistry has proved so difficult.

* *Accordingly, there is need to continue as well as expand current efforts to explore the adhesive mechanisms of several different marine animals.*

DENTAL IMPLANTS

Even if no more teeth were lost, the backlog of need for replacement is so great that it would continue to demand attention until the year 2000 A.D. Suitable artificial dental implants could relieve the problem in two ways: by replacing individual teeth; and by serving as anchoring posts to stabilize partial or full dentures. The requirements for successful dental implants are greater than for medical implants completely sealed inside the body's tissues. A dental implant must not only penetrate into bone, but it must also penetrate through the overlying soft tissue and into the mouth cavity, where infection is an ever present danger. Thus, the development of a successful dental implant offers a uniquely difficult research challenge.

While single-tooth implants of plastic have been studied in animals for some time, more recently attention has focused on the possible use of ceramics and metals. Ceramics are also inert and therefore unlikely to be toxic. They hold their colors well, can be made more porous or less porous, and are very hard and durable. Titanium is an example of a good metallic candidate material for dental implants.

Since none of the implant materials seem to adhere to the body's fibers that hold natural teeth firm, investigators hope to gain attachment of artificial teeth by making the roots porous. Recent findings indicate that holes of appropriate size in the artificial root will allow either fibers or bone to grow inward and anchor the implants mechanically. This idea is presently being explored with all three of the materials under consideration. Since there has been little study of implants made of metal and ceramics, it is planned to expand the research program in this direction.

* *Needed research would include, in particular, animal implantation experiments with microscopic studies of the attachment, as well as evaluations of toxicity, and eventually human clinical trials.*

RESOURCES

The proposed expansion of efforts in this field, to be carried out through intramural, collaborative, and grant-supported research, will require additional funds as set forth in the appendix.

BROAD FRONT OF RESEARCH ON ORAL DISEASES
Summary

Diseases and disorders of the mouth and related structures are unique in their characteristics. They have tremendous potential for far outstripping all manpower and financial resources available to cope with them. The need for more effective control and preventive measures is thus urgent and critical. Research leads that hold promise for reducing the incidence and toll of oral diseases are summarized here.

Only brief reference is made to the basic research that undergirds these exciting developments. It should be recognized, however, that the control and prevention of oral diseases is dependent on basic research, the bedrock of all scientific and technological progress. As new insights and understanding emerge from fundamental studies, they progressively advance the state of the art toward ultimate solutions.

This report speaks only to major oral diseases and problems, specifically those aspects that afford the greatest scientific opportunity for solution. It takes note not only of promising leads but also the types of scarce research personnel that will be required to pursue them in the next few years. NIDR scientists and grant-supported investigators have largely laid the foundation of knowledge on which these prospective preventive measures can be built. As they continue to advance the state of the art, new leads will be identified for additional targeted research programs likely to accelerate the conquest of oral diseases.

POTENTIAL PAYOFFS

Pain Control

The problem of pain in dentistry is two-fold. It is symptomatic of certain oral conditions. It is associated, together with fear, dread, and anxiety, with almost all dental procedures. This serious, pervasive problem has been grossly neglected, and any hope for improved care and relief must depend on intensive, systematic study. Plans call for urgently needed studies to determine:

* *Cause of conditions and mechanisms of action in pain associated with oral-facial disorders, to improve therapy*

* *Safety and acceptable techniques for administration of presently available anxiety-reducing agents as well as psychotherapeutic drugs of the future*

* *Problems related to general anesthesia in dentistry and performance of such agents under actual dental treatment conditions*

Dental Caries

Designed to make the universal problem of tooth decay largely preventable, the National Caries Program of NIDR is pursuing promising leads directed toward protecting the teeth, modifying the diet, and combating decay-producing bacteria. Research plans include.

* *Determination of most effective approaches to topical use of fluoride for caries control*

* *Development of optimally effective sealants offering protection against decay for prolonged periods*

* *Assessment of benefits derived from substitution of other types of sugar for caries-producing sucrose*

* *Investigation of effectiveness of dietary additives, such as phosphates*

* *Examination of the effects of trace elements, other than fluorine*

* *Identification of agents which will dissolve or alter composition of caries-inducing bacterial plaque*

* *Studies on effectiveness of agents which would alter the metabolic by-products or inhibit the growth of caries-inducing bacteria*

* *Investigation of particular mechanisms of local immunity to caries*

Periodontal Disease

The chief cause of tooth loss after age 35, periodontal disease, is, in general, poorly controlled, and methods of tooth replacement are often unsatisfactory. New findings on the role of bacteria, inflammation, and other factors hold promise for better understanding and control of this disease.

Plans call for:

* *Expanded studies to identify specific disease-causing bacteria and their mode of action*

* *Intensive studies of factors responsible for degradation of periodontal connective tissue and bone, including the inflammatory process and the production of structure-destroying enzymes*

* *Development of new chemical agents designed to prevent harmful plaque-forming bacteria from adhering to the tooth surface and to suppress their growth.*

* *Development of means to stimulate production of antibodies against harmful microorganisms*

* *Development of ways to counteract allergic reactions of tissues to particular antigens (agents that stimulate production of specific antibodies) from plaque bacteria*

Ulcers of Lips and Mouth

Of all these complex diseases of the soft tissues of the mouth, affecting 20 percent of the population at any given time, only the cause of herpetic infections is well established. Recent advances in virology and immunology hold promise for the success of a targeted program leading to early effective treatment and prevention of herpetic infections not only in the mouth but in other vital organs as well. Plans for an organized program encompass:

* *Research development of an effective vaccine to prevent the infection*

* *Testing and clinical evaluation of anti-viral drugs for effectiveness in treating patients with acute viral infections*

* *Concurrent studies to uncover the factors responsible for occurrence and persistence of infections*

Deformities of Face and Mouth

These problems encompass varying degree of disfigurement and impaired function. They range from cleft lip and palate, which afflict about 7,000 babies each year, to malocclusion, which affects about one-third of school-age children with sufficient severity to require orthodontic treatment. To provide knowledge on which future preventive methods can be built, it is planned to conduct studies to:

* *Differentiate between hereditary and environmental factors in causation of clefts and other oral-facial defects*

* *Better understand factors predisposing to oral-facial anomalies, to make it possible to identify high-risk pregnancies and improve the quality of genetic counseling*

* *Determine how normal sequences in fetal growth are altered in the formation of various kinds of clefts and other oral-facial defects, and develop and test preventive therapy*

* *Better understand, correct, and prevent related speech disorders*

* *Develop improved materials and techniques for prosthetic devices for victims of oral-facial injury or disease*

* *Examine complex interaction of genetic and environmental influences on pre- and post-natal growth and development of face to discover what initiates malocclusion and how it develops*

* *Study of basic biological controls of muscle and jaw growth for potential application in intercepting malocclusion*

Restorative Materials

Scarcely anyone escapes the need for some type of restorative material to repair damaged oral tissues, to preserve the integrity of the mouth, and to restore both function and esthetic appearance. The development of improved dental materials would significantly advance the everyday practice of dentistry. Plans call for expanded studies to:

* *Develop improved filling materials, for back as well as front teeth, that more closely match ideal specifications for function, appearance, and application*

* *Explore adhesive mechanisms of several different marine animals to facilitate development of adhesive material for dental use*

* *Evaluate effectiveness and safety of metallic and ceramic implants in animal experiments and eventually in human clinical trials*

TRAINING

Historically, dentistry has lagged behind medicine in the numbers of research-trained investigators-educators. Thus, today in the United States there is only one dental researcher for every 44 dentists, whereas there is approximately one biomedical researcher for every 7 physicians.

Although an acute shortage of research-trained investigators-educators to staff dental schools already exists, it is expected to become more pronounced in the near future. The nation's 53 currently operating dental schools are now staffed by some 2,500 full-time equivalent faculty members. This figure must be doubled to meet estimated faculty needs of new and expanding schools in the next five years.

In particular, there is great need for clinical scholars with a broad range of training who are capable of coordinating efforts of dental school departments, clinics, centers, and hospital programs, as well as improving dental care delivery systems and contributing significant new research knowledge. To date, dental schools have had to rely to a major degree on part-time practitioners, who lack the necessary training to qualify as educators.

Although productive, NIDR training programs in the past have been unable to provide a sufficient number of personnel required by the dental schools and research institutions, particularly in the clinical disciplines. For this reason, a new type of large-scale training program, which will provide breadth in relevant basic science disciplines while focusing on clinical problems, has now been initiated. Since pain control represents new program emphasis, this important field of study, notably lacking in qualified personnel, requires special support for training as well as research.

RESOURCES

To carry out this five-year plan, NIDR will not only draw on its own scientists but will enlist the talents of investigators in a wide range of academic, industrial, and other research institutions through grants and contracts. The additional resources of NIDR-supported Dental Research Institutes--of which there are five now in existence--also will be used to further these selected research objectives. Because of the special partnership arrangement between the Federal Government and the total university which characterizes these institutes, they represent unique instruments for carrying out targeted types of programs.

Appendix A attached presents, in summary and in detail by major program emphasis, the dollars and positions which will be required to implement the plan set forth in this document.

NIDR FIVE YEAR BUDGET BY SPECIAL EMPHASIS AND SUPPORT PROGRAMS
For House and Senate Appropriations Committees
(In Thousands)

	1971 Amount	1972 Amount	1973 Amount	1974 Amount	1975 Amount	1976 Amount
*SPECIAL EMPHASIS PROGRAMS:						
Pain Control.....	196	1,079	1,779	2,569	3,302	4,035
Dental Caries.....	7,220	10,520	14,800	16,960	19,640	17,750
Periodontal Disease.....	3,725	5,887	7,645	9,693	13,878	17,146
Ulcers of the Lips and Mouth.	305	1,035	2,020	3,070	4,075	4,846
Deformities of the Face and Mouth.....	4,246	5,528	7,052	8,705	10,438	12,292
The Science of Materials and Restoration of the Mouth...	2,756	3,422	4,294	5,412	6,767	8,223
Subtotal, Special Emphasis Programs.....	18,448	27,471	37,590	46,409	58,100	64,292
SUPPORT PROGRAMS UNDERPINNING SPECIAL EMPHASIS PROGRAMS:						
Basic Research Programs.....	7,295	8,671	10,305	12,033	14,120	16,527
Clinical Support Programs....	1,602	1,841	2,189	2,543	2,921	3,398
Dental Research Institutes...	4,700	7,400	8,700	10,900	12,000	13,200
Subtotal, Support Programs.....	13,597	17,912	21,194	25,476	29,041	33,125
Total, Special Emphasis and Support Programs.....	32,045	45,383	58,784	71,885	87,141	97,417

*Amounts for all years include grant-supported, intramural, and collaborative research; training programs and fellowships. See pages 36-41 for itemized budgets.

Program Budget by Fiscal Year
(In Thousands)

Special Emphasis Area: PAIN CONTROL

Activity	1971 Amount	1972 Amount	1973 Amount	1974 Amount	1975 Amount	1976 Amount
GRANTS:						
Research.....	76	301	573	998	1,388	1,738
Fellowships.....	0	50	100	150	180	250
Training.....	0	260	450	600	800	990
DIRECT OPERATIONS:						
Intramural research.....	120	218	331	421	484	557
Collaborative research and development.....	0	250	325	400	450	500
TOTAL ESTIMATE.....	196	1,079	1,779	2,569	3,302	4,035

Program Budget by Fiscal Year
(In Thousands)

Special Emphasis Area: DENTAL CARIES

Activity	1971 Amount	1972 Amount	1973 Amount	1974 Amount	1975 Amount	1976 Amount
GRANTS:						
Research.....	1,900	2,900	3,200	3,300	3,400	3,000
Fellowships.....	360	420	500	560	640	550
Training.....	660	1,000	1,500	1,900	2,400	2,200
DIRECT OPERATIONS:						
Intramural research.....	1,100	1,500	2,200	2,500	2,700	2,500
Collaborative research and development.....	3,200	4,700	7,400	8,700	10,500	9,500
TOTAL ESTIMATE.....	7,220	10,520	14,800	16,960	19,640	17,750

Program Budget by Fiscal Year
(In Thousands)

Special Emphasis Area: PERIODONTAL DISEASE

Activity	1971 Amount	1972 Amount	1973 Amount	1974 Amount	1975 Amount	1976 Amount
GRANTS:						
Research.....	1,684	2,187	2,915	3,822	4,895	5,629
Fellowships.....	417	450	490	525	565	595
Training.....	501	850	1,200	1,700	1,990	2,380
DIRECT OPERATIONS:						
Intramural research.....	1,123	1,600	2,040	2,546	3,428	4,042
Collaborative research and development.....	0	800	1,000	1,100	3,000	4,500
TOTAL ESTIMATE.....	3,725	5,887	7,645	9,693	13,878	17,146

62-645 O - 71 - pt. 3 - 33

Program Budget by Fiscal Year
(In Thousands)

Special Emphasis Area: ULCERS OF THE LIPS AND MOUTH

Activity	1971 Amount	1972 Amount	1973 Amount	1974 Amount	1975 Amount	1976 Amount
GRANTS:						
Research.....	60	360	710	1,160	1,660	2,000
Fellowships.....	15	55	100	140	160	175
Training.....	80	220	410	520	600	695
DIRECT OPERATIONS:						
Intramural research.....	150	300	500	700	805	926
Collaborative research and development.....	0	100	300	550	850	1,050
TOTAL ESTIMATE.....	305	1,035	2,020	3,070	4,075	4,846

Program Budget by Fiscal Year
(In Thousands)

Special Emphasis Area: DEFORMITIES OF FACE AND MOUTH

Activity	1971 Amount	1972 Amount	1973 Amount	1974 Amount	1975 Amount	1976 Amount
GRANTS:						
Research.....	2,542	2,842	3,142	3,592	3,992	4,472
Fellowships.....	132	270	420	580	720	840
Training.....	732	1,200	1,760	2,300	2,820	3,340
DIRECT OPERATIONS:						
Intramural research.....	840	1,126	1,455	1,753	2,096	2,500
Collaborative research and development.....	0	90	275	480	810	1,140
TOTAL ESTIMATE.....	4,246	5,528	7,052	8,705	10,438	12,292

Program Budget by Fiscal Year
(In Thousands)

Special Emphasis Area: THE SCIENCE OF MATERIALS AND RESTORATION OF THE MOUTH

Activity	1971 Amount	1972 Amount	1973 Amount	1974 Amount	1975 Amount	1976 Amount
GRANTS:						
Research.....	1,072	1,413	1,865	2,485	3,193	4,000
Fellowships.....	250	260	280	320	400	460
Training.....	904	984	1,094	1,284	1,570	1,855
DIRECT OPERATIONS:						
Intramural research.....	30	70	120	138	159	183
Collaborative research and development.....	500	695	935	1,185	1,445	1,725
TOTAL ESTIMATE.....	2,756	3,422	4,294	5,412	6,767	8,223

APPENDIX

December 30, 1970
Corrected

TOTAL NIDR FIVE YEAR BUDGET BY TRADITIONAL BUDGET ACTIVITY
For House and Senate Appropriations Committees
(Amounts in Thousands)

Activity	1971 Pos.	1971 Amount	1972 Pos.	1972 Amount	1973 Pos.	1973 Amount	1974 Pos.	1974 Amount	1975 Pos.	1975 Amount	1976 Pos.	1976 Amount
GRANTS:												
Research		15,597		21,720		26,063		31,952		37,072		41,563
Fellowships		1,601		1,686		2,098		2,514		2,940		3,186
Training		5,206		8,100		10,544		13,060		15,656		17,763
DIRECT OPERATIONS:												
Laboratory and Clinical Research	216	4,614	248	6,313	278	8,458	292	10,259	310	12,427	324	14,352
Collaborative Research and Development	9	4,349	15	6,784	22	10,484	25	12,794	33	17,564	40	19,084
Biometry, Epidemiology, and Field Studies	23	678	31	780	40	1,137	40	1,306	40	1,482	40	1,469
Review and Approval of Grants	33	573	39	810	42	963	46	1,162	47	1,258	47	1,472
Program Direction	23	370	25	467	27	568	28	643	31	782	32	866
TOTAL NIDR ESTIMATE	304	32,988	358	46,660	409	60,315	431	73,690	461	89,181	483	99,755

1/ Excludes estimates for General Research Support Grants and Reimbursement to the National Institutes of Health Management Fund for centrally furnished services.

Mr. NATCHER. Mr. Shriver?

WAYS OF EXPANDING ACCESSIBILITY OF DENTAL SERVICES

Mr. SHRIVER. Doctor, during our hearings on maternal and child health programs earlier this year, we heard that one-half of all children under 15 in the United States have never been to a dentist and that the rate is higher for children in rural areas.

I realize your Institute does not get into this phase of dental care. Would you have some suggestion as to how this situation could be remedied particularly in the rural areas?

Dr. KRESHOVER. I think, ultimately, only through the better and the increased utilization of auxiliary personnel, of allied subprofessional personnel supporting the very limited number of professional manpower and dentists that we have available in our country today.

While we could project certainly an expansion of dental schools, an increase reservoir of practicing dentists, it is a firm conviction today I believe of organized dentistry, that it can't do the job without delegating increasing responsibilities to well-trained auxiliaries functioning as paraprofessional personnel under the general direction of professional dentists.

I think only then can we reach into the rural areas, reach into the primary school settings where young children at those vital ages can receive adequate attention.

I think it also would be important to point out that while many of our young people and their families are well aware today, or becoming more aware today, of the importance of retaining their teeth through proper treatment of dental caries, of doing something about periodontal disease, we haven't done nearly enough in the area of malocclusion. The rather costly kind of treatment that is required usually brings benefit only to levels of our society that can afford to go to the orthodontist.

I would remind you that there are some 33 percent of our school-age population in this country, talking about grade school now, i.e. children under 16 years, who require some treatment that is beyond the need for esthetics. These are children in urgent need of treatment for functional reasons.

STATUS OF PAIN RESEARCH

Mr. SHRIVER. It seems to me if the study you mentioned a moment ago relative to pain and discomfort of going to the dentist is successful, both adults and children would probably be more willing to go.

Dr. KRESHOVER. I think, Mr. Shriver, this does give me an opportunity, if I may, to comment very briefly on the new program that we are getting underway now in the area of pain control.

It is an area that has been very sadly neglected in earlier years. We recognize, for example, that there are two kinds of senses of pain that relate to dentistry.

There is the pain that brings a patient to his dentist and then there is the anticipation of pain in the experience of dental treatment that keeps a patient from going to the dentist.

So I think we have a rather important consideration here of pain in two dimensions, at least; one concerned with an understanding of the mechanisms of pain, of how pain occurs, of what we can do about alleviating pain in disease. And the other consideration having to do with the behavioral aspect of what we can do about bringing people to the dentist for treatment, to overcome his anxiety if this is one of the factors, that might keep a patient from going to the dentist.

Mr. SHRIVER. I am sure it is.

How is this study proceeding; or this program?

Dr. KRESHOVER. It is only now getting underway. We have no funding for it at the present time.

Mr. SHRIVER. Is anything in this budget?

Dr. KRESHOVER. The funding is being requested now for the first time in our 1972 budget request before you.

PROGRESS IN SEALANT RESEARCH

Mr. SHRIVER. Can you estimate when the studies on the adhesive sealant will be completed?

Dr. KRESHOVER. It is in progress right now as you know, Mr. Shriver, insofar as clinical trial are concerned. At the present time we are led to believe that certain sealants are extremely effective to the point of some 90-percent reduction in dental decay over the period of 2 years now of observation in the clinical trials we have had underway.

Mr. SHRIVER. How long before it will be available to the public?

Dr. KRESHOVER. I would say, if all things that are underway at the present time have the outcome we would anticipate, perhaps as early as a year from now utilization of sealants may very well be on the open market.

Mr. SHRIVER. This will be available to dentists?

Dr. KRESHOVER. Yes, sir.

Mr. NATCHER. Mr. Hull?

TRAINING FUNDS

Mr. HULL. As in practically every other area we have studied, the funds under this program for fellowship and training have been reduced. With the needs of the Nation as great as they are and with the interest the administration tells us it has for health, how can such action be justified?

Dr. KRESHOVER. The limitation in support for training programs and fellowships, Mr. Hull, that the Dental Institute is experiencing today is only a part of what applies to the NIH across the board.

All of the NIH is currently in a position where Dr. Marston and his staff are assessing training and fellowship programs and we are merely taking our prorated share of the curtailments that apply across the board.

I commented on this earlier before you came into the room.

Dr. MARSTON. Mr. Hull, I think the roughly $900,000 decrease here shouldn't be interpreted as a decrease because this is a part of the $23 million that is transferred to the manpower bureau.

So that while I would agree with your conclusion that the program level in 1972 will be less than in 1971, in general the dollar amounts of support will stay the same although it does show a $900,000 transfer from—I think this is the figure—from the Dental Institute to the manpower bureau.

Mr. HULL. Does the reduction of the fellowship and training programs have any effect on the decisions of such universities as St. Louis University to discontinue their dental schools?

Dr. KRESHOVER. Not directly, sir; no.

NIDR AID TO DENTAL SCHOOLS IN DIFFICULTY

Mr. HULL. Also, what might the Institute do to help schools in such serious difficulties?

Dr. KRESHOVER. There are two kinds of institutions, as you well know. There are the private institutions that depend largely on private endowment for their support and the State-supported institutions that depend largely on appropriations from their State legislatures.

The contributions of the National Institute of Dental Research to these dental institutions is largely, if not entirely, in the area of science for the support and conduct of research and for the training and education of scientists who will make careers in the area of dentistry.

Accordingly, insofar as the educational process is concerned in these institutions, the National Institute of Dental Research can make little impact to influence the capital resources required for their sustenance.

PROPOSED SUPPORT FOR FAILING MEDICAL SCHOOLS

Dr. MARSTON. As far as the manpower activities in NIH are concerned, we have had a growing problem for medical and dental schools who are in financial trouble. As you know, the existing manpower legislation does provide for Federal assistance on the basis of financial problems.

The administration-proposed legislation this year is based, as far as this particular point is concerned, on the concept that the Federal Government should make a clear statement of what its support is going to be. In other words, that we have great trouble in continuing to have the Federal Government plan to bail out any institution that gets into financial trouble for whatever reason.

Therefore, the Secretary and Dr. Endicott have testified to the need for a per capita type of support to institutions which will give a clear indication of what the Federal Government's commitment is to the medical and dental schools. I believe it is a reasonable hope that State and private sources, knowing what the Federal commitment is, will then be in a much better position to decide what their commitment to the support of these institutions is.

We have great trouble, from the standpoint of policy, in being in the position of essentially saying that any institution that gets into trouble can depend on the Federal Government to bail it out no matter what the purposes are. This is one of the key points I think in the whole legislative proposal we have made to Congress this year.

It has been oversimplified by talking about first dollar support versus last dollar support. I suspect that if the two private schools in trouble now had, a number of years ago, been able to plan on the basis of this type of Federal policy, at least their job would have been easier. Don't you think so, Doctor?

Dr. KRESHOVER. Yes.

PREVENTIVE DENTAL CARE

Mr. HULL. On this same line, how many of the diseases the Institute is working on could be avoided by proper early care?

Dr. KRESHOVER. Most certainly adequate care could do much to eliminate from our population certain kinds of periodontal disease which are based principally on an inflammatory process, an infectious process which comes as a consequence of poor oral hygiene.

Second, through adequate care, again, we could do much to prevent tooth decay, dental caries.

We can do little today to prevent, by any kind of control measure or preventive approach, certain soft tissue ulcerations of the mouth, notably herpetic infections. We can also do little today about oral cancer other than early detection through repeated visits to one's physician or one's dentist.

We can do little today to prevent malocclusion or the oral and facial clefts that case such serious deformity; and we can do little today to correct, in a preventive sense, the abnormalities of speech which are so widely spread among our young population.

THE HIGHEST PRIORITY NIDR PROGRAM

Mr. HULL. What is the most serious problem the Institute is working on now?

Dr. KRESHOVER. I would like to think that all of our problems are of a serious nature. The way I would elect to respond to your question is from the standpoint of our priority of attention to cetrain of these areas.

At the present time principal priority is being given the field of dental caries. This is where we have recognized unique opportunities to do something in a reasonably short period of time to, hopefully, completely prevent the disease. This is not to say that some of the other problems that we are confronted with today and that we are trying to do something about aren't also extremely serious.

But from the standpoint of priority, our principal emphasis right now is in the area of dental caries.

Mr. HULL. Thank you, Doctor.

Mr. NATCHER. Mrs. Reid?

OTHER PRIVATE AND GOVERNMENTAL RESEARCH

Mrs. REID. Doctor, did I understand you to say there are no private organizations in dental research?

Dr. KRESHOVER. In the sense that there is an American Cancer Society, a heart association and rheumatism association, dentistry does not have this kind of lay support in an organized sense.

Mrs. REID. What about other Government agencies? Are there any other agencies engaged in dental research?

Dr. KRESHOVER. Yes, Mrs. Reid, there are. Dental research is a very important activity in several branches of the Department of Defense. There is a research institute of the U.S. Army which is at Walter Reed. There is a small research unit concerned with problems of dentistry that is in the Navy at the National Naval Medical Center. The Air Force has a small unit in dental research. The Veterans' Administration also has a small program in dental research. However, compared with the activities that are the responsibility of the National Institute of Dental Research, these are very small indeed.

COORDINATION OF GOVERNMENTAL DENTAL RESEARCH

Mrs. REID. Is there coordination in these efforts and cooperation between the agencies?

Dr. KRESHOVER. The coordination is most informal. It is a community of scientists all of whom in a rather small field like dental science do have an opportunity to get to know each other.

We have many collaborative efforts underway with friends and associates in the several research units that I mentioned.

PROSPECTS FOR PREVENTING TOOTH DECAY

Mrs. REID. You indicated that your emphasis is on preventing dental caries, and last year in response to one of my questions you said you felt dental caries may be preventable by 1980. Do you still feel that way?

Dr. KRESHOVER. We are very optimistic with the science base that is now established. With a concerted effort to bring new knowledge to as rapid a point of application as we can, within the course of the next decade we might very significantly reduce the current prevalence of dental caries. We do not anticipate within this period of a decade that we will find dental caries no longer a disease entity in the sense that we have overcome a problem like poliomyelitis.

Dr. MARSTON. One of the reasons, Mrs. Reid, that one can speak in this way is that we already have a stepping stone that takes us about two-thirds of the way there. If fluoride is universally applied, we will have moved a long way toward taking care of a majority—50 percent to two-thirds—of the problem of dental caries.

This is quite different from some other areas in which we have constantly been cautious about overpromising. We know in dental caries that, on the basis of present knowledge, we already have the information to substantially decrease dental caries in the country.

LAG IN DENTAL RESEARCH

Mrs. REID. Do you feel dental research has lagged in comparison to research in other medical fields?

Dr. KRESHOVER. Yes, it has, for a number of years. The principal direction of emphasis in dental research in the earlier years of dentistry was pretty well characteristic of dentistry as a practicing profession; i.e. it had a great emphasis on technology, the manual arts, the replacement of lost parts with great emphasis on esthetic results.

The upsurge of challenging opportunity and interest that has come to dentistry in recent years has been one that brings it importantly into the broad arena of biology and medicine, one where we recognize that dental diseases are biological in nature, that we do have to understand the nature, the character of disease, the cause of disease, and then to do something ultimately to the point of prevention rather than correction and rehabilitation which has been the principal past emphasis in dentistry.

REDUCING ORTHODONTIC SERVICE COSTS

Mrs. REID. Has anything been done or being done to make orthodontistry less expensive and available to more people?

Dr. KRESHOVER. There is considerable being done in this area. As you have indicated, orthodontic treatment is very costly, and it is very prolonged as far as treatment procedures are concerned. There are new techniques that are being assessed today in the area that we describe as rapid orthodontics. These include such approaches as serial extraction of teeth. Surgical approaches whereby prognathism, or protrusion of the lower jaw, for example, can be corrected, are accomplished by actually cutting through the mandibular bone, removing segments, and sliding the protruding mandible back. I can also cite the opportunities for an orthodontist to utilize auxiliary personnel in his practice, thereby enabling him to see many more patients than he sees right now.

The evidence, as I described earlier, shows that malocclusion as a serious defect affects many more of our child population in the country than one would expect by seeing the number of children without braces and the relatively few who do have orthodontic care today. The figure I mentioned earlier was that some 33 percent of our school-age children in this country urgently need orthodontic care, not for reasons of aesthetics, not to correct something that would bring greater beauty to a child, but rather because of functional disturbance, an inability to chew properly, ill effects as they relate to nutrition and to speech.

LIMITED ACCESSIBILITY OF SERVICES

Mrs. REID. The reason they don't have this treatment is because of the——

Dr. KRESHOVER. Accessibility largely. The fact that there is great clumping of our dental manpower resource in the metropolitan areas. The fact that specialists seek opportunities to practice in metropolitan areas and in settings where medical centers and dental schools exist.

We are not getting adequately into the rural areas; we are not reaching the mass of our child population as urgently as they require this kind of attention today.

NEED TO INCREASE THE DENTIST SUPPLY

Mrs. REID. I asked a question last year about the number of graduating dentists, whether they have kept pace with the increase in the population and you indicated last year you felt they had.

Do you feel that is still true?

Dr. KRESHOVER. The total dental student enrollment today in our 53 operating dental schools is some 16,000 which means we are graduating each year something in the range of 3,500 to 3,700 students. The number of dentists in supply today are just slightly over 100,000.

We recognize that today we perhaps need closer to 120,000 to do the job that has to be done.

Mrs. REID. This would cover all specialties?

Dr. KRESHOVER. This would be across the board, covering all specialized areas.

It has been projected that by 1980, at the present rate of expansion of our dental schools, we will only have increased by some 17,000 dentists. In other words, we might have close to 119,000 dentists in functioning duties by 1980 whereas we would project a need for some 175,000 dentists by that time.

I think this is a misleading picture if we comment only on professional dentists because we do need, as I indicated earlier, allied personnel to do the job that must be done with increased responsibilities, delegated duties.

It has been projected that from the current supply of some 140,000 allied personnel, we must go by 1980 to something in the range of 340,000 allied auxiliary personnel.

Mr. MICHEL. Are orthodontists considered to be dentists, Doctor?

Dr. KRESHOVER. Yes, they are.

DELEGATION OF RESPONSIBILITY TO ALLIED PERSONNEL

Mr. SMITH. Before you leave that question, isn't it true that the dental profession generally is making much greater progress in using allied personnel than the medical profession?

Dr. KRESHOVER. In some ways, Mr. Smith, I believe the dental profession is. I believe it has now had a long experience in the training of allied personnel. The principal problem is not so much the training of allied personnel but rather the selling of the concept of a delegation of increasing responsibility to allied personnel.

In this regard I don't think it would be at all fair to say that dentistry stands in a position ahead of many of the fields of medicine.

My grandmother, for example, was a midwife married to a physician and we were rather ashamed in the family that we had a grandma who was a midwife. Today midwifery is coming into its own I gather.

Mr. SMITH. The State regulations and so forth do not present the barrier for dentists they do for the medical profession.

Dr. KRESHOVER. There is a very serious barrier in terms of licensure. Dental hygienists in many States, even though they are given the opportunity to assist dentists in the care of the mouth through prophylactic procedures, for example, are not permitted by law to go below

the gum line or the free margin of the gingiva. There are very rigid laws.

Mr. SMITH. They have been able to delegate and statistics show they are using more allied personnel without the need for changing State laws.

Dr. KRESHOVER. I would not be surprised a lot of this is with us today, but as far as broad acceptance by our States' licensure groups are concerned, we have not yet reached the time in dentistry when the hoped for scope of delegated responsibilties has been achieved.

Mr. SMITH. Are you doing anything in your shop to help promote whatever changes are needed to permit greater delegation?

Dr. KRESHOVER. Primarily this is being exercised through the American Dental Association and also the Division of Dental Health which is a component of the Bureau of Health Manpower Education contained within the new structure of the National Institutes of Health. Possibly that will be described later.

Dr. MARSTON. I would agree wholeheartedly that, through the so-called four-handed dentistry programs that have been sponsored by the Bureau and the ADA, we have a much clearer idea of what would be a good and workable system of dental assistants than we do in medicine.

We have the Duke program and we have a number of other programs in medicine to train individuals who help doctors, such as orthopedic and pediatric assistants. But we are much further along in the field of dentistry in having a clear concept of what would be a workable and beneficial group of individuals to augment markedly the dentists in the country.

As you know, we are pushing this quite hard in the field of dentistry whereas in medicine there is still some uncertainty whether a system that works in a rural practice in North Carolina is going to be as useful in a hospital practice in an inner-city. So, we are trying a variety of experiments.

PROMOTING WOMEN IN DENTISTRY

Mr. SMITH. Is there any substantial progress being made in overcoming the barriers that keep women from going into dentistry in greater numbers?

Dr. KRESHOVER. We still have a long way to go if we are going to catch up, for example, to the Scandinavian countries and to the number of women dentists in Latin America. I can't give you specific statistics. All I can say is that as I visit our dental institutions in this country, there are more women studying dentistry. Whereas a single women in a dental class would have been an unusual occurrence some 10 years ago, I believe that most dental schools today would be able to enjoy at least, and that is a good word, as many as a half a dozen women per class of 90 to 100.

Mr. NATCHER. Mr. Patten.

ACCIDENT TOOTH PROBLEMS

Mr. PATTEN. Some of the worst dental problems come from automobile accidents. They claim about 55,000 people are killed annually in the United States from auto accidents. We must have had hundreds of thousands with fractured jaws and severe damage.

I think many of the dentists right now are in the operating room taking care of matters that came as a result of accidents. Yet you haven't given us one suggestion for new devices under your new program. We are going to have seat belts.

Do you think we ought to ride around with a mask like the goalie on the New York Rangers to protect our teeth? Probably you do have thoughts on that.

I am concerned about my senior citizens. Many of our people are afraid to go to the dentist because they can't afford the cost.

In all of my time in industry they have a doctor available, medical service, but I never heard of any of them having a dentist around or giving dental care.

CANCER OF THE MOUTH

You mentioned the fact that it is so imperative to have early diagnosis of cancer. Your figures absolutely amaze me—they were so small. 12 fellows in my group have been cut for cancer in the mouth. In every case nobody saw it until it was really late and the cutting had to be severe.

So the thought comes to me what can we do, how many dentists today would recognize cancer if they saw it early? It would strike me early inspection would save many a heartache.

You say in 90 percent of the early cases you have a satisfactory result, but you didn't make a suggestion as to what we should do day in and day out.

Dr. KRESHOVER. We do with regard to smoking in oral cancer. One of the most serious lesions that is identified in the mouth is so-called leucoplakia. This is a white patch that appears on the soft tissues usually on the inside of the cheek, on the tongue, on the lips. It is notoriously prevalent among smokers, particularly pipe smokers, and has a significant incidence of malignant transformation.

Mr. NATCHER. Mr. Conte?

NIDR'S FIVE-YEAR DENTAL RESEARCH PLAN

Mr. CONTE. Last year the committee asked the Institute to submit a realistic plan for the optimum development of the Nation's dental research effort during the next 5 years. I know that it is being placed in the record, but would you summarize the main recommendations of

this plan for the committee, please? How much would it cost to implement these recommendations?

Dr. KRESHOVER. The plan to which you refer, Mr. Conte, reflects the professional judgment of the Institute's leadership with advice and consultation from the National Advisory Dental Research Council. In accordance with the committee's request, the plan speaks to the optimum development of the Nation's dental research effort during the next 5 years. Since it is an Institute document, I would like to emphasize that it should in no way be interpreted or considered as an official or endorsed proposal from either the NIH or the Department of Health, Education, and Welfare.

By way of summary then, Mr. Conte, the plan emphasizes major oral diseases and problems, and specifically calls attention to those aspects which promise the greatest opportunity for solution. It identifies six major fronts of scientific attack and notes any promising leads which now exist as well as the manpower resources required to pursue them.

Pain in dentistry is a serious and pervasive problem which has been grossly neglected. It is associated, together with fear, dread, and anxiety, with almost all dental care. Our plans then call for urgently needed studies to improve therapy in relieving pain associated with oral-facial disorders, to develop safe and acceptable techniques for administration of anxiety-reducing drugs, and to assess the problems related to the use of general anesthesia in dentistry.

In another special emphasis area referred to in this report, the Institute is actively pursing research leads which hold promise of making the universal problem of tooth decay largely preventable by the end of the decade. It has focused its efforts on three prime targets: protecting the teeth, modifying the diet, and combating decay-producing bacteria. With adequate budgetary support, we continue to believe that dental caries will be very greatly reduced as a serious and significant public health problem by 1980.

As I'm sure this committee knows, Mr. Conte, the chief cause of tooth loss after age 35, periodontal disease, is, in general, poorly controlled, and methods of tooth replacement are often unsatisfactory. However, I firmly believe that new findings on the role of bacteria, inflammation, and other factors hold real promise for better understanding and prevention of this disease.

In a fourth special initiative area described in our 5-year report, we emphasize that diseases of the soft tissues of the mouth, notably including certain ulcerations, affect some 60 percent of the population, with complications ranging from annoyance through severe pain to possible death. It is significant, therefore, that recent advances in virology and immunology hold promise for the success of a targeted research and development program leading to early effective treatment and prevention of herpetic infections not only in the mouth but in other vital organs as well.

In the important area of oral-facial growth and development, deformities of the face and mouth range from cleft lip and palate, which afflict about 7,000 babies each year, to malocclusion, which affects about one-third of school-age children with sufficient severity to require

orthodontic treatment. Our 5-year report points up, Mr. Conte, the knowledge upon which future preventive methods can be built.

Turning now to the final area of attention described in our 5-year plan, I would say that scarcely anyone escapes the need for dental fillings and other materials to repair damaged teeth and other oral tissues, to preserve the integrity of the mouth, and to restore both function and esthetic appearance. Accordingly, the development of improved dental materials, as they would significantly advance the practice of dentistry, is an especially high priority effort of our Institute at this time.

The appendix to the plan which has been prepared for this committee includes the dollar figures we estimate as necessary to implement our recommendations. Full implementation of all the recommendations in fiscal year 1972 would require $10 million above that provided in the budget which is before you. The proposed distribution in the program areas is detailed in the 5-year report. Again, Mr. Conte, I would emphasize that these are my personal professional judgment figures and go well beyond the current fiscal 1972 budget request before the committee that I believe provides good opportunity to move forward in certain key program areas of very high priority.

TOOTH DECAY IN ADULTS AND CHILDREN

Mr. CONTE. How serious a problem is tooth decay for adults as compared with children?

Dr. KRESHOVER. Epidemiological studies have shown that the prevalence of dental caries increases with advancing years, beginning in early childhood. However, the rate of increase, which incidentally varies in different ethnic groups, tends to slow in adult years. This is especially so in the 25- to 35-year age span. While these surveys show general trends of incidence and prevalence, it is of some interest to point out that in some populations where caries is low, the progression of disease may be very minimal following the appearance of the initial lesion. This could, I would suppose, be interpreted as a building up of resistance to caries with advancing age. With regard to the seriousness of dental caries in young versus older people, it is well established that involvement of the primary dentition, or so-called baby teeth—particularly in the event of a subsequent pulp or root apex infection, or loss of the tooth itself—can have very damaging effects on the development and ultimate position and alinement of the succeeding permanent teeth which erupt into the mouth after shedding of the deciduous or baby teeth. However, it should be pointed out that caries at any age is a serious matter.

PERCENT OF POPULATION HAVING FLUORIDATED WATER

Mr. CONTE. What percent of the U.S. population live in areas where there are fluoridated water supplies?

Dr. KRESHOVER. Mr. Conte, at the present time approximately 78 percent of the U.S. population live in communities with public water systems, and of this number, about 47 percent—or approximately 80

million people—receive the benefits of optimal fluoride levels in controlled programs where fluorides are added to the water as required for the desired protective effect. An additional 6 percent of the population living in areas with public water systems have the benefit of optimal fluoride levels that are naturally present. This leaves some 48 percent of our population who reside in areas with public water systems that do not have adequate levels of fluoride to provide protection against dental caries. Just to round out the picture, it should be recalled that some 44 million people in this country live in areas that have no public water systems and, therefore, must depend upon other measures for adjustment of fluoride levels where optimal amounts are not present in the drinking water from wells and springs.

STATE OF DEVELOPMENT OF ADHESIVE SEALANT

Mr. CONTE. When will your large-scale clinical studies regarding the effectiveness of the new adhesive sealant be completed and how soon could it be made available to the general public?

Dr. KRESHOVER. In a previous appearance before this committee, Mr. Conte, I reviewed the promising results of a study then underway under the direction of Dr. Buonocore at the Eastman Dental Center in Rochester, N.Y., which showed a protection against caries in young children of more than 95 percent. This study, covering a 2-year period, tested an adhesive sealant of acrylic composition which requires an ultraviolet light exposure to bring the soft plastic, painted on the tooth surface, to a condition of hardness. It is significant that the coating is able to stay firmly in place for as long as 2 years. Although these excellent results are unquestioned, we are currently watching with great attention the outcome of similar clinical trials to confirm the Rochester findings under different conditions of community use; where, for example, we will know that other dental personnel can apply the technic with equal effectiveness in different populations. I would hope, as I said earlier in answer to a similar question from Mr. Shriver, that in about a year from now this adhesive sealant technic might be ready for widespread use. It should be pointed out, however, that we are currently supporting other studies to evaluate different chemical formulations of adhesive sealants that will take somewhat longer to establish clinical effectiveness. In general, our approach today is to examine not only different therapeutic benefits of sealants but also the very practical feature of whether their effectiveness can be demonstrated in community situations under varying conditions of use.

AVERAGE LIFE OF AMALGAM FILLINGS

Mr. CONTE. What is the average lifespan of amalgam fillings and by how much do you think it can be increased?

Dr. KRESHOVER. It has been said, not without some truth, that the average lifespan of amalgam restorations is 35 years, plus or minus 34. While this is a most confusing statistic, it does demonstrate several things; the most important perhaps being the factor of how variable is the skill of the dentist in preparing the filling and placing it ex-

pertly in the patient; and also the fact that there are a number of different amalgam products on the market, and these also may vary appreciably in their quality and performance characteristics. It is coincidental that only a few months ago the Dental Institute held a workshop which brought together many experts in this field, and the consensus was that not only is our knowledge of the long-term effectiveness of amalgam restorations deficient, but high priority must be given to the support of research that will assure its improvement in physical and chemical properties. Regrettably, despite the widespread use of amalgam alloy in dentistry throughout the world, its deficiencies are a cause of frequent failure with consequent occurrence of new carious lesions. Also, the related cost for replacement is severe. While much too early to give you detailed information, recent research offers some promise of a new composite amalgam possessing properties that increased its resistance to corrosion, fracture, and crushing forces, as well as giving it higher tensile strength. Such developments offer reasonable promise that amalgam alloys with long-life effectiveness may shortly be available.

DETECTION OF PERIODONTAL DISEASE

Mr. CONTE. How soon must the common form of periodontal disease be detected before it causes irreversible damage to the teeth?

Dr. KRESHOVER. I should point out first, Mr. Conte, that there are many kinds of periodontal disease just as there are many kinds of cancer, and that the term periodontal disease, used in the singular, is merely a catchall title for what are probably a variety of lesions and disease entities. The most common of these is chronic periodontitis which, in this country, seems to have its greatest prevalence and severity in persons over 35 to 40 years of age. While the consequences of lost teeth and other possible systemic damage from the infectious and inflammatory process of periodontal disease are particularly evident in adulthood, it should be borne in mind that when this stage is reached, the disease is frequently irreversible.

Studies in India, Ethiopia, Thailand, and other countries, as well as more limited observations in the United States provide important evidence that periodontal diease all too frequently strikes during childhood. Indeed, one study in this country shows an incidence of as much as 50 percent in a 6- to 17-year-old group. Obviously then, Mr. Conte, diagnosis can and must be made early in life if successful treatment is to be instituted.

ENVIRONMENTAL FACTORS IN ORAL CLEFTS

Mr. CONTE. What are some of the environmental factors that appear to cause oral and facial clefts?

Dr. KRESHOVER. It is extremely difficult, Mr. Conte, to separate or distinguish the so-called environmental factors as causes of cleft lip and palate from genetic influences. It is primarily for this reason—to understand the seemingly complex interplay between hereditary and environmental factors—that we have been intensively studying the

problem in experimental animal model systems. As I pointed out earlier this morning, there is good evidence today that a variety of so-called environmental factors may combine with genetic components to cause oral-facial clefts. Among these are certain drugs with particular chemical configurations, amniotic sac pressure, stress to the pregnant mother, and positioning of the fetus with respect to pressures transmitted to the tongue and its interference with midline palatal closure and fusion.

RELIABILITY OF ORAL PRECANCER SCREENING TECHNIQUES

Mr. CONTE. How reliable and useful are present screening techniques for identifying individuals who may have precancerous areas in their mouths?

Dr. KRESHOVER. Since oral cancer, as I believe I had occasion to emphasize in my testimony last year, affects some 16 males and three females for every 100,000 adults in this country and causes about 7,000 deaths each year, the importance of early diagnosis and treatment cannot be overemphasized. Also, since clinical studies have clearly shown the precancerous nature of several types of mouth lesions, most notably leukoplakia—which is characterized by a rough white patch on the mucosa—and so-called submucous fibrosis, it is most urgent that frequent and regular examinations by both the dentist and physician be sought by everyone regardless of sex or age. The importance of this is perhaps best demonstrated by the 90 percent of males with lip cancer who can enjoy so-called 5-year cures because of early diagnosis and treatment.

Screening examinations for oral cancer should be available in the offices of appropriately trained dental practitioners, and if not, should be made possible by consultation with or referral to a competent doctor. Certainly, there is adequate experience, to date, to show the effectiveness of the so-called exfoliative cytological techniques which are merely microscopic examinations of cells that are shed or obtained from a suspected tissue surface by scraping. It should be pointed out that this simple procedure is not necessarily conclusive in itself, but rather provides an early warning signal to proceed with a biopsy examination by a competent surgeon and pathologist. Since the availability of oral cancer screening programs must be expanded, it is important, in further answer to your question, Mr. Conte, that the Dental Institute initiate studies along this line.

RESEARCH IN DENTAL ANESTHESIOLOGY

Mr. CONTE. What effect does your present evidence indicate that anesthetic agents have on ambulatory patients?

Dr. KRESHOVER. I should say at the outset, Mr. Conte, that there are many reasons that the Dental Institute must give high priority attention to the subject of anesthesiology and the entire field of pain control, of which it is an integral part. These are touched on in our 5-year report that you already asked me about. Although a principal reason for study of this subject is how little we know about it, the extensive use of anesthesia in dentistry—both local and general—emphasizes the

need for not only better undersanding of the physiological effects of currently used agents, but the development of improved ones. Among the requirements of anesthetic agents for dental use is that their administration not interfere with free access to the site of operation or treatment; that is, the mouth; and also that the anesthesia be in as light a plane as possible and with little or no aftereffects so that the patient can be truly ambulatory. Some of the effects to be guarded against are, of course, alterations in blood and pulse pressure, abnormal changes in oxygenation of the blood, and electrocardiographic and electroencephalographic changes. While anesthetic agents in current use, if expertly applied, are safe indeed, we must, nevertheless, continue to search for even more effective drugs and techniques of application.

SHORTAGE OF CLINICAL INVESTIGATORS

Mr. CONTE. How severe is the current shortage of competent clinical investigators?

Dr. KRESHOVER. While I can offer no specific numbers, by actual count, to demonstrate the severe current shortage of clinical investigators, the dearth of qualified scientists to extend basic knowledge of disease mechanisms gained in our basic science laboratories to clinical programs of testing and demonstration is all too apparent. This need is particularly evident in studies of dental caries, periodontal disease, oral ulcerative lesions, and the complex variety and expressions of congenital oral-facial malformations. Not only is it important to increase this scientific manpower resource, but our expanding and new dental schools which will provide academic instruction for tomorrow's professionals must have clinical faculty well grounded in research methodology. For these reasons, the Dental Institute is looking particularly to clinically oriented departments in graduate school settings; to a variety of training programs in such essential fields as speech, epidemiology, behavioral science, orthodontics, surgery, and clinical pathology; and to the recently established clinical training program cooperatively directed by Harvard University and the Forsyth Dental Center.

REASONS THAT COMMUNITIES FAIL TO FLUORIDATE

Mr. CONTE. What are the reasons why water fluoridation may not be practical in certain areas of the country?

Dr. KRESHOVER. The answer to your question, Mr. Conte, was, of course, partially touched on in my earlier comments regarding fluoridation in general. In the first place, I can think of no reason whatever for fluoridation not being immediately instituted in every community in this land that has a public water system furnishing drinking water to its inhabitants that does not already have a naturally occurring optimal level of one part per million of fluoride.

Quite obviously the principal and invalid reason for this not being the case is the dissemination of false propaganda kinds of information to communities that allow themselves to be mislead and confused on an issue that has been scientifically tested.

With regard to other reasons for the benefits of water fluoridation not being utilized, I would cite inaccessibility of certain regions to modern water distribution systems as most important. In such instances, alternative measures of fluoride application could and should be used, as, for example, by tablet ingestion, or individual home fluoridation units where well or spring water supplies are used. I should also add at this point, Mr. Conte, that our Institute is supporting a controlled study in Colombia, South America, on the use of table salt as a vehicle for fluoride when water fluoridation is not feasible.

Mr. CONTE. Thank you.

Mr. NATCHER. We want to thank you and your associate, Dr. Kreshover, for appearing before the committee at this time.

Dr. KRESHOVER. Thank you very much.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Amounts Available for Obligation

	1971	1972
Appropriation	$35,257,000	$38,829,000
Real transfer to:		
"Departmental management"	-10,000	---
Real transfer from: "National Institute of General Medical Sciences" (Proposed transfer for increased pay costs).	+183,000	---
Comparative transfers to:		
"Office of the Director"	-31,000	---
"National Library of Medicine"	-112,000	---
"Health Manpower"	-985,000	---
Comparative transfer from:		
"Health Manpower"	+401,000	---
Total obligations	34,703,000	38,829,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
115	Research		$16,962,000		$18,886,000		+$1,924,000
	General research support grants		(1,028,000)		(908,000)		(-120,000)
	Categorical clinical research center		(380,000)		(380,000)		(---)
	Dental research institutes		(4,700,000)		(6,200,000)		(+1,500,000)
123	Fellowships		1,601,000		1,367,000		-234,000
125	Training		4,285,000		4,285,000		---
	Direct operations:						
127	Laboratory and clinical research	216	5,937,000	219	6,547,000	+3	+610,000
130	Collaborative research and development	9	3,877,000	11	5,408,000	+2	+1,531,000
132	Biometry, epidemiology and field studies	23	747,000	26	938,000	+3	+191,000
133	Review and approval of grants	33	852,000	33	929,000	--	+77,000
134	Program direction	23	442,000	23	469,000	--	+27,000
	Total obligations	304	34,703,000	312	38,829,000	+8	+4,126,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	304	312	+8
Full-time equivalent of all other positions	16	16	--
Average number of all employees	310	319	+9
Personnel compensation:			
Permanent positions	$4,324,000	$4,775,000	+$451,000
Positions other than permanent	131,000	155,000	+24,000
Other personnel compensation	56,000	60,000	+4,000
Total personnel compensation	4,511,000	4,990,000	+479,000
Personnel benefits	513,000	554,000	+41,000
Travel and transportation of persons	178,000	233,000	+55,000
Transportation of things	46,000	54,000	+8,000
Rent, communications & utilities	120,000	156,000	+36,000
Printing and reproduction	67,000	76,000	+9,000
Other services:			
Project contracts	3,360,000	4,760,000	+1,400,000
NIH management fund	1,751,000	1,909,000	+158,000
Other	626,000	687,000	+61,000
Supplies and materials	490,000	568,000	+78,000
Equipment	196,000	307,000	+111,000
Grants, subsidies & contributions	22,848,000	24,538,000	+1,690,000
Deduct quarters and subsistence charges	-3,000	-3,000	---
Total obligations by object	34,703,000	38,829,000	+4,126,000

Summary of Changes

1971 estimated obligations	$34,703,000
1972 estimated obligations	38,829,000
Net change	+4,126,000

	Base		Changes from Base	
	Pos.	Amount	Pos.	Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase cost	---	---	---	+$196,000
2. Annualization of positions new in 1971	---	---	---	+54,000
3. Within grade increases	---	---	---	+138,000
4. FTS rate increase	---	---	---	+12,000
5. Extra day of pay	---	---	---	+13,000
B. Program:				
1. Research grants	---	16,962,000	---	+2,188,000
2. Laboratory and clinical research	216	4,491,000	+3	+250,000
3. Collaborative research and development	9	3,849,000	+2	+1,500,000
4. Biometry, epidemiology and field studies	23	678,000	+3	+150,000
C. Payment to "National Institutes of Health management fund" for centrally furnished services	---	1,706,000	---	+158,000
Total, increases	---	---	+8	+4,659,000
Decreases:				
A. Built-in:				
1. Research grants	---	16,962,000	---	-144,000
B. Program:				
1. Research grants	---	16,962,000	---	-120,000
2. Fellowships	---	1,601,000	---	-234,000
3. Laboratory and clinical research	---	4,491,000	---	-35,000
Total, decreases	---	---	---	-533,000
Total, net change	---	---	+8	+4,126,000

Explanation of Changes

Built-in increases--These increases will provide $196,000 for annualization of 1971 pay increase; $54,000 for annualization of new positions in 1971; $138,000 for within grade increases effective in 1971; $12,000 for increased costs in 1972 of using the Federal Telecommunications System; and $13,000 for extra day of pay in 1972.

Research grants--The increase of $2,188,000 includes $638,000 for competing grants in the regular program and $1,500,000 for continuation requirements in the Dental Research Institute program. The request also includes a decrease of $264,000 of which $120,000 is in general research support grants, a program included in each NIH appropriation containing research grant projects, but administered separately by the Division of Research Resources, and a built-in decrease of $144,000 in noncompeting requirements in the regular program.

Fellowships--The decrease of $234,000 represents a reduction of 10 fellowship awards in the regular program to a 1972 level of 82 awards.

Laboratory and clinical research--The increase of $250,000 and 3 positions will allow for expansion of research in dental caries under the National Caries Program. The increase is offset by a decrease of $35,000 in non-initiative programs. There is also a program increase of $78,000 in the NIH management fund for centrally furnished services.

Collaborative research and development--The increase of $1,500,000 and 2 positions will provide funds to support contracts related to the cause and prevention of dental caries under direction of the National Caries program.

Biometry, epidemiology and field studies--The increase of $150,000 and 3 positions will allow for expansion of field studies related to research under the National Caries Program.

Significant Items in House and Senate
Appropriation Committee Reports

Item	Action Taken or to be Taken
1971 House Report	
1. Committee urges the Institute to consider how greater emphasis might be applied to research in Periodontal disease. (Page 21)	1. Basic research has produced a body of knowledge which can be further developed with the expectation that by 1980, means will have been found for making dental caries almost completely preventable. Unfortunately a similar body of knowledge does not yet exist on periodontal disease. The Institute will continue to pursue basic research in this area in the hope that promising leads for prevention and control of periodontal disease may be found.
2. Committee hopes that the Institute will give greater emphasis to research on causative factors with the ultimate goal of preventing cleft lip and cleft palate. (Page 21)	2. The Institute will give high priority to research grant applications and other research efforts which focus on the genetic and environmental causes of cleft lip and cleft palate.
3. Committee asks the Director of the Dental Research Institute to submit a realistic plan for the optimum development of the Nation's dental research effort during the next five years. (Page 21)	3. Based on his professional judgement and the advice of the National Advisory Dental Research Council, the Director has submitted a 5-year plan for the optimum development of the Nation's dental research effort.
1971 Senate Report	
1. The Director of the Dental Research Institute should submit a realistic plan, based on his professional judgement and the advice of the Institute's Advisory Council, for the optimum development of the Nation's dental research effort during the next five years. (Page 38)	1. Based on his professional judgement and the advice of the National Advisory Dental Research Council, the Director has submitted a 5-year plan for the optimum development of the Nation's dental research effort.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation Requested
Public Health Service Act		
Section 301--Research and Investigation, in general	Indefinite	$38,829,000
Title IV, Part C--National Institute of Dental Research	Indefinite	$38,829,000

PUBLIC HEALTH SERVICE ACT

The legislative authority which provides for the award of grants for research, research training, and fellowships is included in section 301 of the Public Health Service Act.

The Public Health Service Act, Title IV, National Research Institutes, Part C, National Institute of Dental Research--

"Section 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').

"Section 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 non-profit institutions."

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer to:		
Departmental management	-$10,000	To establish the Facilities Engineering and Construction Agency.
Real transfer from:		
National Institute of General Medical Sciences	+183,000	Proposed transfer for increased pay raise costs.
Comparative transfer to:		
Health Manpower	-985,000	Transfer of institutional support funds to Health Manpower.
Office of the Director	-31,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director.
National Library of Medicine	-112,000	To provide an equitable distribution of the Management Fund in 1972.
Comparative transfer from:		
Health Manpower	+401,000	Transfer of research and training grants from Dental Health.

National Institute of Dental Research

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$13,933,000	$14,681,000	$20,000,000	$17,340,000
1963	17,199,000	19,199,000	22,199,000	21,199,000
1964	19,809,000	19,689,000	19,809,000	19,689,000
1965	20,209,000	20,090,000	20,190,000	20,190,000
1966	22,177,000	22,177,000	23,677,000	23,677,000
1967	24,884,000	28,308,000	28,308,000	28,308,000
1968	30,307,000	30,307,000	32,307,000	30,307,000
1969	30,414,000	29,553,000	30,414,000	29,983,500
1970	29,289,000	29,289,000	32,000,000	30,808,831
1971	34,563,000	35,257,000	36,257,000	35,257,000
1972	38,829,000			

National Institute of Dental Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	304	$5,024,000	312	$5,544,000	+8	+$520,000
Other expenses.....	---	29,679,000	---	33,285,000	--	+3,606,000
Total.....	304	34,703,000	312	38,829,000	+8	+4,126,000

General Statement

The National Institute of Dental Research conducts and supports basic, clinical, and applied research and research training, in the causes, diagnosis, prevention, and cure of oral diseases and disorders: (1) intramural laboratory, clinical and field research is conducted, (2) dental and medically-related research and research training is supported by assisting individuals, universities, institutions, and agencies through grants-in-aid for research projects, training, fellowships, and dental research institutes, (3) collaborative and developmental research programs aimed at specific dental problems are conducted and supported, and (4) dissemination of research findings and related information is supported. The improvement in oral health of all individuals through the greater understanding of the biological phenomena underlying oral diseases and disorders, and the advancement of capability for the diagnosis, treatment, and prevention of oral disease constitute the long-range objectives of the Dental Institute.

Tooth decay ranks equally with impaired eyesight and defective hearing as widespread health problems. This major health problem spares only two per cent of our total population, occupies over half of the average dentist's time and afflicts 50 per cent of our children under two. The dentist's chair alone cannot provide the solution to this problem.

Development of a scientific base of knowledge which will permit significant advances against dental caries has paralleled somewhat the upsurge in demand for health care. Prospects are promising for success of an accelerated and concerted attack against this disease. Dental caries may be almost completely preventable within the next decade by exploiting this base of knowledge by a vigorous research effort. An increase of $2,900,000 is included in these estimates for further expansion of the National Caries Program to enable the Institute to accelerate the development and application of knowledge in anticipation of eradicating tooth decay.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Research projects	$10,854,000	$11,398,000	+$544,000
Special programs	5,108,000	7,488,000	+1,380,000
Total research grants	16,962,000	18,886,000	+1,924,000

Introduction

Research grants are used to support a broad range of scientific investigations encompassing both basic and clinical studies. These projects, ranging from highly focused studies to multidisciplinary programs, have the ultimate goal of yielding new treatment techniques and preventing the various dental diseases and conditions which affect nearly everyone in the course of a lifetime. Research grants support scientists or groups of scientists at universities, dental and other colleges, hospitals, research institutions, and other nonprofit institutions.

The Extramural Programs have been restructured recently into six major areas more representative of clearly delineated programmatic goals. These categorical areas are:

Dentitional Diseases Program
Periodontal Diseases Program
Developmental Biology and Oral-Facial Anomalies Program
Biomaterials Program
Soft Tissue Stomatology Program
General Oral Sciences Program

As a new mechanism of research support, the National Institute of Dental Research initiated in FY 1971 a Special Dental Research Award Program to stimulate and help newly-trained investigators remain active in dental research. These investigators represent a vital resource for maintaining an adequate science base in the field of oral health. A number of these small grants are included in the research grants distribution tables under the item listed as competing projects.

Program Plans for 1971 and 1972

Dentitional Diseases Program

This program, formerly the Dental Caries and Hard Tissues Program, places major emphasis on dental caries but also encompasses research on tooth abrasion, tooth erosion, and research on the properties and composition of teeth.

Dental caries is a complex disease involving an interrelationship between the host, diet, and microorganisms. Scientific evidence indicates that the lesion or cavity results after bacteria ferment carbohydrates, producing acid which dissolves the enamel.

To make the most effective use of available research grant funds, investigators, in 1972, will be encouraged to undertake research which offers the best hope of developing an easily-applied and inexpensive caries prevention method. Investigators will be particularly encouraged to develop and test new antibiotics and new antibacterial agents which will either

specifically prevent the growth of cariogenic organisms or suppress the formation of plaque. Encouragement will also be given for new research proposals designed to develop and test sealants to protect the tooth surface from the acids produced by organisms in the mouth.

Search will also continue for a better understanding of the role of salivary factors in dental caries, and of natural dietary factors in the development of caries-resistance and susceptibility. Research on the mechanisms of fluoride action will also continue with the anticipation that the knowledge gained can be used to establish rapid laboratory methods for screening other potential anti-caries agents.

Periodontal Diseases Program

Periodontal disease is the oral condition which affects the gums and other supporting tissues which hold the teeth in place. Since this disease is the main cause of tooth loss in adults past thirty-five years of age, it represents a major health problem in the nation and world. Currently, two out of every three Americans over 40 years of age suffer from this insidious disease. Moreover, it is estimated that more than 25 million persons are in critical need of periodontal treatment. Without treatment, periodontal disease attacks relentlessly and causes progressive infection, inflammation, and loss of teeth. With the increasing life span of the average citizen, more and more people have periodontal disease. Thus, it is imperative that research on the disease process be expanded, so that rational programs of control and prevention can be developed.

Ongoing studies on the nature of periodontal disease are continuing to examine various phenomena which seem to be involved in the pathologic sequence. In exploring the questions of which bacteria cause the disease and what the disease mechanisms are, both germ-free rats and experimental human subjects are being studied in highly controlled situations. The human studies have indicated that Gram-negative bacteria alone can cause gum inflammation, the first stage of periodontal disease. In germ-free rat studies, pure cultures of certain oral organisms isolated from humans have caused periodontal disease whereas other human and animal organisms did not. Further study in humans and germ-free rats during the coming year is expected to produce information that will clarify these findings.

It is believed that the earliest changes in periodontal disease are brought about by bacterial substances which directly damage the surface epithelium. Such injury allows bacterial endotoxins, antigens, enzymes, chemotactic agents, and yet unknown toxins to penetrate more easily into the periodontal tissues and set off a chain of host inflammatory events which are primarily immunological in nature. In the coming year research will concentrate heavily on continued studies of the inflammatory process and the role of the immune system. Specific substances involved in immunologic inflammation will be searched for and measured in the diseased tissues themselves. Studies will be made of how these substances are related to structure-destroying host enzymes. Approaches will also be made to discover how certain white cells of the body's infection-fighting system, such as neutrophils and lymphocytes, may participate in disease. With increased emphasis in research on molecular mediators of inflammation it may be possible to eventually develop and use specific inhibitors and anti-inflammatory agents in treatment of the disease.

Expansion of studies to understand and control the factors responsible for the degradation of connective tissue and bone have been marked for immediate emphasis during the next year. Plans are being made to develop a multi-disciplinary approach to the response of connective tissue to inflammation

with particular attention to those factors contolling the production of collagenase and other enzymes which degrade connective tissues, and bring about loss of supporting bone.

Developmental Biology and Oral-Facial Anomalies Program

The Developmental Biology and Oral-Facial Anomalies Program (formerly the Oral-Facial Growth and Development Program) supports research on hereditary and environmental factors which cause oral-facial malformations. It is hoped that these investigations will lead to effective and feasible preventive measures. This program area also seeks to increase research efforts directed toward improved treatment for both esthetic and functional deficiences.

Groups of consultants have been convened over the past few years for the purpose of ascertaining the "state of the art" in these problem areas. These scientific assessments have been useful and effective in program planning.

Developmental Biology

Research in developmental biology--in embryology and genetics, for example--will continue to be supported so that more knowledge can be gained about the development, growth, and eruption of teeth. These biological processes have a bearing not only on malocclusion, but on many other oral disabilities. Thus, investigations supportive to the broad area of oral-facial growth and development will continue to be funded. Included are studies of normal and abnormal growth, development, and function of the oral-facial complex.

Cleft Lip/Palate

The support of two research areas which are highly pertinent to the rehabilitation of an individual afflicted with cleft lip/cleft palate will continue to be highlighted. Whether a clefted person can speak clearly or whether this speech is nasal and hard-to-understand depends in large part on the effectiveness of surgery to close the cleft. Assessment of surgical techniques will thus continue to receive attention. Also, long-term, follow-up studies on late adolescents and young adults will be pursued to determine the nature and magnitude of psychosocial problems associated with lip and palatal defects.

With emphasis on prevention, studies to better identify and understand environmental and genetic factors which predispose the child to develop cleft lip/cleft palate will be strongly encouraged.

Malocclusion

Severe malalignment of teeth and underdeveloped or overdeveloped jaws affect the child at an early age. These disfiguring conditions threaten the mental health of the individual as well as affecting speech and other vital functions of the mouth and dentition. In the next year, epidemiological studies will be supported in order to assess both prevalence and severity. In addition, longitudinal studies of oral-facial growth and development will be continued because the knowledge to be gained should help orthodontists better predict growth and thereby make for more simplified treatment methods.

Biomaterials Program

The objective of this program is to increase the availability and efficacy of dental care by fostering the development of new and improved materials and methods of treatment. Under this mission, support is provided to

both basic and applied research projects which involve a multitude of physical and biological disciplines.

Since the specialized tissues of the mouth cannot replace themselves when they are lost, repairing the damage from dental diseases relies largely on the effective use of restorative materials.

The most conspicuous research progress made in this program area and perhaps in the whole arena of dental research has been the continued success of studies in which the biting surfaces of teeth have been protected against decay for two years by a coating of plastic. This study has progressed sufficiently well to warrant large-scale field trials involving hundreds of human subjects. Several such studies are already underway. It is fully expected that expanded use of the preventive measures developed in this project will have a strong impact in reducing the number of teeth lost from decay throughout the world.

More effective and efficient dental adhesives, either for sealing the biting surfaces against decay or for sealing the margins of fillings, are being sought continuously from various sources. In one approach, studies are being made of sea animals that produce compounds which stick under water. This year two contracts to explore the adhesive mechanisms of seven or more marine animals were initiated. In order to fully examine the feasibility of this promising idea, it is planned to expand and continue these efforts for at least the next two years.

While artificial dental implants made of plastic have received investigative attention in animals for nine years and are now about to be assayed in humans, dental implants of metal and ceramic have not been adequately studied. This year widespread research interest has been expressed in the possibilities of titanium and calcium aluminate ceramic implants of defined porosity. It is anticipated that several promising projects will get underway this year.

Soft Tissue Stomatology Program

Oral Ulcerations

Diseases of the oral soft tissues affect 20 percent of the population at any given time, and about 70 percent of these individuals experience recurring episodes. These diseases create significant problems for approximately four million Americans. Symptoms range from severe pain, in the case of acute ulcerative conditions, to possible death in newborn infants and children. With one exception, the causes of ulcerative disorders of the oral soft tissues are unknown. The exception is primary and recurrent herpes simplex, one of the most common virus infections of man. Thirty percent of the young adult population in the United States suffer from recurrent attacks which are characterized by swollen lips, itching, burning, pain, and possible disfigurement. More severe cases are accompanied by fever, fatigue, and emotional trauma. In addition, these individuals have difficulty in eating and speaking. While the oral cavity is the primary site for herpes simplex virus infections, there is mounting evidence that this virus is also the causative agent of (1) infections of the eyes (repeated attacks are known to produce blindness); (2) non-epidemic viral encephalitis (often resulting in death); and (3) viral-induced skin disease. More recently, this virus has been implicated as a life-threatening factor in patients on a regimen of immunosuppressive drugs employed in the treatment of systemic disorders and organ transplants. There is speculation that the virus also may play a role in carcinoma of the cervix. Finally, the Epstein-Barr (EB) virus, which resembles herpes simplex virus, may be the etiologic agent for infectious mononucleosis and Burkett's lymphoma, a neoplastic condition of the jaw.

Support of research on the pathology, etiology, epidemiology and prevention of oral soft tissue lesions is of major concern to the National Institute of Dental Research. Therefore, the Institute will continue to encourage research programs and collaborative studies leading to the cure, and most importantly, the prevention of recurrent herpetic disorders.

Oral Cancer

It is estimated that in 1970 there will be over 15,000 new cases and 6,800 deaths from cancer of the oral cavity and pharynx. Oropharyngeal cancer is not one of the major causes of death but there are few, if any, diseases which cause greater disfigurement. People who die from this disease, about half of all patients, experience a lingering and painful death.

If cancer is not detected early and is allowed to grow to a large size (one inch in diameter) before it is treated, a surviving patient may have to face life with only half a tongue, part of a jaw, part of a face and in many cases, devoid of a larynx (voice box). These patients have a major problem in readjustment, as do their families and business associates. To rehabilitate such a person and make his appearance acceptable often requires long periods of expensive plastic surgery or costly maxillo-facial prosthetic devices which need constant attention and frequent replacement.

On the other hand, if oral cancers are diagnosed and treated early, over 90 percent can be arrested by simple, local removal of the cancerous growth. In most patients who undergo early treatment for cancer, there is no mutilation and the surgery performed does not interfere with normal speech and eating. A major problem in early diagnosis is the 18-20 percent of all adults who have, within the mouth, a wide variety of benign (non-cancerous) lesions, only a small portion of which ever develop into cancer.

The National Institute of Dental Research will support program efforts to:

1) develop new and inexpensive screening techniques to identify individuals who may have precancerous areas in their mouths, and
2) continue studies concerned with changes occurring in premalignant and malignant oral tissues (leukoplakia, leukoedema, and erythroplasia).

Salivary Gland Disorders and Saliva

Millions of microorganisms, including pathogenic viruses and bacteria, are constantly entering the human body through the mouth. Ordinarily, these organisms would produce local and systemic deseases were it not for the protective influence of the oral secretions. When the salivary glands do not function properly, the body's resistance to infection is lowered. Research programs into the nature, structure and function of the major salivary glands and their secretory products are being actively supported.

Saliva is one of the body fluids which contains an antibody called immunoglobulin A (IgA). This substance has recently been identified as one of the biological agents which has the capacity of rendering viruses and bacteria incapable of inducing pathogenic infection. Paradoxically, IgA is also implicated in autoimmune and hypersensitivity reactions which may precipitate pathologic conditions such as aphthous stomatitis and Behcet's disease in humans. Studies on the mechanisms of IgA synthesis in and secretion from salivary gland cells will provide information essential to the major program proposed for the control and prevention of oral ulcerative conditions attributable to herpes simplex virus.

Emphasis will continue to be placed on studies to elucidate the role of the autonomic nervous system in salivary functions. This information will provide a baseline for clinical diagnosis and treatment of a wide range of salivary dysfunctions such as hypotyalism seen in the aged.

One of the more recent and more important areas of salivary gland research involves non-cancerous lesions and diseases which appear as enlargement of the salivary gland. Although these diseases are common, their etiologies are largely unknown. It is planned to support a limited number of grants to define the pathogenesis of these problems.

Dental Pulp Studies

The dental pulp offers an experimental model of value in studying the effects of various stimuli (physiological, neurohumoral and pharmacological) on circulation and the effects of changes in circulation on the repair of dental structures. Support of programs in this area along with basic scientific studies of blood vascular dynamics of the pulp chamber and neurohumoral aspects of the pulp will continue at a modest level. A limited number of training programs in endodontic research will also be supported.

General Oral Sciences Program

This program area was newly established by the Institute during the latter portion of FY 1970 to bring together those extramural research activities that either lacked clear relevance to a particular disease-oriented program area or had significance for more than one of the disease-oriented program areas. It encompasses those basic biological and behavorial sciences of greatest relevance to our understanding of oral and dental diseases.

Pain Control and Anesthesiology

Because of the centrality and critical importance of the problem of pain to dentistry, broad investigations of etiology and control, including anesthesiology, have high program priority. A particular research gap is the need to gain a better understanding of the cardiovascular effects of widely used dental anesthetic agents on ambulatory dental patients. Such patients leave the dental office within an hour after surgery and expect to resume their normal activities at least by the next day. Most of the previous work in this field has been devoted to hospitalized patients, and evidence exists to suggest that the effects on ambulatory patients may be quite different. Accordingly, continuing efforts will be made to further develop this important field.

In the related area of local anesthesia, the effects of various local and systemic factors that may influence the duration of intraoral anesthesia produced by various agents are being investigated.

Other General Oral Biology Studies

A basic project of potentially great significance being supported involves the study of the regulation of blood flow in the gingival microcirculation. This work could shed new light on the role of the host in the etiology of periodontal disease.

Dental Research Institutes

Five institutes or centers are being supported in 1971. Their research programs are continuing to be developed and expanded into new areas. The number of collaborative programs is increasing, not only to utilize appropriate strengths existing in surrounding institutions, but to make the resources of the

institutes available to these institutions. The centers are beginning to have a strong impact on dental education in dental schools associated with them. Highly qualified teachers, who would not otherwise be available to the dental schools, are helping to produce curriculum changes resulting in increased awareness and understanding of the importance of research to high quality dental health care.

While the institutes are increasingly playing an important role as regional centers, the need for a larger function is becoming apparent. In an area which has been historically deficient in research, as contrasted with medicine, and which is characterized by care problems of grave magnitude, these institutes must serve as national resources. They have clearly demonstrated their potential for assuming this responsibility.

Each institute is individualistic and is addressing its program to different aspects of the total oral health problem. One institute, for example, is concerned with in-depth studies of the cranio-facial region, from which hopefully will emerge new insights leading to new diagnostic, therapeutic, and preventive approaches to a great array of problems of growth and development.

In 1972, four of the institutes will be moving into their second five-year periods of support, while the fifth will be in its third year of development. Additional funds will be used to further expand and strengthen these five programs. Emphasis will be placed on building strong clinical research components related to the basic research programs of the centers. It is essential to correlate the accumulation of basic and clinical knowledge to provide a more rapid benefit to the public through improved oral health care.

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting continuations	134	$8,158,000	126	$8,014,000	-8	-$144,000
2. Competing projects	49	2,571,000	76	3,259,000	+27	+688,000
3. Supplementals	(8)	125,000	(1)	125,000	(-7)	---
4. Subtotal regular program	183	10,854,000	202	11,398,000	+19	+544,000
5. General research support	---	1,028,000	---	908,000	---	-120,000
6. Categorical clinical research centers	1	380,000	1	380,000	---	---
7. Dental Research Institutes	5	4,700,000	5	6,200,000	---	+1,500,000
8. Total research grants	189	16,962,000	208	18,886,000	+19	+1,924,000

Research Grants Program Analysis

	1970 Actual	1971 Estimate	1972 Estimate	Increase or Decrease
Dentitional Diseases Program..	$3,116,000	$3,915,000	$4,354,000	+$439,000
Periodontal Diseases Program..	1,323,000	1,357,000	1,357,000	---
Developmental Biology and Oral-Facial Anomalies Program.....	2,455,000	2,525,000	2,525,000	---
Biomaterials Program.....	1,201,000	1,525,000	1,630,000	+105,000
Soft Tissue Stomatology Program.....	997,000	1,022,000	1,022,000	---
Oral Neoplasia.....	105,000	89,000	89,000	---
General Oral Sciences Program.....	421,000	421,000	421,000	---
Subtotal regular program.....	9,618,000	10,854,000	11,398,000	+544,000
General research support grants.....	1,119,000	1,028,000	908,000	-120,000
Scientific evaluation grant...	42,000	---	---	---
Categorical clinical research centers.....	337,000	380,000	380,000	---
Dental Research Institutes....	3,400,000	4,700,000	6,200,000	+1,500,000
Total research grants.....	14,516,000	16,962,000	18,886,000	+1,924,000

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Total fellowships.....	$1,601,000	$1,367,000	-234,000

Program Plans for 1971 and 1972

The shortage of trained clinical investigators, well-grounded in research methodology and able to engage in new and imaginative programs to solve oral health problems, is of paramount concern. The funds available for fellowships will therefore be used largely to train clinical investigators. Postdoctoral and special fellowships, as well as research career development awards, will be used for this purpose.

Fellowship Program Analysis

Fields	1970 Actual	1971 Estimate	1972 Estimate	Increase or Decrease
1. Dentitional Diseases Program....	$234,000	$244,000	$204,000	-$40,000
2. Periodontal Diseases Program....	243,000	255,000	215,000	-40,000
3. Developmental Biology and Oral-Facial Anomalies Program.....	381,000	398,000	358,000	-40,000
4. Biomaterials Program.....	119,000	125,000	75,000	-50,000
5. Soft Tissue Stomatology Program.....	378,000	396,000	356,000	-40,000
6. General Oral Sciences Program.....	174,000	183,000	159,000	-24,000
Total.....	1,529,000	1,601,000	1,367,000	-234,000

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting.....	58	$1,033,000	57	$1,054,000	-1	+$21,000
b. Competing.....	3	35,000	3	37,000	-	+ 2,000
2. Supplementals.....	(5)	5,000	(5)	6,000	-	+ 1,000
3. New awards.....	36	528,000	22	270,000	-14	-258,000
Total fellowships.....	97	1,601,000	82	1,367,000	-15	-234,000

Fellowships (By Type of Program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Predoctoral.....	5	$28,000	2	$11,000	-3	-$17,000
2. Postdoctoral.....	29	251,000	27	241,000	-2	-10,000
3. Special.....	26	369,000	24	368,000	-2	- 1,000
4. Development awards.....	33	831,000	25	625,000	-8	-206,000
5. Career awards.....	4	122,000	4	122,000	-	---
Total fellowships.....	97	1,601,000	82	1,367,000	-15	-234,000

Training Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Total training grants.....	$4,285,000	$4,285,000	---

Program Plans for 1971 and 1972

The training programs of the National Institute of Dental Research have had a singular impact upon dental education and research in this country. By adding to the sparse supply of trained dental school faculty, they have contributed to the better preparation of a greater number of students for professional practice. They have also made it possible for scientists from various disciplines to contribute their talents to the solution of complex oral problems of overwhelming dimensions.

As public demand for dental care increases, the need for dental research training becomes even more compelling. In particular, there is a critical lack of competent clinical investigators, with strong backgrounds in the sciences and in-depth training in the clinical specialties, to develop new preventive and control measures that will diminish the need for care. The first trainees of two combined PhD-DDS training programs, begun in 1964 and 1965, are now being graduated, but their number is necessarily limited.

NIDR will seek to expand its efforts to produce competent clinical investigators. A major step in this direction was taken during Fiscal Year 1970, when a new training center was established in a large university-hospital consortium.

Distribution of Training Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting.....	83	$3,817,000	65	$3,353,000	-18	-$464,000
b. Competing.....	2	78,000	12	474,000	+10	+396,000
2. Supplementals.....(16)		350,000	(13)	300,000	(-3)	-50,000
3. New grants.....	--	---	4	118,000	+4	+118,000
4. Scientific evaluation....	(1)	40,000	(1)	40,000	--	---
Total training grants.	85	4,285,000	81	4,285,000	-4	---

Training Grants (By Type of Programs)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Graduate Training Grants:						
1. Basic sciences.....	67	$3,353,000	63	$3,320,000	-4	-$33,000
2. Clinical sciences.....	18	892,000	18	925,000	--	+33,000
3. Scientific evaluation...	(1)	40,000	(1)	40,000	--	---
Total training grants.	85	4,285,000	81	4,285,000	-4	---

Laboratory and Clinical Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	216	$3,496,000	219	$3,799,000	+3	+$303,000
Other expenses	---	2,441,000	---	2,748,000	--	+307,000
Total	216	5,937,000	219	6,547,000	+3	+610,000

Introduction

As in previous years, the public health mission of the intramural research program continues to be that of developing new information regarding the cause of a variety of oro-facial malfunctions, including dental caries, periodontal disease, oral cancer and abnormal oro-facial developments. Clearly, the ultimate aim is to achieve new and more effective means of treatment and/or prevention of these physically and economically debilitating conditions.

The causation of each of the abnormal states listed above is most certainly attributable to multiple factors, about which all too little is known. In most, the factors involved have not yet been defined adequately enough to yield promise of immediate evolution into preventive measures. As a consequence, the intramural research approach involves a tripartate commitment of its resources to basic laboratory investigations; to clinical and applied investigations relating to the solution of specific questions which stem from progress made at the basic level; and to epidemiologic and field studies directed toward: (1) clinical trials of newer therapeutic or preventive concepts, which have evolved from basic and applied studies; or (2) further definition of the nature and distribution of oro-facial disease on an epidemiologic or geographic basis.

With specific regard to dental caries, however, this systematic research approach has, over the past 20 years, led to the aquisition of a substantial body of knowledge concerning the etiology and pathogenesis of the disease. Largely on the basis of this accumulated information, a more directed effort toward the eradication of caries as a public health problem has now been undertaken. In 1968 the Dental Institute initiated a National Caries Program, guided by a Caries Task Force, involving all relevant scientific competencies within the total Institute. This program has the highest priority in the utilization of intramural manpower and resources.

Program Plans for 1971 and 1972

Intramural Contribution to NIDR's National Caries Program

The expanded intramural effort in dental caries, now an integral aspect of the Institute's National Caries Program, is directed toward the attainment of a more thorough understanding of oral bacteria; specifically, those strains of oral streptococci which appear to be integrally involved in the etiology of caries. These organisms are characterized by their ability to adhere tenaciously to the enamel surface, as a component of dental plaque; by preferential utilization of dietary sucrose for their growth and metabolism; and, most significantly, by their propensity for producing large amounts of acid as a consequence of sucrose metabolism. It is the latter property,

coupled with the close enviornmental relationship to the tooth surface, which presumably renders these organisms highly cariogenic. Their cariogenicity has been amply demonstrated in animal experiments. Indeed, organisms of similar properties have been isolated from human caries lesions and shown to produce caries when implanted in the mouth of test animals, including monkeys.

Recognizing that specific organisms may be the key to dental caries, research is being focused on areas which will serve to define more precisely their absolute role in the caries process, to determine the efficacy of local treatment by antibiotic or by related bactericidal agents; and to test new biological approaches aimed at altering the metabolism of the organisms so as to render them harmless. With regard to the latter approach, Institute scientists are now much involved in experiments relating to the possible efficacy of a specific enzyme dextranase, whose chief effect would be that of preventing the adherence of streptococci to the tooth surface, thereby breaking the vicious circle of events which seems so essential to their role in the genesis of decay.

Topical application of fluoride in fitted vinyl mouthpieces, undertaken in the school enviornment with appropriate professional supervision, has already been shown to exert striking benefits to children of primary school age in areas where water fluoridation is not practicable. These long-term studies are being further expanded to determine whether the benefits of topical application in mouthpieces augment those already extant in areas where community water supplies are fluoridated. Another program of considerable promise is related to an assessment of the long-term benefits which the topical mouthpiece method may provide to preschool children who have not yet developed their adult dentition.

In the absence of complete public acceptance of water fluoridation as a public health measure and in view of economic and logistical factors which militate against achieving total effectiveness for this mode of delivery in any case, intramural research efforts to develop alternative methods of protection which might supplement or some day even supplant water fluoridation are continuing. For the coming year particular emphasis will be directed toward the study of nutritional supplements, including trace elements and phosphate compounds with specific regard to determining the basis for their apparent anti-caries activity in animals and the degree to which this action may be extended to the human situation.

A question of fundamental importance to the Caries Program is now receiving concerted attention by intramural scientists. This relates to the development of valid diagnostic criteria for dental decay; criteria which can be applied prior to the time that frank decay occurs. Virtually all clinical trials relating to the testing of new therapeutic measures for decay prevention currently depend upon analysis of full-blown lesions in the tooth, which have progressed beyond the point of reversibility. Since the decay process is a relatively slow one, and since significant amounts of dental caries must be present in order to derive accurate statistical inferences, trials of this sort currently require a minimum period of two years. Accordingly, it is of both practical and ethical importance to establish standards which can be applied long before the irreversible stage of decay has been reached.

Periodontal Disease

With the growing concern regarding the role of dental plaque in the etiology of dental caries has developed an increasingly attractive hypothesis that similar adherent masses of bacteria, food debris and gummy materials which comprise the plaque may, over a period of some years, be instrumental in initiating gingival inflammation, and ultimately, periodontitis. Research results have already indicated quite clearly that the organism or organisms

involved in periodontal disease do not resemble the streptocci which are now being scrutinized with respect to caries. On the other hand, a specific filamentous microorganism, previously isolated from human diseased gums, has how been shown in experimental animals to elicit a disease state closely resembling periodontal disease. It shares with cariogenic streptococci the capacity for producing large amounts of gummy extracellular material which, as in the case of the streptococci, also tends to hold the organisms in the close approximation to the tooth surface at and below the gingival margin. Research continues with respect to the basic characteristics of this organism, and increased emphasis is being given to the possibility that its occurrence and its deleterious effects may be facilitated and/or enhanced by pre-existing dental plaque containing cariogenic streptococci. These two aspects of the Institute's research effort, both bearing on dental plaque as the common denominator in caries and periodontal disease, are being carried on in close and effective collaboration.

In addition, basic and clinical studies with respect to the biology of the gums and adjacent tissues continue to provide information which may ultimately contribute to preventive and therapeutic approaches to periodontal disease from the point of view of increasing host resistance to the infectious process. Major support will be given to the ongoing effort to define the nature of those factors, particularly intrinsic enzymes, involved in normal synthesis and breakdown of the major structural proteins of the gums (collagen and elastin), functions which are seriously distrubed in periodontal disease.

Oral Cancer

Delineation of the unique properties of the oral mucous membrane appears essential to any ultimate understanding of malignant change in the mouth. Studies of this type will be continued although at a lower level of activity than in previous years.

Growth and Development

Disordered oro-facial growth is manifested as a spectrum of malfunction, ranging from seriously handicapping cleft palate to malocclusion. Research efforts directed to the goal of providing a more rational understanding of the genesis of these conditions remains a significant aspect of intramural programs.

The role of genetic factors, as defined by laboratory, clinical and field studies of animals and man, continues to be the subject of systematic exploration by intramural scientists. Similarly, the role of environmental factors, particularly those which may exert a deleterious influence during embryonic development, continues to be explored. These studies have now been extended to non-human primate species, in order to obviate doubts which have arisen as to the applicability to man of results derived from studies of lower animal forms.

The net increase of $610,000 includes $250,000 and three positions for program increases, $104,000 for cost of within grade increases, $9,000 for extra day of pay, $32,000 for annualization of positions new in 1971, $120,000 for annualization of 1971 pay increase, and $152,000 for centrally furnished services from the National Institutes of Health management fund. These increases are offset by a decrease of $57,000 in non-initiative programs.

Collaborative Research and Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	9	$197,000	11	$255,000	+2	+$58,000
Other expenses	---	3,680,000	---	5,153,000	--	+1,473,000
Total	9	3,877,000	11	5,408,000	+2	+1,531,000

Program Plans for 1971 and 1972

The Institute's resources for collaborative research and development are largely focused on the special initiative program to prevent or control dental caries within this decade. Accordingly, the National Caries Program of the NIDR will be expanded pursuant to the plan prepared for the Secretary of Health, Education, and Welfare in January 1970. With the advice and endorsement of the institute's advisory committee ("Caries Task Force") the following categorical areas in collaborative research and development will be augmented under the anticipated increases.

Dentobacterial plaque prevention--More extensive and intensive studies, laboratory and clinical will be mounted in such areas as antimicrobial agents, metabolic regulators, enzymatic plaque removal, and immunological methods.

Tooth surface protectors--Additional developmental projects, field investigations, and clinical trials will be initiated with respect to sealants, plaque repellent surface modifiers, and fluorides.

Dietary additives--Further laboratory studies and clinical trials will be conducted on such dietary factors as phosphates, trace elements, sugar substitutes, and antimetabolites.

Multifactorial oral health procedures--Studies will be mounted involving a combination of two or more procedures such as restoration of carious areas, oral hygiene procedures, topical fluoride, and use of adhesive sealants.

Epidemiology--Surveys will be made to obtain more accurate prevalence data in unique populations, root caries surveys, and microbiological surveys.

Basic investigation--Expansion of studies of tooth transplant rejection.

A portion of collaborative funds would be used also to augment basic investigations representing direct extensions of ongoing intramural projects.

In addition, modest expansion is planned for research and development of promising new adhesive restorative materials. By reducing the sacrifice of sound tooth in cavity preparation, such materials should greatly prolong the useful life of the teeth. Concommitantly, the cost of restoring teeth damaged by caries would be reduced by simplifying the preparation of cavities for filling and by reducing the frequency with which fillings would need replacement.

Research contracts will continue to be utilized as the principal mechanism for field studies and applied research.

The increase of $1,531,000 includes $1,500,000 and two positions for the National Caries Contract Program, $8,000 for within grade increases, $8,000 for annualization of positions new in 1971, $13,000 for annualization of 1971 pay increase, and $2,000 for centrally furnished services from the National Institutes of Health management fund.

Biometry, Epidemiology and Field Studies

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	23	$450,000	26	$536,000	+3	+$86,000
Other expenses	---	297,000	---	402,000	--	+105,000
Total	23	747,000	26	938,000	+3	+191,000

Program Plans for 1971 and 1972

These funds will provide support for the scientific staff in the design and subsequent analysis of a wide variety of complex experimental investigations, ranging from basic to clinical. Especially essential at this point in time is the role of the Institute's biometric arm in the formulation and analysis of field investigations relating both to factors affecting the prevalence of oral disease in the population at large, and to the effectiveness of new or improved means, agents, or techniques of diagnosis and/or control of oral disease.

In concert with the Institute's ongoing National Caries Program effort, program emphasis will focus on expanded field trials of various caries preventive measures, including the enzyme dextranase.

Similarly, field studies of children and adults will be implemented with respect to the prevalence of cariogenic bacteria of the oral streptococcal type in humans. Of particular importance is the need of attaining more precise information regarding: (1) the mode of transmission of the organism; and (2) the degree of correlation between the severity of dental decay and the extent of streptococcal infection.

The increase of $191,000 includes $150,000 and three positions for expansion of research under the National Caries Program, $1,000 for extra day of pay, $14,000 for annualization of positions new in 1971, $13,000 for annualization of 1971 pay increase, $8,000 for within grade salary increases and a net increase of $5,000 for centrally furnished services from the National Institutes of Health management fund.

Review and Approval of Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	33	$507,000	33	$558,000	--	+$51,000
Other expenses	---	345,000	---	371,000	--	+26,000
Total	33	852,000	33	929,000	--	+77,000

Support for the administration of extramural programs, including research grants, fellowships and training grants, is provided by these funds. Development, review, and evaluation of these programs are the responsibility of the Institute staff and the National Advisory Dental Research Council. Continued surveillance of scientific activities and progress is maintained in addition to recording and reporting the scientific and fiscal data pertinent to all grants.

The increase of $77,000 includes $2,000 for extra day of pay, $8,000 for within grade pay increases, $12,000 for FTS cost increase, $39,000 for annualization of 1971 pay increase, and $16,000 for centrally furnished services from the National Institutes of Health management fund.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	23	$374,000	23	$396,000	--	+$22,000
Other expenses.....	---	68,000	---	73,000	--	+5,000
Total.....	23	442,000	23	469,000	--	+27,000

These funds provide for the support of the Institute Director and his immediate staff. They, in turn, are responsible for the administration and coordination of Institute programs, monitoring new developments in dental research in this country and abroad, and for providing leadership in new approaches to scientific investigations; the advancement of academic science, and the augmentation of the dental research manpower resource of the country.

The increase of $27,000 includes $1,000 for extra day of pay, $10,000 for within grade pay increases, $11,000 for annualization of 1971 pay increase, and $5,000 for centrally furnished services from the National Institutes of Health management fund.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Research Grants. (Public Health Service Act, Part IV, Part C)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$16,962,000	Indefinite	---	$18,886,000

Purpose: Research grants support fundamental, clinical and applied research studies in such areas as dental caries, periodontal disease, oral-facial growth and development and dental restorative materials. Support is furnished for studies designed to advance scientific frontiers and exploit emerging research opportunities. In addition, support is furnished for clinical research centers, dental research institutions and general research support grants.

Explanation: Research funded under this activity ranges from single objective projects to broadly based, multidisciplinary programs involving the collaboration of a number of scientists. These grants are made to scientists or groups of scientists at universities, colleges, hospitals, research institutions, and other non-profit institutions.

Accomplishments in 1971: 189 grants were supported in 1971 compared to 231 in 1970. These grants support research in: Dentitional diseases, periodontal diseases, developmental biology and oral-facial anomalies, biomaterials, soft tissue stomatology, and general oral sciences programs. In the Dental Research Institute program five institutes or centers are now being supported. The centers are beginning to have a strong impact on dental education associated with them.

Objectives for 1972: 208 grants will be supported in 1972 compared to 189 in 1971. Emphasis will be on research which is part of the National Caries Program and areas in which research opportunities are emerging. The National Institute of Dental Research initiated a new mechanism of research support, a Special Dental Research Award Program to stimulate and help newly trained investigators remain active in dental research.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Fellowships. (Public Health Service Act, Title IV, Part C)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,601,000	Indefinite	---	$1,367,000

Purpose: Funds for Fellowships are used for support of clinical and basic research training. Applications under this program are for special fellowships, predoctoral and postdoctoral fellowships and career and career development awards.

Explanation: Highly skilled dental manpower is in increasing demand. To help meet this demand, fellowships are awarded with major emphasis on dental scientists who wish to pursue training in clinical disciplines.

Accomplishments in 1971: There were 97 fellowships supported in 1971 compared to 102 in 1970. Of these, 61 were continuations of previously awarded fellowships and 36 were new awards.

Objectives in 1972: The Fellowship program for fiscal year 1972 will support 82 awards, of which 60 are continuations. The 22 new awards will be awarded generally to applicants in the area of clinical research, allowing for a new emphasis and expansion of support for clinical research investigators.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Training Grants. (Public Health Service Act, Title IV, Part C)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$4,285,000	Indefinite	---	$4,285,000

Purpose: Training grants assist public and other non-public institutions in offering training programs to individuals interested in careers in dental research and related fields.

Explanation: Training grants are the principal means of providing support for individuals training for careers in dental research and teaching. Training grants also provide additional training for individuals with the necessary clinical skills in the disciplines associated with career development; e.g. embryology, anthropology, and genetics.

Accomplishments in 1971: In fiscal year 1971, the Dental Institute sought to expand the Clinical Research Training Programs, as well as continue the support of several combined degree (DDS-PhD) programs in university graduate schools. These schools are now graduating their first trainees under this combined degree program.

Objectives for 1972: Funds requested for 1972 will provide the same dollar level as in 1971, and will support 81 awards compared to 85 in 1971, a decrease of 4 graduate training grants.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Laboratory and Clinical Research. (Public Health Service Act, Title IV, Part C)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
216	$5,937,000	Indefinite	219	$6,547,000

Purpose: The Laboratory and Clinical Research studies of the Institute are concerned with the causes, treatment, control and prevention of dental diseases and disorders including caries, periodontal pathoses, oral-facial anomalies and oral cancer.

Explanation: Treatment, control and prevention of oral disorders and diseases are studied through both basic and applied clinical research.

Accomplishments in 1971: In fiscal year 1971 the intramural effort, in dental caries, was evaluation of treatment with antibiotics and other bactericidal agents; assessment of the enzyme dextranase; and the testing of techniques to extend the benefits of fluoride to a wider share of the population. Other areas of study included continued research on the basic characteristics of the bacterial agent Odontomyces Viscosus and the functions of the enzymes involved in the synthesis and breakdown of the proteins of the gums as they related to periodontal disease; continued research on soft tissue lesions of the mouth, cleft palate and malocclusion.

Objectives for 1972: The intramural research programs will continue to obtain new information relating to various oral-facial malfunctions, including dental caries, periodontal disease, oral cancer and abnormal oral-facial development. The intramural research approach involves a tripartite commitment of its resourses to (1) clinical and applied investigations of specific questions stemming from progress at the basic level; (2) clinical trials of therapeutic or preventive concepts evolved from basic and applied research, and (3) further definition of the distribution and nature of oral-facial diseases on an epidemiologic or geographic basis.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Collaborative Research and Development. (Public Health Service Act, Title IV, Part C)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
9	$3,877,000	Indefinite	11	$5,408,000

Purpose: The activities of the Collaborative Research and Development Activity are aimed at the reduction and eradication of dental caries, and the development of new adhesive restorative materials.

Explanation: The programs of this activity are carried out by collaborative contracts with other federal agencies, university research centers, and industrial research organizations.

Accomplishments in 1971: Initiated a full scale long term field trial for the reduction of caries by intraoral use of the enzyme dextranase; initiated four long term field trials of an adhesive sealant based on preliminary small scale trials showing that it protected occlusal surfaces of teeth against caries for at least two years; conducted a clinical study of the effects of sugars and other nutrients on dental plaque, preliminary to testing the anticaries effect of trimetaphosphate as food additive; initiated a clinical study to correlate the fluoride and other trace element content of dental enamel with caries experience; initiated projects to evaluate new marine and synthetic adhesives that might lead to improved filling materials.

Objectives for 1972: An increase of $1,516,000 and 2 positions in 1972 will be used to implement, on a larger scale, the National Caries Program in such projects as the following: (1) clinical research with enzymes active on dental plaque; (2) intensive local application of fluoride to the teeth; (3) development of means to deliver suitable amounts of fluoride to the more than 40,000,000 persons in the United States who do not have access to community water supplies; (4) extended laboratory and clinical research with new improved adhesive sealants; (5) clinical research to determine whether certain phosphates can be incorporated in the diet effectively to reduce caries in humans; (6) demographic and laboratory investigations to determine if caries can be prevented by dietary intake of certain groups of trace elements; and (7) a coordinated testing program to select antibiotics and antiseptics suitable for use in human oral hygiene, particularly to control caries producing bacteria.

62-645 O - 71 - pt. 3 - 36

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Biometry, Epidemiology and Field Studies. (Public Health Service Act, Title IV, Part C)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
23	$747,000	Indefinite	26	$938,000

Purpose: This activity is concerned with the planning, conduct and analysis of epidemiologic and field investigations.

Explanation: Epidemiologic and field studies are involved with such matters as prevalence of disease and effectiveness of new or improved methods of diagnosis, control and prevention. These studies are performed by Institute scientists supported from direct operating funds.

Accomplishments in 1971: Research has continued in the design and subsequent analysis of a wide variety of experimental investigations ranging from basic to clinical and including factors affecting the prevalence of oral disease in the population at large and the effectiveness of new and improved techniques for diagnosis and/or control of oral disease.

Objectives for 1972: As part of the National Caries Program expanded field trials of various caries preventive measures will be undertaken. Field studies of children and adults will be implemented with respect to the prevalence of cariogenic bacteria of the oral streptococcal type in humans. The mode of transmission of the organism and the degree of correlation between the severity of dental decay and the extent of streptococcal infection are other areas in which more precise information will be compiled.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Review and Approval of Grants. (Public Health Service Act, Title IV, Part C)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
33	$852,000	Indefinite	33	$929,000

Purpose: This activity provides support for the administration of extramural programs, surveillance of scientific activities and reports on the fiscal and scientific data relevant to all transactions.

Explanation: It is the responsibility of this activity to review and evaluate the research grant, fellowship and training grant programs, and to insure the effectiveness and efficiency of the total dental science programs in academic institutions.

Accomplishment in 1971: This activity conducted the scientific and administrative review of all research grants, fellowships and training grant applications submitted to the Institute for funding and maintained surveillance over all active grants. In addition, the staff established policy and guidance for the operation of the program.

Objectives for 1972: This activity will continue to provide scientific and administrative review of all Institute grants and surveillance over active grants.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Program Direction. (Public Health Service Act, Title IV, Part C)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
23	$442,000	Indefinite	23	$469,000

Purpose: This activity provides support for the Institute Director and his immediate staff, who are responsible for the administration, coordination and direction of the Institute programs.

Explanation: The Institute Director and his immediate staff are responsible for keeping abreast of new developments in the field of dental research and relevant higher education, and for providing leadership of promising new approaches in scientific investigations and relevant manpower training.

Accomplishments in 1971: Administrative policies and procedures were devised and implemented for the operation of the National Caries Program. Operational objectives and plans were formulated and approved under NIH and DHEW guidelines.

Objectives for 1972: This activity will continue to provide support for the administration, coordination, and direction of Institute programs.

New Positions Requested
Fiscal Year 1972

	Grade	Number	Annual Salary
Laboratory and clinical research			
Senior Dental Surgeon	C.O.	1	$20,175
Microbiologist	GS-14	1	19,643
Laboratory Assistant	GS-4	1	5,853
		3	45,671
Collaborative research and development			
Contract Administrator	GS-14	1	19,643
Clerk-Typist	GS-5	1	6,548
		2	26,191
Biometry, epidemiology and field studies			
Senior Scientist	C.O.	2	40,350
Statistical Clerk	GS-4	1	5,853
		3	46,203
Total new positions, all activities..		8	118,065

WEDNESDAY, MAY 5, 1971.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

WITNESSES

DR. G. DONALD WHEDON, DIRECTOR
DR. ROBERT Q. MARSTON, 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
DONALD F. CYPHERS, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
GERALD F. MEYER, CHIEF, HEALTH BRANCH, DIVISION OF BUDGET

Object Classification (in thousands of dollars)

Identification code 09-30-0884-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	8,426	8,871	9,277
11.3	Positions other than permanent	176	198	183
11.5	Other personnel compensation	49	53	55
	Total personnel compensation	8,651	9,122	9,515
12.1	Personnel benefits: Civilian employees	851	899	929
21.0	Travel and transportation of persons	199	230	240
22.0	Transportation of things	64	68	68
23.0	Rent, communications, and utilities	215	230	240
24.0	Printing and reproduction	161	180	189
25.0	Other services	12,938	15,065	12,643
26.0	Supplies and materials	1,416	1,540	1,550
31.0	Equipment	391	485	384
41.0	Grants, subsidies, and contributions	106,585	109,670	108,660
	Subtotal	131,471	137,489	134,418
95.0	Quarters and subsistence charges	−18	−18	−18
99.0	Total obligations	131,453	137,471	134,400

Personnel Summary

Total number of permanent positions	604	627	627
Full-time equivalent of other positions	38	38	38
Average number of all employees	630	618	645
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0884-0-1-651	1970 actual	1971 est.	1972 est.
Program by activities:			
1. Grants:			
(a) Research	88,717	88,858	92,091
(b) Fellowships	6,757	5,740	5,094
(c) Training	16,703	15,072	11,475
Total grants	112,177	109,670	108,660
2. Direct operations:			
(a) Laboratory and clinical research	16,304	18,353	16,561
(b) Collaborative research and development	7,783	5,936	5,453
(c) Biometry, epidemiology, and field studies	711	877	916
(d) Review and approval of grants	2,225	2,278	2,414
(e) Program direction	323	357	396
Total direct operations	27,346	27,801	25,740

Program and Financing (in thousands of dollars)—**Continued**

Identification code 09-30-0884-0-1-651		1970 actual	1971 est.	1972 est.
	Total program costs, funded [1]	139,523	137,471	134,400
	Change in selected resources [2]	−8,070	----------	----------
10	Total obligations	131,453	137,471	134,400
	Financing:			
25	Unobligated balance lapsing	225	1,853	----------
	Budget authority	**131,678**	**139,324**	**134,400**
	Budget authority:			
40	Appropriation	146,334	138,339	134,400
40	Portion withdrawn (Public Law 91-204, sec. 410)	−9,080	----------	----------
40	Pay increase (Public Law 91-305)	285	----------	----------
41	Transfer to other accounts	−5,861	−30	----------
43	**Appropriation (adjusted)**	**131,678**	**138,309**	**134,400**
46.10	**Proposed transfer for wage-board pay increases**	----------	**72**	----------
46.20	**Proposed transfer for civilian pay act increases**	----------	**823**	----------
46.30	**Proposed transfer for military pay act increases**	----------	**120**	----------
	Relation of obligations to outlays:			
71	Obligations incurred, net	131,453	137,471	134,400
72	Obligated balance, start of year	74,571	69,392	67,505
74	Obligated balance, end of year	−69,392	−67,505	−70,648
77	Adjustments in expired accounts	−1,730	----------	----------
90	Outlays, excluding pay increase supplemental	134,902	138,394	131,206
91.10	Outlays from wage-board supplemental	----------	68	4
91.20	Outlays from civilian pay act supplemental	----------	776	47
91.30	Outlays from military pay act supplemental	----------	120	----------

[1] Includes capital outlays as follows: 1970, $969 thousand; 1971, $485 thousand; 1971, $384 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $41,643 thousand; 1970, $33,573 thousand; 1971, $33,573 thousand; 1972, $33,573 thousand.

NOTES

Includes $671 thousand in 1971 and $662 thousand in 1972 for activities previously financed from: Research resources, 1970, $703 thousand.

Includes $1,023 thousand in 1972 for activities previously financed from: National Institute of Allergy and Infectious Diseases, 1970, $1,023 thousand; 1971, $1,023 thousand.

Excludes $869 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	*1971*
National Institute of Child Health and Human Development	107	---
Health manpower	755	---
National Library of Medicine	256	---
National Eye Institute	---	69
Office of the Director	70	810
National Heart and Lung Institute	---	78

Excludes $3,597 thousand in 1972 for activities transferred to: Health manpower, 1970, $3,597 thousand; 1971, $3,597 thousand.

INTRODUCTION OF DR. WHEDON AND ASSOCIATES

Mr. NATCHER. We will take up next the National Institute of Arthritis and Metabolic Diseases. We have Dr. G. Donald Whedon with us as the principal witness.

You have with you certain of your associates, Dr. Whedon. Would you like to introduce them?

Dr. WHEDON. It is a pleasure to be with you. On my left is Gilbert Baylis, executive officer for the Institute, and on his left is Donald Cyphers, our budget officer. With me also is Dr. Benjamin Burton, associate director of the Institute.

Mr. NATCHER. Thank you very much. We will put your biographical sketch in the record.

(The biographical sketch follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES BIOGRAPHICAL SKETCH

Name.—Dr. G. Donald Whedon.

Position.—Director, National Institute of Arthritis and Metabolic Diseases (NIAMD).

Birthplace and date.—Geneva, N.Y., July 4, 1915.

Education.—A.B., 1936, Hobart College; M.D., 1941, University of Rochester School of Medicine; Sc.D. (hon.), 1967, Hobart College.

Experience.—Director, NIAMD, 1962-present; Assistant Director, NIAMD, 1956–62; Chief, Metabolic Diseases Branch, NIAMD, NIH, 1952–65; Physician, Outpatient Department, New York Hospital, 1947–52; assistant physician, Outpatient Department, New York Hospital, 1944–47; assistant professor of medicine, Cornell University Medical College, 1950–52; instructor of medicine, Cornell University Medical College, 1944–50; assistant in medicine, University of Rochester School of Medicine, and assistant resident physician in medicine, Strong Memorial Hospital, 1942–44; Interne in medicine, Mary Imogene Bassett Hospital, Cooperstown, N.Y., 1941–42.

Association memberships.—Association of American Physicians; the Endocrine Society (Postgraduate Committee, 1962–65); American Rheumatism Association; American Diabetes Association; American Federation for Clinical Research; New York Academy of Sciences; American Association for the Advancement of Science; American Medical Association; American Physiological Society; The Gerontological Society; American Institute of Nutrition; Pan American Medical Association; American Gastroenterological Association, Aerospace Medical Association.

Special awards, citations, or publications.—Certified, American Board of Internal Medicine, 1950; American Board of Nutrition, 1968; assisted DGMS in organizing program of multicategorical clinical research centers in leading American medical institutions, 1959–61; Subcommittee on Calcium, Committee on Dietary Allowances, Food and Nutrition Board, National Research Council, 1959–64; Editorial Board, Journal of Clinical Endocrinology and Metabolism, 1960–67; Editorial Board, Calcified Tissue Research, 1967–present; 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 over 50 scientific papers on metabolic and physiologic studies of convalescence, immobilization, paralytic poliomyelitis, diseases of bone particularly including osteoporosis, human energy metabolism and space medicine.

GENERAL STATEMENT

Mr. NATCHER. We will be happy to hear your statement, Dr. Whedon.

Dr. WHEDON. Mr. Chairman and members of the committee: I

greatly appreciate this occasion to report on progress made by the National Institute of Arthritis and Metabolic Diseases, and to assess briefly our needs for the fiscal year 1972. In this calendar year of 1971, we are beginning the third decade of Institute operation. We shall continue to broaden and intensify the attack on basic biological as well as on clinical problems which fall within our purview.

Mr. Chairman, I believe it would be appropriate to sketch the background of the salient Institute programs, and to mention a few examples of research progress of this past year. In order to present a broader description than is possible in this brief presentation, we have prepared detailed special reports in a number of major fields which I can present to the committee if you wish.

RESEARCH ON ARTHRITIS, RHEUMATOID DISEASES

The arthritic and rheumatic disorders are the Nation's most prevalent painful, crippling diseases, afflicting almost 17 million people. About 100 disorders are listed under the combined heading of arthritis and rheumatism; among the major types are rheumatoid arthritis, degenerative joint disease or osteoarthritis, and arthritis associated with metabolic or biochemical abnormalities, such as gout. Although such is a separate clinical entity, they all have several features in common: dysfunction, deformity or pain in the joints or surrounding tissues.

Research is continuing on the likelihood that rheumatoid arthritis is initiated by an autoimmune reaction, in which the body overreacts to proteins originating within the body's own tissues. Such immune processes may be triggered by changes brought about by an infectious agent or agents. In our attempts to isolate such an agent, we have detected virus-like particles in the affected kidney tissues of patients with systemic lupus erythematosus, a connective tissue disease related to rheumatoid arthritis. Our findings do not establish a viral cause for this disorder, but presence of virus-like particles is of diagnostic importance and may shed light on the infectious aspects of rheumatoid disease. In the meantime, we are also continuing our research on new and improved agents for the management of arthritis.

DIABETES

According to health surveys, the prevalence of diabetes in the United States has more than doubled since 1950. There are approximately 4 million diabetic people in this country, while another 5 million of our present population are expected to develop the disease during their lifetime.

The rising incidence of diabetes and the fact that the disorder ranks eighth on the list of diseases causing death make continued, intensive and effectve research on diabetes an unceasing obligation on our part. A major goal in diabetes research is understanding the basic impairment of insulin action, and why the body is unable to utilize carbohydrates normally for energy expenditure and storage. We are also concerned with finding ways to suppress the development of com-

plications of the disease, including arteriosclerosis, nerve damage, kidney failure, and blindness.

Another important goal is understanding of the modes of action of the oral antidiabetic drugs. This past year, some of the results of a 10-year study on the effects of the first of these drugs were made public. Conducted by 12 leading medical centers with research grant support from this Institute, to determine whether this oral drug might protect diabetics against the late complications of this disease, the conclusions of this university group diabetes program study have indicated, on the contrary, the possibility of harmful effects from one of these drugs, at least insofar as cardiovascular mortality is concerned. Based on the findings of this well-coordinated and controlled clinical study, it is the consensus of diabetes study groups representing the American Medical Association, the American Diabetes Association, and the Food and Drug Administration, that this oral hypoglycemic agent should be used only in diabetics with adult onset diabetes whom it is not feasible to treat by diet alone or by diet plus insulin.

CYSTIC FIBROSIS AND OTHER METABOLIC DISEASES

Cystic fibrosis is a serious hereditary disorder of children, and is frequently fatal. Our clinical studies have provided advances in the diagnosis and treatment of cystic fibrosis, and now we are placing a new and greater emphasis on basic studies of this disorder in such disciplines as biochemistry, genetics, and molecular biology.

An extremely important aspect of basic metabolic research in recent years has been the investigation of diseases for the possibility that a hereditary defect such as the inability to produce a key enzyme may be responsible for the disordered processes found. Of the therapeutic approaches to these so-called "molecular diseases" due to hereditary enzyme deficiency, corrective induction or transfer of enzyme activity would be most desirable. Now a grantee of this Institute has accomplished one of the first examples of "molecular therapy", predicted to be the treatment of the future in the management or correction of enzyme-deficient metabolic diseases. The grantee successfully transplanted specific enzyme-producing normal rat cells into rats jaundiced because of a hereditary enzyme deficiency. After transplant the rats developed the normal capacity to handle bile. This finding represents a unique biological model with potential implications for treating some types of inborn errors of metabolism. Our aim is to discover the metabolic defect or defects in cystic fibrosis and other metabolic diseases so that their defects may be corrected.

KIDNEY AND UROLOGIC DISEASES

The importance we place on kidney and urologic diseases is predicated upon the toll of suffering caused by these disorders. Almost 8 million Americans are afflicted with diseases of the urinary tract and the kidneys, and an estimated 55,000 individuals die each year of irreversible kidney failure. Along with our research program concentrating on the nature of uremia, the fatal end-stage of kidney disease,

we are conducting studies to improve kidney transplantation. It is in the latter area that one of our grant-supported investigators has made a significant finding involving closer immunologic matching of donor and recipient tissues. Utilization of a kidney preserving device developed by another scientist working with NIAMD grant support has permitted an important modification of standard phenotyping and cross-matching procedures. Under the new system, the recipient's leukocytes are typed and cross-matched to the cadaver donor's kidney cells as well as leukocytes. Many apparently "good" matches based on leukocyte-leukocyte typing alone can now be revealed as merely "fair" on the basis of the more complete double matching system, and poor outcome of cadaver transplants due to rejection can be more easily predicted and avoided.

THE ARTIFICIAL KIDNEY PROGRAM

Our artificial kidney program, a collaborative research and development activity, seeks to provide compact, efficient, and less expensive artificial kidneys, and improved dialysis methodology. This program also supports related research on uremic toxins and clinical studies to combat the complications of kidney failure. We have now reached a phase in which many improved, lifesaving artificial kidneys are being developed, while others are passing their final clinical tests or will soon be coming off the assembly line.

DIGESTIVE AND NUTRITIONAL DISEASES

The impact of gastroenterology is vast not only from the standpoint of the number of individuals afflicted, but also because of the extensive number of diseases encompassed, including peptic ulcer and ulcerative colitis, and diseases of the liver, gallbladder, and pancreas. Some of the most exciting research in peptic ulcer today revolves around gastrin, the hormone which stimulates secretion of gastric juices. The synthesis of gastrin by Institute grantees has provided an important research tool for studying peptic ulcer, in which an excess of acid digestive juices is secreted. Now, another group of grantees has shown in rats that experimental induction of immune antibodies against gastrin can inhibit the potent gastric acid stimulatory action of gastrin. This finding suggests possible novel clinical approaches to counteracting excessive gastric acid secretion in disease states such as peptic ulcer.

For a number of years our epidemiologic team in Arizona has been studying diabetes, arthritis, and gallbladder disease among the Indians of the Southwest. I am pleased to report that we have now established a permanent clinical research section at the new Phoenix Indian Medical Center to intensify our research with patients with these disorders.

Our Institute is responsible for a large portion of the nutrition research supported by the National Institutes of Health and of the medically oriented nutrition research supported by the Federal Government. Our program activities cover the full spectrum of nutrition research from basic metabolic and physiologic studies to projects designed to determine how best to alleviate malnutrition and nutritional

deficiency diseases. In addition to research activities in this country, the malnutrition segment of NIH's United States-Japan Cooperative Medical Sciences Program, administered by us, supports research aimed at practical solutions to nutrition and nutrition-related problems of countries in Southeast Asia.

ENDOCRINE DISORDERS

Endocrine disorders, such as hyper- and hypothyroidism, growth retardation and osteoporosis, are known to strike many Americans. Our main thrust in endocrinology is to learn the precise mechanisms by which hormones influence metabolism, and it is in this regard that I shall mention two significant developments this past year.

After 32 years of research, the human pituitary growth hormone (HGH) previously isolated and identified by an Institute grantee, has now been reported synthesized by the same scientist.

Another important basic finding by an intramural scientist and an Institute grantee resulted in the successful synthesis of the active portion of the parathyroid hormone and the discovery of precise mechanisms through which it controls calcium metabolism in the body. The synthesis will have important implications both for better understanding of the biochemical operation of other hormones and for improved diagnosis and treatment of a number of human disorders, including hyperparathyroidism, kidey stones, and metabolic bone diseases.

HEMATOLOGY

Among our research goals is precise elucidation of the specific defects in various blood disorders, including the anemias and sickle cell disease. Sickle cell anemia is a grave, hereditary blood disorder that affects the Negro population almost exclusively, and is difficult to treat. Normally, red blood cells, or erythrocytes, which transport oxygen throughout the body, are round; in sickle cell anemia, under conditions of diminished oxygen tension, the round red cell changes to a crescent shape, which then clogs capillaries, sometimes causing clots and depriving organs of their supply of blood.

A new treatment for acute attacks of sickle cell anemia that is reported to reverse sickling crises as well as to block further sickling of susceptible red cells has been suggested by a research team extrapolating from concepts of the molecular theory of sickling advanced by an Institute scientist in Bethesda, who demonstrated that abnormal linkage occurs between certain hemoglobin chains in sicklin-prone red cells. Investigators aimed their therapeutic strategy at chemical destruction of these abnormal bonds through use of urea, a common chemical. With coordinated support from this and other Institutes at NIH, research studies will be extended with the aim of improving the treatment of sickle cell anemia.

COORDINATION OF NIH SICKLE CELL ANEMIA RESEARCH

Mr. NATCHER. Before you leave that subject, we had testimony yesterday by the Heart Institute on this same subject matter and I

believe there are other Institutes. Is there full cooperation between the Institutes so you are not duplicating research efforts?

Dr. MARSTON. For the sickle cell anemia program I established a task force of the involved Institutes to work together in the development of the plan. I then made the decision to have this coordinated under the Deputy Director of the Heart Institute, Dr. Ringler. There has been very close and continued cooperation and will continue to be in the future.

Mr. NATCHER. Proceed.

SKIN DISORDERS

Dr. WHEDON. Diseases of the skin include psoriasis, a disfiguring disorder which numbers as its victims four million Americans. The total number of those afflicted with this and other skin diseases is large, and we are vigorously pursuing research in psoriasis and in other such skin diseases as atopic dermatitis, pemphigus, and discoid lupus erythematosus.

NIAMD RESEARCH TRAINING AND FELLOWSHIPS

Another important responsibility of this Institute is the support of research training of young biomedical scientists in its area of purview. This program has contributed greatly to revitalization of many research fields, and has encouraged some of the best young minds to enter a career in biomedical research. More specifically, inasmuch as this Institute is responsible for a great number and variety of diseases, our training programs also constitute a major mechanism for development of new teachers in the various medical specialties in medical schools. In dealing with this country's shortage of physicians to deliver adequate health care to our population, remedial steps must involve not only the production of more physicians, but must also be concerned with equipping these new physicians with new knowledge and improved diagnostic and therapeutic methods with which to teach and practice medicine more effectively. This Institute is proud of the achievements of its training programs and hopes to continue them at an effective level in fiscal year 1972.

In conclusion, Mr. Chairman, I am submitting an overall request for 1972 of $135,433,000, an increase of $1,008,000 from the 1971 operating level of $134,425,000. I shall be happy to answer any questions.

TRANSFERS OF NIAMD FUNDS IN 1971

Mr. SMITH. Doctor, I noticed in your budget you are transferring money from the 1971 appropriation to pay for other offices' salaries and expenses in five instances. Did we give you too much money last year or how do you happen to have enough money to do that?

Dr. WHEDON. These transfers noted on page 136 are part of the changes in bookkeeping which take place at the National Institutes of Health, and they represent what I regard as modest sums of money, but they do result even with adjustments for the pay raise and that sort of thing in a small reduction of programs in our appropriation.

Mr. SMITH. It is more than just bookkeeping, it is a transfer out of your funds over to someone else's. Did you have that money to spare? If you did, did we give you too much last year?

Dr. MARSTON. What the majority of these funds represent, Mr. Smith, is the fact that whereas the administration accepted essentially all of the congressional increases with the exception of the $15 million for construction and with a few other small exceptions. The training grants area was one of the areas in which the administration did not accept the increases that Congress voted above the administration budget.

Those funds, however, were used in 1971 for pay raises. As Dr. Whedon has pointed out, his Institute has a heavy responsibility as far as funds for training programs at NIH.

Mr. SMITH You answered half of it I guess. In other words you are saying the administration thought we appropriated more money than was needed, but what about the people running the Institutes. Do you think you had more money than you needed?

Dr. MARSTON. Let me be clear on the figure. We are spending $97 million more for research than the administration proposed in the 1971 budget, but the funds that constituted an increase for training grants we were not allowed to spend for training grants but are using it for other purposes.

Mr. SMITH. Do you agree that you have $3 million to spare, Doctor?

Dr. WHEDON. The $3 million figure that you see was actually a transfer to the Bureau of Health Manpower of NIH.

Mr. SMITH. But you also have transfers to the National Eye Institute, and the National Heart and Lung Institute. The point is, do you think you had that money to spare or did you need it?

Dr. WHEDON. As I indicated in my statement, Mr. Smith, we have felt a great deal of pride in and sense of importance of our training program. We have had excellent applications which have been sent to us which we have been unable to fund.

The answer is that we could have used that money in support of research training, for production not only of medical scientists but also of the teachers so much needed in the many clinical specialties for which NIAMD is responsible.

Mr. SMITH. What about in program fields other than research training? Is that the only place you could have used it?

Dr. WHEDON. No; we could have used funds also in an even more serious situation in support of our research grants. For example, in fiscal year 1971 we would have needed some $30 million to have paid all of our approved grants. We are currently able to fund about 35 to possibly 40 percent of the research grant applications which come to our Institute approved as meritorious by the NIH study sections.

APPROVED BUT UNFUNDED NIH RESEARCH GRANT APPLICATIONS

Mr. SMITH. With regard to these research grants, and Dr. Marston I want you to provide some material at this point—in this Institute you say you are able to fund 35 percent. That doesn't really tell us how many you should approve.

In other words, perhaps some applications should not be approved, perhaps some of them would be good, but to fund them might in effect reduce the grants that could be funded by some other institutes. Rather than dealing with one institute because I think it is misleading to do so, I would like for you to provide an overall capitulation of the number of research grants that if you were not within budgetary restrictions, you would like to fund?

Dr. MARSTON. Yes, sir. I want to be sure that the information that comes to you is most useful. I think there are various ways of measuring that. One way we have used in recent years is to estimate how much it would take to maintain the program level to offset inflation. This is a fairly factual figure I would feel comfortable with.

The other way involves more difficult judgments. We can estimate what it would take to fund, say, 50 percent of approved grants. I don't want to give you information that might be misleading because it has so much of a judgmental aspect.

Mr. SMITH. I think you ought to give it to us for all the institutes in one package. If one institute is increased substantially more than another, I think it might be reducing the number of grants funded somewhere else that should have just as high or higher priority.

Dr. MARSTON. We do a fairly careful screening. We have central clearance of the applications that come in and we control centrally the assignment of applications for projects that may apply equally to two institutes. We go through our dual process of review but only fund from the one institute that is most appropriate.

Mr. SMITH. In addition to that, I think we need here for each of the institutes how much would be required to fund those research grants that you believe would be of good quality if you were not under budgetary restrictions.

Dr. MARSTON. All right, sir.

Dr. WHEDON. Would you like us to do this for each institute in the location in the budget where it appears? For example, in NIAMD we estimate a need for an additional $34 million to fund all meritorious research grants approved by study sections and our national council.

Mr. SMITH. I asked the heart people yesterday and they said $8 million. I think when you start asking one at a time, perhaps people at that institute may not see the overall picture and it might be better to do it all in one place.

Dr. MARSTON. I might say that one of the things that bears on this question is our concern, in recent years, over the necessity of negotiating downward our previous commitments. You will notice from the 1972 budget that we have tried to avoid that to the degree possible.

Mr. SMITH. Of course, I am not expecting you to include within the figures what really amounts to an increase in Federal aid to education. I am really talking about not changing formulas and so forth, but really getting the research grants that should be funded in your estimation based upon the applications you have and the effect it would have upon other institutes.

Dr. MARSTON. The importance of the work, the quality of the grants we are not able to fund. Yes, sir.

(The information follows:)

Estimated fund requirements for approved unfunded[1] NIH research grants regular program for fiscal year 1972 (in thousands)

	1972 estimate
National Cancer Institute	$21,317
National Heart and Lung Institute	9,588
National Institute of Dental Research	2,014
National Institute of Arthritis and Metabolic Diseases	28,693
National Institute of Neurological Diseases and Stroke	14,722
National Institute of Allergy and Infectious Diseases	10,735
National Institute of General Medical Sciences	26,925
National Institute of Child Health and Human Development	26,098
National Eye Institute	2,502
National Institute of Environmental Health Sciences	831
Total	143,425

[1] It has always been the policy of NIH to further review those grants falling within the lowest 10 percent of approved grants to determine the desirability of awarding from available funds. The table represents the amount which it is estimated would be needed provided there were no budgetary restrictions and assuming the lowest 10 percent of approved competing grants would remain unfunded.

PROGRAM REDUCTIONS

Mr. SMITH. I notice also that you have on page 149, four reductions in programs and no increases. That also makes it look like we gave you too much last year doesnt it?

Dr. WHEDON. Mr. Smith, what has taken place at the National Institutes of Health is a very careful review of the relative importance of various programs among the various institutes.

Mr. SMITH. Was your institute downgraded this year then?

Dr. WHEDON. Our institute was not one of the favored ones, and it was felt that given a choice of use of funds, these funds should be used in other places. That accounts for our drop of $2 million for new and competing research grants, of $600,000 in fellowships, and also a small decrease in our intramural operation in Bethesda.

We also had a further reduction in our collaborative research and development of $500,000 taken from the artificial kidney program of which I spoke in my statement.

Mr. SMITH. I can understand how you apparently got downgraded but where did the money go? Other than to cancer, who got upgraded?

Mr. MEYER. Mr. Chairman, the Dental Research Institute did receive some increase this year. In addition to that, the Heart Institute received some increase this year predominantly for sickle cell anemia.

Mr. SMITH. That was only $3 million and they didn't even get program level increases in some of their other fields.

Mr. MEYER. I am sure that is correct.

Dr. MARSTON. Could we supply a list of the increases and decreases?

Mr. SMITH. I think it would be helpful at this point because there

seems to be in the record here an indication there are some adjustments in grading the importance of the various institutes and if some have been downgraded, surely some others should have been upgraded.

Dr. MARSTON. I think it is inevitable in the development of a budget. I have the major ones before me at present. I could give them now or for the record.

Mr. SMITH. For the record.

(The information follows:)

NATIONAL INSTITUTES OF HEALTH—PROGRAM INCREASES AND DECREASES, BY APPROPRIATION

[In thousands of dollars]

	Mandatories	Program decrease	Program increase	Total budget authority (including carryover)
1971 total NIH comparable				1,682,731
(1971 NIH research)				(1,166,259)
Biologics standards	281	−50		231
National Cancer Institute	4,871	−5,884	4,889	3,876
National Heart and Lung Institute	3,414	−7,650	8,101	3,865
National Institute of Dental Research	349	−411	4,188	4,126
National Institute of Arthritis and Metabolic Diseases	4,681	−3,673		1,008
National Institute of Neurological Diseases and Stroke	2,373	−5,334		−2,961
National Institute of Allergy and Infectious Diseases	3,737	−2,519		1,218
National Institute of General medical Sciences	3,803	−8,045	115	−4,127
National Institute of Child Health and Human Development	860	−3,804	12,500	9,556
National Eye Institute	5,904	−3,769	99	2,234
National Institute of Environmental Health Sciences	1,094	−62	4,249	5,281
Research resources	138		1,500	1,638
John E. Fogarty International Center for Advanced Study in the Health Sciences	55	−418		−363
(1972 NIH research)	31,560	−41,619	35,641	(1,191,841)
Health manpower	1,039	−39,922	155,459	116,576
National Library of Medicine	471			471
Buildings and facilities			266	266
Office of the Director	556			556
Scientific activities overseas (special foreign currency program)		−3,690		−3,690
Payment of sales insufficiencies and interest losses	917	−1,679		−762
Cancer conquest program			100,000	100,000
1972 total, NIH	34,543	−86,910	291,366	1,921,730

TRANSFERS FOR PAY COSTS

Mr. MEYER. With respect to your earlier question, Mr. Chairman, on the transfer for the pay raise, I think I have some responsibility to try to answer that question better than we did.

This relates to funds that were originally not made available to the Institute for expenditures, that were held in reserve. Subsequently to that they were released in order to meet pay raise costs in other accounts where they had not been.

Mr. SMITH. It was a budgetary decision?

Mr. MEYER. It was. And the decision as to which account they went to was strictly a decision based on which accounts were in the red and needed the pay raise. It was not a decision the Arthritis Institute played a hand in and they shouldn't be considered responsible for it.

CLINICAL RESEARCH STUDIES OF INDIANS

Mr. SMITH. As you know, there are many Members of Congress very much interested in programs to help the Indians and in our report last year we indicated a definite interest in your supporting certain clinical research studies at the Indian Medical Center at Phoenix. Tell us about these studies and what support you are furnishing this year and plan for next year.

Dr. WHEDON. As I mentioned briefly in my statement, we opened a clinical research section of 25 beds on the top floor of the new Phoenix Indian Medical Center in January of this year. Largely as a result of the interest of this committee we have received additional staffing authority and have undertaken an intensive recruitment program to properly staff our research section with research clinicians, scientists, and support personnel.

The Director is Dr. Scott M. Grundy who has come to us from the Rockefeller Institute as an experienced investigator in gallbladder disease; he is also interested in diabetes. Dr. Grundy has already taken on some of his supporting staff and nearly all of the beds are occupied as part of his very active research on gallbladder disease with particular interest in factors causing the development of gallstones. This is a particularly promising area of research both because of the high incidence of gallstones among American Indians and because of recent research supported by us. This research has shown that with cholesterol gallstones the problem is in the liver which for reasons as yet unknown in these patients makes a bile which is very high in cholesterol content. These studies of gallbladder disease will be continued, of course, and later on studies will be initiated on diabetes; this also is a very appropriate disease to study in the Pima Indians of Arizona because its prevalence among them is 10 to 15 times the national average.

UNITED STATES-JAPAN COOPERATIVE MEDICAL SCIENCE PROGRAM

Mr. SMITH. What is the significance of the transfer of part of the United States-Japan research program to you from the Institute of Allergy and Infectious Diseases?

Dr. WHEDON. The United States-Japan cooperative medical science program is made up of six parts. The first five parts are for research programs in various infectious diseases, such as cholera, leprosy, parasitic diseases, tuberculosis and virus diseases. The sixth program is in malnutrition and was managed from our Institute even though the funding was in NIAID. This year it was merely judged more efficient from a fiscal point of view to shift to this Institute the funds for the malnutrition program since we were in charge of the program management anyway.

With regard to your second question, Mr. Smith, the purpose of the United States-Japan program may not be clear. It was initiated in 1965 with the express major purpose of sponsoring research by the two countries on diseases of the countries of Southeast Asia. Consequently, a number of projects are taking place in the various countries of that

part of the world and specifically involve patients with diseases that are very important there and are not among the leading diseases in this country. Thus, we would expect to learn much more about these diseases in a situation in which they are very prevalent.

Cases of such nutritional deficiencies are found in the United States but not in large numbers in any one location; thus it would be fairly difficult to find here the necessary numbers of such patients for long-term studies in one place. On the other hand, the United States-Japan program enables us to study these nutritional deficiencies in a habitat in Southeast Asia where large numbers of patients are readily available in single communities and for long periods of time. As a side effect, nevertheless, we do expect to obtain medical and scientific knowledge which will be of either direct or indirect benefit to the health of our own citizens in this country.

OTHER NUTRITION RESEARCH ACTIVITIES

Mr. SMITH. In addition to activities under the United States-Japan program, what else are you doing in nutrition?

Dr. WHEDON. Mr. Chairman, I may mention several accomplishments over the past year in the field of nutrition starting with the study of vitamin D which is very active at the present time. Last year we reported that a compound had been discovered closely related to vitamin D, 25-hydroxycholecalicferol is two to three times as active as 25 HCC. In other studies just recently reported it appears that 25 HCC is likely the major form in which vitamin D is transported in blood and that the new compound 1, 25 di-HCC may be the truly active form. The results of this research hold promise for better understanding and treatment of vitamin D resistant rickets and of related demineralizing bone diseases.

In the case of another vitamin, vitamin A, investigators in the National Eye Institute and in this Institute working together in Bethesda have found a promising treatment for retinitis pigmentosa, a chronic disease of the eye which may end in blindness. Large doses of vitamin A have been found effective for improving the sight in two cases with a particular kind of this disease. Investigators are now attempting to see the possible relationship of impaired vitamin A utilization in other form of retinitis pigmentosa and the possible usefulness in treatment of large doses of this vitamin.

In the face of a worldwide shortage of dietary protein, our Institute has directed considerable efforts at development and clinical testing of high-protein foods or food supplements derived from inexpensive indigenous sources. This is particularly important because such research, if successful, helps underdeveloped countries to help themselves so that they do not have to rely on supplies of expensive food proteins, many times donated in large quantities by the United States and other developed countries.

In one instance of successful studies along this line an Institute grantee working in Peru has now established in prolonged feeding trials that properly processed cottonseed flour, at adequate levels of intake, can serve as the main or sole source of protein for rapidly growing infants and children at least for a short period of time.

In another such study supported by our Institute in India, the Central Food Technological Research Institute of Mysore has developed a new product which permits the doubling of the locally available, sparse conventional milk supply while still retaining the essential desirable nutritive qualities of milk for the feeding of infants and preschool children. The new product, already commercially produced, is "toned milk" ("Miltone"), regular buffalo milk (or in some cases cows' milk) which has been stretched through the addition of an equal quantity of peanut protein isolate (pure peanut protein, a nutritionally desirable protein as long as it is mixed with some milk protein). This "toning" permits the doubling of the volume of the final product, to which also some vitamins and additional hydrolized starch syrup are added as a source of extra carbohydrates.

Mr. Chairman, for the purposes of these hearings we have prepared a special report which covers in greater detail research accomplishments of this Institute in the field of nutrition. With your permission we would like to submit this report to the committee for further information.

(The information follows:)

SPECIAL REPORT: NUTRITION*

The National Institute of Arthritis and Metabolic Diseases (NIAMD) is currently responsible for a large portion of all *medically* oriented nutrition research supported by the Federal Government. It also shares with the National Institute of Child Health and Human Development and, to a lesser degree with other NIH institutes, the responsibility for the nutrition research supported by the National Institutes of Health (NIH). The NIAMD traces its tradition of nutrition research back to Dr. Joseph Goldberger's classic work on pellagra, a vitamin deficiency disease problem assigned to him by the Public Health Service in 1914. His student, Dr. W. H. Sebrell, who continued his work, served as first Director of the Institute and later as Director of the NIH until 1955.

In addition to direct research activities in the laboratories and clinics in Bethesda, NIH supports a wide variety of research projects through grants to research centers and medical institutions throughout the United States and abroad. These activities cover the full spectrum of nutrition research from fundamental metabolic and physiologic studies of dietary requirements of the various nutrients, to programs designed to determine how best to alleviate malnutrition and nutritional deficiency diseases both in the United States and abroad.

Scope of the Grants Program

The grants program is divided into two major groupings: physiology of normal nutrition and nutritional disorders. Projects in the physiologic processes of normal nutrition involve body composition, digestion and absorption of nutrients in the gastrointestinal tract; appetite regulation and food intake; the biochemistry and physiologic role of nutrients and their fate in the body; quantitative requirements of proteins and amino acids, carbohydrates, fats and fatty acids, minerals, trace elements, vitamins, and fluids and electrolytes; interrelationships between different nutrients and between nutrients and hormones, and nutrients and enzymes; and the relationship of the intestinal flora to nutrition.

Research in abnormal nutrition involves discovery and definition of deficiency states, nutrient toxicity, obesity, malabsorption of specific nutrients, and the relationship of diet to specific disease entities, such as celiac disease and others. Another major subdivision of these research grants relates to nutrition in specific diseases or stress states, such as in diabetes, bone and joint disease, liver disease, gastrointestinal disease, infectious diseases, disorders of immunity,

*Prepared February 1971 by the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare in connection with 1972 appropriation hearings.

anemia, endocrine disorders, gallbladder disease, inborn errors of metabolism, skin disorders, kidney disease and kidney stones, and stress (including surgery, trauma, wound healing and environmental extremes).

In addition to this broad research grants program, the Institute finances and administers a substantial and comprehensive program providing research fellowships and graduate research training grants in nutrition.

Special Nutrition Research Studies

Two unique continuing endeavors include conduct of malnutrition research abroad and design and assessment of diets for kidney failure patients.

Specific research projects carried out abroad among populations with nutritional deficiency diseases are aimed at finding solutions to complex malnutrition problems. These projects are largely funded through the U.S.-Japan Cooperative Medical sciences program for Southeastern Asia, and through Public Law 480 "counterpart funds," U.S. owned local currencies in developing countries derived from the sale of surplus agricultural commodities.

The second type of endeavor, is pursued by the Institutes' artificial kidney-chronic uremia program. This program is a special research and development contract effort aimed at developing more effective dialysis hardware and methodologies, as well as methods for optimal rehabilitation of patients in chronic renal failure through use of particular diets, when dialysis with artificial kidneys or organ transplantation cannot be obtained or are not indicated.

RESEARCH ACCOMPLISHMENTS

The numerous significant research findings contributed this past year, by grant-supported investigators and reported here, do not represent the Institute's total effort, but rather illustrate the variety of problems associated with nutrition research, as well as the broad coverage of research supported. Foremost among these recent findings are studies that have led to a treatment of vitamin D resistant rickets, a new concept for providing total nutrition by intravenous infusion, and improved management of the thiamine depletion syndrome in alcoholic patients.

Treatment for Vitamin D Resistant Rickets

Vitamin D, ingested in small amounts in food or formed from a precursor substance in skin exposed to ultraviolet light or sunlight, is necessary for intestinal calcium absorption and for maintenance of normal bone metabolism. Cholecalciferol ("vitamin D_3") had long been considered the active form of this vitamin, until two years ago when grant-supported investigators at the University of Wisconsin isolated a new and significantly more active molecule, 25-hydroxycholeciferol (25–HCC). Subsequently they demonstrated its effectiveness in disorders of calcium metabolism which did not respond to the vitamin D preparations previously available. These studies suggested that an inability to convert ingested vitamin D to its active form (perhaps because of a missing enzyme essential for such a conversion) was responsible for the vitamin D resistance observed in these disorders. This apparent inability of the body to use vitamin D in the amounts required by normal individuals is a feature of some disorders, among them chronic renal disease and so-called "vitamin D resistant rickets." The investigators indicated that the new-found compound may provide answers to many basic questions of calcium absorption and physiology, and of bone formation; hopefully it would also lead to more effective treatment of disorders previously characterized by an apparent vitamin D resistance.

Last year these same scientists demonstrated that the liver is the major, if not the only, site of vitamin D conversion into its metabolically active form, 25–HCC. This work suggested that bone dystrophies and higher vitamin D requirements observed in patients with severe chronic liver disease may be due to the liver's inability to transform vitamin D into 25–HCC.

The investigators now have shown that patients with vitamin D-resistant rickets respond symptomatically, chemically, and radiographically to high doses of 25–HCC with no evidence of toxicity. Tritiated vitamin D (vitamin D containing radioactive hydrogen ions for biochemical tracing purposes) was administered orally to four patients with either vitamin D-resistant rickets or osteomalacia and to two normal control subjects, to determine their ability to metabolize vitamin D_3 to 25–HCC. Blood values of 25–HCC in normal subjects 24

and 48 hours later were four percent and ten percent, respectively, of the extractable label, but the four patients failed to achieve an appreciable 25–HCC concentration at any time, indicating their failure to metabolize vitamin D.

Five patients from two pedigrees of vitamin D-resistant rickets then were treated orally for 6–10 months with gradually increasing doses of 25–HHC in oil. All patients showed clinical, chemical, and radiological evidence of response: normal serum calcium and serum phosphorus levels, decrease in alkaline phosphatase levels; and X-rays showed complete healing of all fractures, marked increase in mineralization, and return to normal bone architecture. 25–HHC was found to have a short duration of action compared to vitamin D_2 or D_3, and 4,800 units per day appeared to be the minimal "healing" dose. These findings suggest that 25–HCC may prove to be a safe, effective treatment for vitamin D-resistant rickets.

Total parenteral nutrition via "artificial gut system"

Although intravenous administration of essential nutrients can restore and maintain normal nutritional status for many months in patients devoid of effective bowel function, problems of effective long-term access to appropriate blood vessels have prevented efforts to provide prolonged total parenteral feeding in the past.

Now an Institute grantee at the University of Washington has solved this problem through development of what he terms an "artificial gut" system: a system of total parenteral nutrition which utilizes the permanently implanted arteriovenous (AV) shunt that he had originally devised for artificial kidney patients. This standard AV shunt has been employed safely and effectively in artificial kidney patients for as long as ten years as a ready point of repeated access to the circulation.

For this new system, the grantee converted the same shunt to maintain permanent access to the circulation for prolonged, repeated, intermittent intravenous feeding. A silicone rubber side arm, which is filled with heparin and capped when not in use, is used to introduce concentrated sterilized nutrient solutions into the plastic shunt in which blood circulates rapidly and constantly. Thus, dilution of these irritating, and potentially sclerosing solutions occurs within the shunt and not in natural blood vessels susceptible to damage.

This unique home or ambulatory system can be self-operated around the clock to provide temporary or continual parenteral nutrition. Patients with a measure of residual bowel function, who require infusion only at night, need only uncap the side arm and connect it to a gravity-powered infusion (night-mode) system at the bedside. This home system has proved workable, safe and easy to use. It permits infusion of a 50 percent dextrose solution at rates sufficient to supply 2500 to 5000 glucose calories per 24 hours. Infusion experience in three patients for several months showed no adverse effects.

A portable infusion (day-mode) system has also been devised for those patients who require total parenteral nutrition. A battery-operated pulsatile pump delivers sterile nutrient solutions carried in a 500 milliliter plastic bag. At night the patient disconnects the portable infusion apparatus and attaches the bedside infusion system.

Use of the artificial gut system to maintain nutritional status is foreseen in patients with chronic bowel disease, or with too little remaining bowel following massive bowel resection, and in the temporary treatment of ileocolitis, mesenteric thromboembolism, and various bowel diseases in infants, as well.

Thiamine Deficiency in Alcoholism Corrected

Clinical and laboratory evidence have shown that thiamine deficiency often occurs in alcoholic individuals despite intake of established daily minimal requirements of the vitamin. This has been attributed to failure to absorb thiamine hydrochloride (THCL), a widely used food and pharmaceutical supplement, to which some individuals are refractory.

Previous studies have shown that intestinal absorption of THCL was rate-limited and was markedly reduced by either alcohol or dietary deficiency.

A New Jersey College of Medicine grantee has examined the efficacy of thiamine propyl disulfide—TPD, another form of thiamine—in correcting the thiamine depletion syndromes in alcoholic patients. His initial studies on THCL and TPD absorption in normal and alcoholic subjects with and without thiamine

deficiency have shown that TPD absorption was not rate-limited and that it far exceeded that of THCL.

The therapeutic effectiveness of THCL and TPD was then investigated in eight alcoholics with Wernicke's encephalopathy, a severe central nervous system manifestation of advanced chronic thiamine deficiency. Whereas 50 mg. of THCL had no effect after 24 hours, the same dosage of TPD raised depressed blood and spinal fluid levels of thiamine to normal values, reflected positive thiamine utilization, and resulted in disappearance of the characteristic oculomotor palsy within 6–12 hours. No adverse effects were noted when TPD was given continuously for 3–6 months.

These observations are interpreted as evidence that intestinal transport of orally administered TPD far exceeds that of THCL and permits a bypass of the intestinal block characteristic of thiamine depletion syndrome refractory to oral thiamine hydrochloride. Based on his results, the investigator has recommended that TPD should be considered preferentially for use as a food supplement to prevent thiamine depletion syndromes.

Obesity

One of the quantitatively most important nutritional problems in the U.S. today is not *under*consumption of nutrients, but *over*consumption of calories. Nearly 20 percent of all adults are overweight to a degree that impairs their health and longevity. Diet and obesity appear to be extremely significant factors in causing, preventing, and treating disorders such as atherosclerosis and hypertension, diabetes, and gallbladder disease.

Last year Institute-supported investigators reported numerous significant findings. Their research showed that adolescent girls, as a group, overestimated calories in starchy foods and underestimated them in meat portions, a bias that may be preventing fat girls, and boys, from losing weight; that exercising animals were leaner than sedentary controls of the same weight, pointing to a fat mobilizing and protein-conserving effect of exercise; and that a minimal level of carbohydrates is necessary in a reducing diet to effect protein sparing (and thus conserve lean muscle tissue) and to avoid excessive ketosis due to precipitous fat breakdown.

This past year grantee scientists investigated body tissue changes in intermittent starvation and caloric restriction, efficacy of thyroid medication in obese patients in weight-reduction programs, and size of fat cells from life-long obese patients. All proved to be fruitful endeavors indeed.

Metabolic effects of short-term fasting have been studied since 1959, but only a few studies have focused on measurement of the type of tissue lost during starvation or tissue changes which occur following starvation. Therefore, it remained unclear whether *short*-term fasting would effectively accelerate fat loss in obesity treatment.

For these reasons, grantee researchers at Georgetown University School of Medicine designed the following study to evaluate tissue changes which occur during intermittent starvation and caloric restriction. Changes in body weight, nitrogen, water, and total body fat were evaluated, with two independent techniques, in four hospitalized obese patients during seven consecutive 16-day periods. Each patient was starved for 16 days and then fed an 800-calorie liquid diet for 16 days before being fasted again.

During every starvation period the major component of body weight loss was not fat, but water and protein. (The average fat loss accounted for 20 percent of weight loss during short-term starvation.) This body weight loss was greatest during the first period of total fasting and somewhat less during the later periods of fasting.

Calculated loss of body fat, in contrast, was not significantly different during any of the four consecutive periods of total fasting, and was constant throughout periods of starvation or of caloric restriction. The average cumulative fat loss during 48 days of total starvation was not significantly different from the average fat loss during 48 days of caloric restriction to 800 calories/day.

Other researchers have suggested that with *prolonged* starvation, protein loss diminishes and fat utilization increases proportionately; more intensive research is needed along this line.

Although administration of thyroid medications to obese patients has been common and controversial practice for over half a century, few definitive studies

of their effect on weight loss have been reported. Recently, Institute-supported investigators at Yale University School of Medicine conducted a well-controlled study to delineate any possible benefits of a thyroid preparation for treatment of massive obesity.

Seventeen massively obese patients, weighing from 242 to 393 pounds, were placed on an 800-calorie diet, and were given either L-triiodothyronine or a placebo over a six month period. In 8 weeks, hospitalized patients treated with the thyroid compound had lost significantly greater weight (29.1 lbs.) than those patients in the control group (17.2 lbs.). At 12 and 24 weeks, however, there were statistically no significant differences in weight loss in the two groups. Thus this type of thyroid supplementation demonstrated an advantage only for the first 2 months. *Further* treatment did not result in any accelerated weight loss.

These investigators recommend this regimen only in healthy, well-motivated, massively obese (over 100 pounds above ideal weight) patients who do not have hypertension, diabetes requiring insulin, or arteriosclerotic heart disease, and are agreeable to prolonged, concomitant diet therapy and long-term followup. They advise that since cardiac arrhythmias constitute a significant risk, the thyroid medication should be given only during hospital supervision.

Other recent studies have focused attention on the increased number of fat cells which occur in the development of human obesity. A grantee investigator at Tufts University School of Medicine, Boston, has measured the size of subcutaneous fat cells from 10 life-long obese patients and compared them with samples of subcutaneous fat cells from 12 lean patients undergoing laparotomy.

Results showed that obese patients had large cells averaging 0.78 nanoliters in volume, whereas the average volume of fat cells from the control subjects was only 0.26 nanoliters. In the latter group, fat cell volume was positively correlated with body weight, but such a correlation did not exist among the obese patients, among whom many obese subjects had an increased *number* of fat cells. In both groups, with weight loss the size of individual fat cells decreased, but the total number of fat cells did not.

These studies indicate that grossly obese patients who gained weight from early childhood have a markedly increased number of fat cells storing an increased quantity of fat in each cell. During weight reduction the fat cells decrease in size, but the number appeared to remain essentially unchanged, implying that mature fat cells are not replaced at a measurable rate.

Utilization of new protein sources

In the face of a world-wide shortage of dietary protein Institute grantees have directed many efforts at large-scale development and clinical testing of protein blends and concentrates from such diverse sources as algae, microorganisms, and widely available indigenous plants.

Metabolic studies conducted earlier by both Johns Hopkins University grantees and by investigators of the British American Hospital in Lima, Peru, supported by the Institute, suggested that convalescent malnourished infants and children might thrive on a diet containing cottonseed flour (CSF) as the only source of protein.

They then followed "height age" and "weight age" in 14 previously malnourished infants and children with an average age of 19 months who received cottonseed flour as their only source of protein for a mean duration of 4.4 months. Three types of cottonseed flour were tested; flour prepared from glandless cottonseed, azeotropic solvent-extracted flours, and flour prepared by heat processing and screw-press extraction.

Previously malnourished infants who are well advanced in their recovery are known to gain weight easily but to lag in linear growth. Accordingly, mean gains in "height age" in these children were somewhat less than can be expected during such feeding trials in normal children. On the other hand, gains in "weight age" characteristically exceeded advances in chronologic age.

These prolonged feeding trials have established that properly processed cottonseed flour, at adequate levels of intake, can serve as the main or sole source of protein for rapidly growing infants and children at least for short periods of time. Studies such as this will enable developing countries to utilize nutritionally adequate, inexpensive proteins, which are otherwise wasted, or at best used as fertilizer, to cope more successfully with protein malnutrition problems.

Evaluation of protein malnutrition

Frank starvation is clinically obvious, but lesser degrees of protein deficiency are difficult to evaluate. Several years ago, an Institute grantee showed that a protein-deficient diet causes a decrease in diameter of the human hair root of the protein-deprived individual. Subsequently, he demonstrated decreased hair root diameter in children with kwashiorkor, marasmus, and milder degrees of malnutrition.

Another grantee at the Medical College of Georgia, now has analyzed hair roots for their protein content, possibly an even more sensitive means of evaluating nutritional protein deprivation. Groups of 10 to 100 hairs were plucked from the scalps of 53 normal control subjects and 28 chronic mental hospital patients with clinically evident malnutrition, and the total soluble protein and total DNA were measured.

Hair root protein in the control subjects averaged 18.04 micrograms per hair root. By contrast, hair roots obtained from patients with known protein deficiency averaged only 1 to 8 micrograms of protein per hair root. Similar values were obtained from hair samples from Biafran patients with established protein malnutrition, while control values from a normal Biafran field worker were in the normal range. Low hair root protein values were even detected in a number of malnourished patients with normal serum protein levels.

Refeeding of several malnourished patients resulted in increased hair root protein content as these patients gained weight. Comparison of individual hair root volume with protein and DNA content indicated that the hair root responds to protein deficiency by a decrease in both cell number and root size, as well as in protein content. In view of the ease of biopsy of this tissue and sensitivity of the hair root to nutritional influences, hair root analysis may be a clinically useful, simple means of evaluating the adequacy of the protein nutritional state.

Monosodium glutamate reevaluated

Monosodium glutamate (MSG), a common food additive, has been associated recently with the so-called Chinese restaurant syndrome, characterized by such transitory symptoms as headaches, burning sensation, and sweating experienced by some individuals after eating Chinese foods. In addition, it has been shown that feeding of MSG to newborn mice and monkeys can result in brain damage, giving rise to concern about ingestion of MSG-containing foods by pregnant women and infants.

Recently, a St. Louis University researcher, supported by the Institute, designed a study to evaluate effects of oral administration of large amounts of MSG to adult humans and gerbils in a formula diet. In this study, eleven adult male subjects were fed 25 to 147 grams of MSG per day for 14 to 42 days in a chemically defined diet formula which supplied all essential amino acids. All subjects tolerated the regimen well, showing no changes in neurologic or hepatic function, save a reduction in serum cholesterol and beta lipoproteins. None developed the Chinese restaurant syndrome, and no changes in weight, irritability, appetite, or metation were noted. The adult gerbils also showed no ill effects from the glutamate-rich diet. Further study will be needed to determine in a well-controlled fashion what effect, if any, MSG may have on young, rapidly growing organisms. Reports of ready access of dietary glutamate to the animal brain at birth but exclusion of it with establishment of an effective blood-brain barrier by the tenth day, nessitate such further study to determine the age of transition from susceptibility to tolerance for MSG in young humans. The present studies suggest, however, that high oral doses of MSG are tolerated by adult humans and gerbils.

Nutrition terminology guide published

A "Guide to Nutrition Terminology" for nutrition literature indexing and retrieval, which establishes a standard terminology for the complex field of nutrition, has been published through sponsorship of the National Institute of Arthritis and Metabolic Diseases and National Institute of Child Health and Human Development, under contract with Vanderbilt University.

The book includes information on subjects traditionally related to nutrition such as clinical medicine, biochemistry, agriculture, and economics. In addition, it reflects such contemporary concerns as the behavioral and social results of malnutrition. While the major emphasis of the "Guide" is on human nutrition,

it has been structured to permit systematic expansion by workers in other fields, such as animal nutrition or food technology. In addition to alphabetical and categorical listings of terms, it contains a glossary designed to indicate how selected terms are used in nutrition.

NUTRITION RESEARCH ABROAD

Only half of the earth's population has an adequate diet, and millions live on the edge of starvation. Technologically advanced countries that produce an overabundance of food certainly possess the knowledge and methods to accelerate food production and distribution in developing countries. The Institute's program, therefore, is directed to research toward improvement of human nutrition abroad in order to enable developing countries to transform drastic food shortages to nutritional adequacy. In Southeast Asian countries results of such research may stimulate an emergence from subsistence to self-sufficiency.

Traditionally, the Institute has conducted nutrition research in developing countries overseas because large populations afflicted with specific nutritional deficiency diseases can be found conveniently and can be studied more effectively there. These investigations have yielded considerable contributions to our own knowledge of normal nutrition and nutritional deficiences, as well as benefits to the nutritional status of the local populations.

Southeastern Asia

The mission of the nutrition portion of *NIH's U.S.-Japan Cooperative Medical Sciences Program* is to support research aimed at practical solutions to nutrition and nutrition-related problems of countries in Southeast Asia. This Program is financed by a separate appropriation carried in the budget of the National Institute of Allergy and Infectious Diseases and is administered for programmatic reasons by the NIAMD. This substantial grant and contract Program supports research in the following priority areas: nutritional anemias; requirement for essential nutrients; relationship between malnutrition and infection; biochemical adaptation to malnutrition; methods for evaluation of nutritional status; investigations into the occurrence and nature of toxic substances in foods; and development of low-cost protein-rich foods, including the genetic improvement of protein concentration and composition in rice.

Rice is the principal food of 60 percent of mankind; however, ordinary commercial rice does not contain enough protein to support normal growth and development of infants and children maintained on a predominant rice diet, and does not protect the adult population from serious protein undernutrition. If the present protein level of rice (approximately 7½ percent) could be elevated by several percentage points, an automatic and sweeping nutritional improvement would take place in all the populations for whom this one crop represents the nutritional mainstay. Such development concomitantly would relieve the current burden of the United States which supplies hundreds of millions of dollars' worth of supplementary foods to developing rice-eating countries. The potential nutritional improvement among Southeast Asian populations and developing rice-eating countries throughout the world is an important aim of the U.S.-Japan Program and of the applied nutrition program of the Institute.

Major findings have emerged from an ongoing research project aimed at improving the protein level of rice. Last year's work on this contract identified about 100 rice varieties which contain between 13½ to 17½ percent protein, and growing experiments are continuing under Southeast Asian climatic conditions to identify specific rare high protein varieties (from among these 100 varieties) which would be agriculturally and commercially feasible in a Southeast Asian setting. Six high protein strains of rice, possessing near-ideal plant characteristics including disease resistance and a high yield per acre, were crossbred successfully with a new rice variety (IR_8) which had been developed previously at the Institute. Further crossbreeding of the resulting hybrids was carried out, and researchers now report that these lines consistently average more than three percentage points higher protein content than conventional rice. These lines are currently being assessed in yield trials at a high level of nitrogen fertilizer. In a related effort to establish a higher protein strain, mutations were induced in rice plants at Japan's Institute of Radiation Breeding. Four high-protein mutants were confirmed as having higher levels of protein, but the lysine (an amino acid) content was not as high as had been desired.

Investigation of the effects of higher protein levels on other grain properties revealed that low and high-protein rice samples of the same variety had the same crude fat content, and similar microscopic structures of protein bodies. To determine the quality of rice protein as a function of protein content a cooperative study was undertaken at the Nutrition Institute of Central America in Panama. Rats fed on milled rice of three varieties differing in protein level showed relative gains in weight related to grain protein content.

Encouraging research progress is being made under other grants and contracts in understanding nutritional problems that may significantly aid efforts in malnutrition prevention in the developing countries of Asia. Important highlights of current research projects are: use of measurements of brain electrical activity to detect central nervous system consequences of early malnutrition; studies of the effects of supplementary feeding upon lowering morbidity and mortality from diarrheal and other infectious diseases; evaluation of effects of amino acid (methionine) fortification in improving the value of soybean protein for feeding children, as well as demonstration of several practical low cost vegetable mixtures for supplementary feeding in infants and young children; and investigation of the widespread occurrence of mold toxins in foods in Southeast Asia. The reader is referred to the Institutes' 1970 Special Report on Nutrition for a summary of liast years' projects which also helped advance the objectives of the U.S.-Japan Cooperative Medical Sciences Program.

Protein Malnutrition Studies in India

Significant achievements are also seen in two interrelated research and development projects administered by the Institute in South India, and funded through Public Law 480 U.S. surplus commodity funds. One project is located at the Central Food Technological Research Institute (CFTRI) in Mysore, and the other at the Christian Medical College (CMC), in Vellore. Both projects are part of a comprehensive program to find a practical answer to the problem of protein malnutrition in a typical underdeveloped-country setting, while simultaneously studying intermediary metabolism and selected metabolic disturbances in patients hospitalized for kwashiorkor (protein malnutrition).

The Mysore project primarily is concerned with the laboratory development of protein-rich food supplements, based on indigenous protein sources, intended to prevent the widespread endemic kwashiorkor prevalent among preschool-age children in India. Secondarily, this project involves animal testing and evaluation of such protein supplements, and studies of intermediary metabolism in kwashiorkor. The Mysore project has also become involved in the problem of aflatoxin, a highly toxic substance produced by mold growth in a wide range of foodstuffs in tropical countries.

Aflatoxin is known to cause liver damage in the young of many animal species and had been linked with childhood liver cirrhosis in India through identification in cirrhotic children's urine, in their mother's breast milk, and in a dietary staple, crude peanut oil.

The recent accidental ingestion by 20 Indian children of one to two ounces of aflatoxin-contaminated peanut protein flour, daily for 5–30 days, has permitted study of its toxic effects in human beings. A one year follow-up study of the children, all of whom had suffered from protein malnutrition, revealed hepatic lesions identical to those in Indian childhood cirrhosis. These early hepatic lesions resembled aflatoxin-induced hepatic lesions in young monkeys, while the hepatomegaly (liver enlargement) typical of protein malnutrition, gradually progressed to the hepatomegaly of Indian childhood cirrhosis. It has been known that the toxic effects of aflatoxin are enhanced in rats by maintenance on a low protein diet. Thus, children suffering from protein malnutrition might develop hepatic lesions while ingesting only 200–400 micrograms of aflatoxin per month from contaminated food. The present data strongly indicate that the counterpart of aflatoxin liver injury in young animals is infantile cirrhosis in children.

The Vellore project encompasses clinical trials of the value of experimental protein blends developed in Mysore in the treatment of patients hospitalized for kwashiorkor, and large-scale feeding tests in controlled institutional and village populations of the prophylactic value of these food supplements in the diet of weaning and school-age children. In addition, selected metabolic disturbances associated with kwashiorkor are studied in hospitalized patients. The reader is referred to the 1969 Special Report on Nutrition by the National Institute of

Arthritis and Metabolic Diseases for a detailed account of the numerous and substantial accomplishments of these projects to date.

The prominent study last year concerned fortification of wheat with lysine, the first, most limiting amino acid in the nutritionally incomplete wheat protein. Like many vegetable proteins, wheat protein is not of high enough biological quality to support rapid growth in children and to serve as the main source of protein in the human diet. (Proteins of high biological value, usually from animal sources, such as milk, eggs, meat and fish, have a qualitatively more complete content of amino acid components). In this study lysine-fortified wheat was examined for its potential in supporting growth of children when it is the only source of dietary protein. During a 6-month experimental period children on a lysine-supplemented wheat diet grew significantly in height compared to the children in the control group. This recently concluded investigation is particularly gratifying as it represents the first conclusive study that lysine fortification of wheat protein can significantly improve the growth of preschool children. The importance of the study lies in the fact that it has demonstrated the potential benefit of what may become an inexpensive, yet effective method of improving protein nutrition which is not dependent on education of individuals toward better nutrition (a slow procedure at best) or on major changes in the dietary habits of local populations in developing countries.

The addition of inexpensive synthetic lysine to wheat from the United States might improve the biologic quality of wheat considerably—to the point where lesser quantities of the expensive and unobtainable animal proteins would be needed to attain satisfactory nutrition in the population. Lysine-supplemetation of wheat is logistically feasible primarily for those population groups residing in cities, or to those consuming centrally processed cereal products. An expanded program, however, might reach large numbers of non-urban peoples as well.

In a related study of the nutritive value of cereals, the amino acid composition of two different diets, in which wheat and rice, respectively, were the sources of dietary protein, was examined for the effects on the growth rate of preschool children. Children, aged 2 to 5 years residing in an orphange, were maintained on two different diets, both providing two grams of vegetable protein and 100 calories per kilogram body weight per day, for a control period of 6 months. The children were divided into two groups matched for height, weight, age, and rate of growth, comparable to Indian rural children of the same age. Twenty-two children were given the wheat-based diet, and 24 were fed the rice-based diet.

The increase in height of those children fed the rice-based diet was 0.67 cm/month and that of the children on the wheat-based diet was 0.43 cm/month. The children maintained a positive nitrogen balance on both diets. Amino acid analysis of the cooked foods showed the wheat-based diet to be limiting in the amino acids lysine, methionine, threonine, and isoleucine, and the rice-based diet limiting in methionine. The normal rate of growth of the children fed the rice-based diet suggested, however, that methioine was *not* actually a limiting factor. Thus, although both diets provided the same quality of protein and calories, the children grew at different rates because the wheat-based diet was limiting in four amino acids, including lysine.

Growth studies in preschool children have also been carried out with lysine and threonine-fortified rice, following a protocol similar to the wheat fortification study. The experimental group was given a diet in which rice fortified with lysine and threonine (the two nutritionally most limiting amino acids in rice protein) was the main-stay of dietary protein. A well-matched control group was given an identical diet, but here the rice was unfortified. The protocol of this experiment called for *complete* consumption of the respective diets by every participant in order to obviate highly varied results based on individual appetite or caprice.

In contrast to the previous study involving lysine-fortified wheat, in this case there was no significant difference between the total growth (height and weight) of the experimental group and the control group. The investigators concluded that under the conditions of this particular experiment, when both groups were made to consume their entire dietary allowance [which fully satisfied all their caloric requirements] the children apparently received a complement of amino acids from their rice-based diet sufficient to attain satisfactory growth; thus in view of the fact that the conrol group achieved normal growh, the experimental group, despie its consumption of added amino acids could not and did not exceed the

growth of the control group. They feel that the addition of lysine and threonine to rice in a predominant rice diet does not impart a nutritional advantage to the rate of growth of preschool children as long as an *adequate* amount of rice is actually consumed, a full complement of calories is supplied, and no other obvious nutritional deficiency exists. Indeed, other nutrition surveys in South India have substantiated these findings; they indicate that in the child populations surveyed the primary nutritional insufficiency was of *calories* and that usually there was an insufficient intake of rice.

The latest current investigations are concerned with quantification of the effects of malnutrition on the physical and mental development of children through utilization of anthropometric measurements and tests of neurointegrative performance; biochemical and clinical studies of protein-caloric malnutrition and allied deficiencies through assessment of intestinal function and riboflavin nutritional status, as well as studies of vitamin A and carotene absorption; and examination of effects of experimental malnutrition in animals, such as acute threonine deficiency in rats.

Benefits to United States from overseas nutrition research

The recent discovery of pockets of malnutrition and nutritional deficiencies within our own population indicates strongly that these studies abroad are not merely altruistic research exercises, but investigations of utmost importance to the welfare of the United States. The scientific findings emanating from this work are enriching the fund of scientific knowledge in the United States. Of particular importance are the contributions concerning intermediary metabolism during protein deprivation and vitamin deficiency which could not have been carried out adequately in the United States because of a lack of sufficient patient material concentrated in any one particular locality. Since the majority of these findings are disseminated to the rest of the world through the medium of the American scientific literature they are enhancing the standing and image of American science. These particular studies are also an example of effective and beneficial use of U.S.-owned counterpart funds ("PL–480 funds") in biomedical studies, demonstrating the value of this funding mechanism which demands no current expenditure of U. S. funds.

These efforts also contribute specifically to the technological know-how of the American food industry, particularly to our knowledge concerning naturally occurring mold toxins in foods, such as aflatoxin. Traces of aflatoxin have been found in U. S.-made peanut butter. There is considerable importation of peanuts (which may be contaminated with aflatoxin) to the United States from abroad, and little is known concerning the presence of aflatoxin in many U.S. feeds or the potential economic importance of such contamination. Laboratory techniques and technologic achievements in aflatoxin destruction through special food processing methods developed in the Institute's Mysore project are of considerable importance in the United States from the standpoint of both public health and agricultural and food economics, particularly since aflatoxin has now been implicated in liver damage in man.

The Mysore-developed protein rich products evaluated in Vellore, together with the Vellore-initiated lysine fortification of wheat, serve as prototypes for similar efforts in other developing regions of the world wherever agricultural necessities and economic and social factors preclude large scale inclusion of animal proteins in the diet. Projects like these, in addition to the scientific aspects beneficial to the United States, are aimed at helping a developing country help itself. Rather than letting the host country rely on gifts of expensive protein-rich foods (such as powdered milk) from the United States which this country cannot afford forever, it gives the developing country the scientific know-how to utilize effectively inexpensive proteins which it can produce by itself. Thus, the country can cope more successfully with the problem of protein malnutrition among its children.

OUTLOOK

Through application of new principles and laboratory techniques learned in recent years from studies mostly supported by this Institute, the evaluation of nutritional status in the absence of overt disease is no longer dependent on ill-defined lesions and symptoms or on the subjective judgment of the examining physician. Improved methods of determining nutritional status and revised

criteria for normal nutritional status have contributed to a new emphasis on the definition and diagnosis of malnutrition.

These advances in knowledge can now form the basis for the more exacting nutrition surveys used to pinpoint pockets of malnutrition in vulnerable population groups in the United States. They will also be necessary in aiding many developing countries to cope with the world-wide famine and malnutrition predicted for the near future if the runaway disproportion between population increase and agricultural self-sufficiency is not drastically reversed.

Once again, the study of nutrition has taken on the vigor which provided its first big advances with the discovery of vitamins and nutrition deficiency diseases fifty years ago. Although the investigations this past year have proven highly productive in adding to our understanding of human nutrition in health and disease, they have also indicated new areas for much-needed new research efforts in order that more wide-spread and more permanent controls of mankind's chronic nutritional disorders may be accomplished. The Institute is anticipating more significant advances in these rsearch endeavors in the coming years.

NURTITION WORK OF CDC AND AGRICULTURE

Mr. SMITH. What are the dividing lines between what you and CDC and the Department of Agriculture are doing on nutrition?

Dr. WHEDON. Traditionally the nutrition research efforts of the Department of Agriculture have been in the area of nutritive composition of agricultural products and human foods. In addition, a major effort is devoted to investigation of the nutritive value of feeds for farm animals and of the nutritional requirements of animals destined for human consumption or for other commercial purposes.

The nutrition activities of NIH are primarily focused on research on *human* nutrition. This encompasses such aspects as the normal nutritional requirements of man during different stages in his life cycle, malnutrition and nutritional deficiency diseases, therapeutic nutrition and special diets in certain diseases, appetite regulation and food intake, digestion and absorption of nutrients in the gastrointestinal tract, the biochemistry and physiologic role of nutrients and their fate in the body, interrelationships between different nutrients and between nutrients and hormones, and nutrients and enzymes, the relationship of the intestinal flora to nutrition, obesity, malabsorption of specific nutrients, and the relationship of diet to specific disease entities, such as celiac disease and others.

Whereas the nutrition effort at NIH is concentrated on research, the Nutrition Program at the Center for Disease Control in Atlanta focuses on application of the known aspects of nutrition on a community level; the CDC nutrition activities emphasize demonstration projects in the community, extending help and direction to State department of public health in matters related to nutrition, the conduct of nutrition surveys of the population where and when indicated, and stimulation of nutrition education efforts on the community level.

PROGRESS IN DEVELOPMENT OF KIDNEY MACHINES

Mr. SMITH. Tell us more about your artificial kidney program. What is new in your development of kidney machines? The justification on page 182 seems to me a little pessimistic.

Dr. WHELDON. I am sorry that our justification conveyed that impression. On the contrary, we are making steady progress in this program, and I would like to mention briefly our progress.

Among our achievements were the development of a new generation of compact artificial kidneys, the so-called hollow fiber dialyzers. The first of these has been introduced into commercial production and sale after having proven extremely effective and relatively simple and inexpensive in use because they can be reused several times before being discarded. Similar compact dialyzers of slightly different design are in the process of development.

Another innovation is a new, easy-to-use, presterilized "envelope dialyzer" which is now produced commercially and which greatly simplifies home dialysis with the conventional Kiil equipment. As you know, dialysis in the hosiptal is extremely expensive and very few patients can afford it; in contrast, dialysis carried out by the patient in the home costs much less. Probably the most inexpensive, highly effective dialysis is obtained with the conventional Kiil artificial kidney. Unfortunately, since dialysis with this machine is also quite complex because the patient must set up and sterilize the machine by himself or with the aid of his spouse, not every patient is mechanically adept enough to do this correctly; failure of complete sterilization of the apparatus, for instance, will lead to a life-threatening infection of the blood. Development of this new envelope dialyzer now enables patients to engage in inexpensive and effective home dialysis who would otherwise have to be dialyzed in the hosiptal which, however, was out of their reach financially.

Another contractor of the program developed a new, clinically successful method of a closed-loop, automated peritoneal dialysis with permanently implanted access devices to the abdominal cavity. This type of dialysis, peritoneal dialysis, involves the repeated washing of the abdominal cavity with a sterile solution to remove uremic waste products. If not automated, the procedures are cumbersome and the cost of the solutions used is quite high. This new sytsem has now been introduced into experimental usage in the home where it promises greater safety and convenience coupled with the greatly reduced cost for the otherwise expensive sterile and pyrogen-free dialysis fluid. As additional favorable experience with this type of system accumulates, it is possible to foresee that automated peritoneal dialysis based on permanently indwelling abdominal catheters will have a place in the broad picture of end-stage kidney disease care—particularly in cases where briefer periods of maintenance therapy are foreseen as, for instance, in the case of patients waiting for renal transplantation where a definite living donor is at hand. This type of dialysis is also a lifesaver in those patients where all available locations for blood vessel shunts for regular hemodialysis have been used up.

Another contract resulted in a significant improvement of the conventional Kiil dialyzer; extended clinical tests during the last year of this new high-performance device give promise that "one shift dialysis" with parallel plate (Kiil type) dialyzers may become a reality. The conventional Kiil type dialyzer is preferred by many clinicians because it appears to result in somewhat better rehabilita-

tion of patients; on the other hand, its use—from 9 to 15 hours per dialysis session—extends beyond a single nursing shift in the hospital. Hospital dialysis within the time limits of a single nursing shift would result in major savings for this currently very expensive method of treatment.

Development of zirconium compounds as selective sorbents for uremic wastes, accomplished under an Institute-supported research contract, has now led to further industrial development of new dialysate delivery systems which use only two liters of dialysate which is being constantly regenerated with the aid of sorbents of uremic toxicants, instead of the conventional 150 to 300 liters of wash-solution. This new development which is now being clinically tested, makes possible the design of compact, portable, suitcase-sized artificial kidneys.

Mr. Chairman, I have considerably more progress to report along these lines. We have prepared a special report which covers in greater detail last year's research accomplishments of our artificial kidney contract program. With your permission we would like to submit this report to the committee for further information.

(The information follows:)

SPECIAL REPORT: KIDNEY DISEASE AND THE ARTIFICIAL KIDNEY[1]

Kidney diseases, artificial kidneys, and kidney transplants, together with a variety of urologic disorders, constitute a high-priority research area for the National Institute of Arthritis and Metabolic Diseases.

End-stage kidney disease is responsible for the deaths each year of about 50,000 individuals. Many thousands of Americans are destined for premature death from renal failure unless better knowledge can be developed concerning basic kidney mechanisms and disease processes, while improvements are made in artificial kidneys and in kidney transplant procedures. Fortunately, current efforts will assure that lifesaving knowledge and techniques will be available.

ADVANCES IN KIDNEY TRANSPLANTATION

Until kidney diseases can be controlled or prevented, end-stage kidney disease will continue to present an emergency situation. Special diet may provide a delaying action; artificial kidneys may enable many patients to remain alive and live relatively normal lives; but in many cases a kidney transplant offers the only truly hopeful solution.

Improved method of tissue matching

Considerable progress continues in the area of kidney transplantation, which integrally includes advances in organ preservation and immunosuppression. In the former field, for example, a grantee of the Institute has shown that tissue matching involving both leukocytes and kidney cells markedly improves the survival rate of transplanted human cadaver kidneys. In 1968, an Institute grantee first devised a method of preserving isolated human cadaver kidneys for as long as 37 hours. Thus, time was gained for proper matching of cadaver kidneys which had become available and of potential recipients by tissue typing and for adequate preparation for surgery. Utilization of this kidney preserving device (The "Beltzer Apparatus") now has permitted an important modification of standard phenotyping and cross-matching procedures to a point where cadaver kidney transplants can do as well as those from "A" matched (on the Terasaki matching scale) siblings. Conventionally, only the leukocytes of the donor and potential recipients are tissue-typed and subsequently the best matching com-

[1] Prepared February 1971 as background information for the Director, National Institute of Arthritis and Metabolic Diseases, Public Health Service, U.S. Department of Health, Education, and Welfare, in connection with the fiscal year 1972 appropriation hearings.

bination is selected. Under the new system, the recipient's leukocytes are typed and cross-matched to the cadaver donor's *kidney cells* as well as leukocytes. Apparently there is antigen on the kidney cells not detected on leukocytes during conventional phenotyping. Thus, many apparent "good" matches based on leukocyte-leukocyte typing alone can now be revealed as merely "fair" on the basis of the more complete double-matching system, and poor outcome of cadaver transplants due to rejection can be more easily predicted and avoided.

Correlation of tissue typing and organ survival

Recently, another Institute grantee, one of the world's foremost authorities on tranplantation immunology, reported on results of a survey, conducted by the University of California, Los Angeles, correlating survival of more than 1,000 kidney grafts with their pre-transplant ratings through tissue typing. The correlation was poor, and the investigator concludes that, while there is every reason to believe that the antigens being identified in typing represent the majority of immunological differences involved in organ transplants, more must be learned concerning precisely *which* of these antigens are critical to survival of the grafts.

Successful cadaver allografts

Meanwhile, University of Wisconsin Medical School grantees have found that some cadaver kidneys provide patients with grafts as satisfactory as those received by other patients from living, related donors. [This finding is contrary to the general experience with cadaver transplants and is limited to instances where the graft has survived over 2 years.] In the Wisconsin study, specific renal function measurements of four cadaver recipients surviving a mean of 29 months without experiencing rejection were compared with those of seven recipients of well-matched organs from living related donors who had maintained optimal stability of renal function a minimum of 1 year following transplants. Kidney function of the cadaver group compared favorably or even exceeded that of the living donor group.

Adjuncts to tissue typing

Experiments by a grant-supported Denver surgical team continue to indicate that antilymphocyte serum (ALS) and antilymphocyte globulin (ALG), a more purified fraction, can aid the body in accepting a new organ.

The globulin tends to suppress the cellular reaction (lymphocyte or "white blood cell" attack) largely responsible for damaging the transplanted organ. Usually prepared in horses or rabbits against pooled human donor lymphocytes, the serum is commonly used in conjunction with other immunosuppressive drugs to combat graft rejection. Since 1966, this team has been employing heterologous ALG with the immunosuppressants azathioprine and prednisone in the management of several hundred heart, kidney, and liver transplant patients, with a consistently superior record of survival of the grafted organs.

Another procedure in which initial encouraging results have merited continued investigation is based on observations by grantees of the National Institute of Arthritis and Metabolic Diseases and the National Heart and Lung Institute at the University of Texas Medical Branch, Galveston. They have been achieving good results in using repeated lymph drainage as a means of removing the white cells that are involved in graft rejection, thus permitting postoperative survival of kidney grafts, while eliminating necessity for postoperative isolation and immunosuppressive drug therapy of patients.

KIDNEY DISEASE RESEARCH

In a large number of studies throughout the nation every aspect of the kidneys and the urinary tract in health and disease is being examined, including renal structure as correlated with function; control of sodium excretion; pathogenesis of congenital malformations; drug-induced kidney damage; effects of streptococci and of antibody-antigen complexes on renal tissues; subcellular reactions to injury in the kidney; vitamin metabolism and chronic renal disease, to mention a few approaches.

Distribution of uromucoid in the kidney

A recent study by Institute grantees at the Michael Reese Hospital and Medical Center and the University of Illinos College of Medicine has helped to pin-

point the origin of uromucoid. This threadlike mucoprotein is the principal substance of urinary casts which obstruct the kidney's excretory ducts in acute renal failure. Using an immunofluorescence technique, the Illinois scientists found that the substance is secreted by cells of collecting ducts, the loops of Henle and distal convoluted tubules. This is a site where urine becomes acidified and causes the secreted uromucoid to precipitate in the form of solid casts.

Secondary Hyperparathyroidism Studied

Other grant-supported investigators at the Washington University School of Medicine, St. Louis, Mo., this past year have described the pathogenesis of secondary hyperparathyroidism in advancing kidney disease, and have demonstrated that early secondary hyperparathyroidism can be prevented in animals by maintaining a low dietary phosphate intake, an observation which may have clinical significance for kidney patients. Inasmuch as secondary hyperparathyroidism and consequent osteodystrophy are seemingly inevitable complications of chronic kidney disease, further elaboration of the mechanisms whereby destruction of nephrons (the multiple tiny blood filtration units of the kidney) leads to hypersecretion of parathyroid hormone is of great clinical concern. The researchers have proposed that with progressive loss of excretory kidney function, transient phosphate retention occurs in the blood and ionized calcium blood levels fall reciprocally. This decrease in blood calcium stimulates compensatory secretion of parathyroid hormone by the parathyroid glands, and phosphate excretion per remaining individual nephron rises, restoring plasma phosphate and then calcium levels toward normal. Parathyroid hormone (PTH) levels, however, remain elevated, and increase with each wave of nephron loss and eventually lead to the excessive bone decalcification characteristically seen in kidney failure.

In experimental studies in dogs which were being made progressively uremic this sequence of events was demonstrated in animals receiving a *normal* phosphate intake. In those receiving a phosphate deficient diet, parathyroid hormone levels did *not* rise above normal even in greatly advanced uremia.

These studies demonstrate that transient phosphate retention resulting from partial nephron destruction appears to play an important role in the pathogenesis of secondary hyperparathyroidism. Although early secondary hyperparathyroidism can be prevented by maintaining a low phosphate intake, from a clinical point of view marked phosphate restriction for a prolonged period of time would not be desirable. If phosphate intake were reduced in direct proportion to residual kidney function beginning early in chronic renal disease, it may well be that secondary hyperparathyroidism could be prevented (at least until the onset of the eventual vitamin D resistance characteristic of uremia) without phosphate depletion and osteomalacia.

Characterization of Streptococcal Components in Glomerulonephritis

After recovering streptococcal substances from the glomeruli of the kidneys of patients with acute glomerulonephritis (as reported last year), grant-aided investigators at New York Medical College have proceeded to characterize these streptococcal components. By labeling with fluorescent dye the immunoglobulin G (IgG) fraction of sera from patients with acute poststreptococcal glomerulonephritis, the researchers were able to demonstrate that apparently only certain group A streptococci were involved in the inflammatory process, and two possible antigens were isolated. One of these, a lipoprotein with a molecular weight of approximately 120,000 appears to be derived from the plasma membrane of these streptococci. Research such as this is pertinent to the possible development of a vaccine to prevent infections with strains of streptococcal bacteria which are capable of inducing acute glomerulonephritis in their host.

Differential Diagnosis of Lupus Nephritis

Lupus nephritis is a term used to describe the renal involvement that may complicate systemic lupus erythematosus. Recent studies have revealed that there is a great variation in the clinical and pathologic manifestations of lupus nephritis; it may appear benign, gradually progressive, or rapidly progressive and fatal.

These observations have led to a study at the University of Connecticut, supported by the Institute, of the natural history of lupus nephritis in 52

patients. Histologic examination of renal lesions have now resulted in the classification of lupus nephritis into three separate groups, each with distinctive clinical manifestations and courses. "Focal lupus nephritis," described in 14 patients, is characterized by a proliferative nephritis involving small circumscribed portions of kidney tissue comprising only a few glomeruli "Diffuse lupus nephritis" (24 patients) involves large portions comprising most or all glomeruli. Other renal abnormalities, including capillary wall thickening, are also more conspicuous and widespread in this type of lupus nephritis. "Membranous lupus nephritis" (14 patients) is marked by diffuse uniform thickening of capillary walls throughout the renal tissue. These three types of histologic change are thought to represent three distinctive clinical entities rather than various stages of lupus nephritis. Further studies of the immunologic abnormalities in the three groups will be required to obtain a better understanding of their pathogenesis.

ARTIFICIAL KIDNEY—CHRONIC UREMIA PROGRAM

If and when kidney transplantation becomes a widely used, routine procedure, the artificial kidney will not be discarded. Many chronically uremic patients are not medically or psychologically suitable candidates for transplantation. Furthermore, patients who are suitable transplant candidates will have to be sustained with an artificial kidney until they are well enough to have a transplantation operation and until a suitable, antigenically matching donor kidney can be found for them. Also they may have to be placed on an artificial kidney after the operation if the donated kidney does not function properly for a time or is rejected.

The problem of perpetual maintenance of patients with artificial kidneys is complicated by the fact that the cost of currently available techniques is too high, both in terms of money and qualified manpower, to permit widespread patient treatment. Also, patients maintained with the aid of artificial kidneys continue to display a number of undesirable symptoms related either to the underlying disease or to the treatment.

The Institute's special Artificial Kidney-Chronic Uremia Program, for which the past year was a fifth anniversary, has been created to deal with these problems. An up-to-date report of progress and future plans follows.

Although artificial kidneys had been known for many years, until 1960 they could be used only a few times in each individual for lack of a practical method for repeatedly connecting the patient's bloodstream with the artificial kidney machine. In that year a group of Institute grantees at the University of Washington developed permanently indwelling plastic blood vessel connections ("cannulas") which made possible the repeated joining of patients with irreversible kidney failure to artificial kidneys for intermittent maintenance treatment.

Subsequently, these investigators proved the feasibility of maintaining life in in such patients for a number of years with the aid of artificial kidney treatments ("hemodialysis") given twice or three times each week. With increasing experience with this new treatment modality it soon became evident that existing artificial kidneys and dialysis methods were as yet not optimal, that maintenance treatment with artificial kidneys was extremely expensive and not within the reach of most individuals who needed it, and that rehabilitation of patients on chronic dialysis, using present methods and equipment, was not always optimal. It was estimated, based on recent experience, that about 7,500 patients of the yearly 55,000 individuals with end-stage kidney disease would possess the necessary medical and psychological prerequisites necessary for successful long-term dialysis treatment. The emergence of this new lifesaving treatment encouraged the Congress, in the summer of 1965, to appropriate funds to this Institute for the pursuit of a planned and centrally directed program of research and development, utilizing predominantly a direct contract approach, aimed at the development of improved and less expensive dialysis hardware and methodologies and at optimal rehabilitation of chronic dialysis patients.

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, 25 outstanding authorities active in the field of chronic uremia, hemodialysis and bioengineering 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.

Problems of highest priority

The following are outstanding problems in dialysis toward which the Institute is directing its current efforts through the Artificial Kidney—Chronic Uremia Program.

1. Cannulas. The life and function of the permanently implanted plastic tubes 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. Isolation and identification of the currently unknown toxic factors in uremia. Any rational development of new, more effective dialysis membranes depends on the discovery of as yet unknown substances which accumulate in the blood of the patient with insufficient kidney function and which are specifically responsible for the toxic manifestations of uremia. Moreover, the possibility exists that once these substances are identified, more direct approaches can be developed to deal with their elimination (their precursors may be deleted from the diet, specific adsorbents may sequester them from the bloodstream or the gastrointestinal tract, or specific drugs may be found to detoxify them).

4. Design of new compact dialyzers and whole artificial kidney systems which are more effective than those currently available, and characterized by low initial and operational costs.

5. 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 risk of transfusion hepatitis.

(b) 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, less likely, 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. In many cases there is a tendency to decalcification of bone with resultant fractures produced by minor stresses.

These problems and the high requirements for personnel are primarily responsible for the current high cost of dialysis, which averages $25,000 per year in patients maintained by hospital center dialysis.

Current activities

At present about 65 carefully selected research and development projects are in existence, financed by the Institute's contract funds. These contracts were placed with universities, nonprofit research laboratories and industrial concerns, and constitute a broad-spectrum approach to the problems of highest priority. Several projects each are focused onto the problem areas mentioned above and to related investigations which promise to make the treatment of end-stage kidney disease less expensive and more effective, including evaluation of special protein-restricted diets in the maintenance of uremic patients for whom chronic dialysis is deemed not feasible or unobtainable, and the maintenance of a national registry of all patients who are currently being maintained with the aid of dialysis.

Accomplishments

Among recent achievements is the development of a new generation of compact artificial kidneys, the so-called "hollow fiber dialyzers." The first of these has been started in commercial production after having proven extremely effective and relatively simple and inexpensive in trial use. Similar compact dialyzers of slightly different design are in the process of development.

Another innovation is the presterilized, disposable "envelope kidney" that saves many hours of preparation time in home dialysis. Developed for use with the

conventional Kiil artificial kidney machine, the envelope kidney is essentially a sealed sandwich of Cuprophan PT–150 membranes supported externally by a fiber screen. Blood ports for attachment to the patient's circulation are included within the sealed package.

Because the membranes are presterilized with ethylene oxide gas, the patient and/or his spouse no longer must begin assembly 8 to 10 hours prior to dialysis to allow for chemical disinfection of the membranes with strong smelling formaldehyde solution. With the new envelope kidney, assembly may begin only an hour prior to dialysis, and can be completed by one person alone. Thus, the patient and his family need no longer feel that dialysis is "part of life nearly 100 percent of the time."

The cost of a pair of envelopes, presterilized and ready for use in a double-layer Kiil artificial kidney, is approximately $6, as compared with about $17 for a prepackaged coil-type dialysis canister, the only other presterilized dialysis unit commercially available at this time.

The rejection rate due to leaks of the assembled envelope kidney has been less than 1 percent during more than 200 clinical dialyses with 14 patients, thus eliminating a frequent and considerable source of frustration and time loss. Preliminary clinical results from trials of the envelope kidney have been excellent, with no adverse reactions, and with blood purification performance as good as or better than with standard membranes in the Kiil apparatus. At this point, no road blocks are foreseen to commercial production and routine use of the envelope kidney.

Hollow-fiber kidney now mass produced

The new and unique hollow-fiber capillary kidney, mentioned in previous reports, has been given extensive clinical tests and mass production has started this year. Made by the Cordis-Dow Company of Miami, Florida, the unit is competitively priced at under $18 and offers several advantages over conventional systems.

The hollow fiber artificial kidney consists of 11,000 hollow cellulose thread-like tubes (simulating kidney capillaries) bundled together into a compact plastic cylinder about the size of a quart milk bottle. Blood is passed through these man-made capillaries and they, in turn, are constantly washed on the outside by a blood-purifying dialyzing solution. The unique construction of the kidney provides an enormous surface area at the cellulosic blood-dialysate solution interphase at which toxic waste products diffuse from the blood into the dialysate fluid. This new dialyzer is designed so well that no external blood pump is needed to drive the blood through it. Moreover, its internal blood compartment volume is so small that only about 70 milliliters of the patient's own blood are needed to prime the unit, thus eliminating the need for compensatory blood transfusions (and their attendant hazard of hepatitis) associated with the use of most conventional artificial kidneys. The new compact capillary kidney is easy to use in a hospital or home dialysis setting since it comes pre-sterilized, filled with saline and ready-to-use.

Other methods under development

While new artificial kidneys are in various stages of development, other methods of removing waste products ordinarily handled by the normal kidney are being studied. These include oral administration of a modified starch to bind urea in the gastrointestinal tract. The resulting urea-oxystarch complex leaves the bowel via the feces and the uremic patient's urea burden is significantly reduced. Such a daily regimen has been shown to reduce the need for dialysis from three times a week to only one time. Preliminary clinical trials of this novel adjunctive treatment have been favorable and additional efforts will be exerted to further develop and refine this approach and to develop other possible intestinal sorbents of uremic toxins.

Hyperparathyroid bone disease arrested

One contractor at the Montreal (Canada) General Hospital has shown in preliminary investigations that dihydrotachysterol arrests the hyperparathyroid bone disease that characteristically accompanies chronic kidney failure and chronic hemodialysis. Hyperparathyroid bone disease, manifested by hypercalcemia, calcification of soft tissue, and decalcification of bone, is a well-recognized accompaniment of renal failure and chronic hemodialysis. Although the

condition usually responds to parathyroidectomy, it has been difficult to manage medically because uremic patients characteristically develop vitamin D resistance with attendant impaired intestinal calcium adsorption.

Dihydrotachysterol, a compound structurally similar to vitamin D, but differing markedly in its biological action, now has been found capable of arresting the hyperparathyroid bone disease seen in patients on long-term dialysis. Marked improvement was observed in all six patients treated in preliminary studies, suggesting that remission of such bone disease is possible by medical means without resort to parathyroidectomy.

Testosterone may aid anemic dialysis patients

The androgenic hormone, testosterone, may be of therapeutic value for anemic uremia patients on regular dialysis, according to a report by grant-aided investigators at the University of Miami. The anemia which often accompanies advanced renal failure, and which may require regular periodic blood transfusions, has been attributed to diminished renal secretion of erythropoietin, a factor which stimulates the production of red blood cells. Although androgenic hormones stimulate renal or possibly extrarenal production of erythropoietin and, thus, are therapeutic in a variety of anemias, their use in anemic uremia patients on regular dialysis therapy had not been explored previously.

Fifteen patients with chronic kidney disease and severe anemia on a program of maintenance dialysis were given weekly intramuscular injections of testosterone enanthate (400–600 mg) for 5–44 weeks. Blood samples for analysis were obtained from each patient's arterial cannula before dialysis, and each patient served as his own control.

Following testosterone therapy, 13 patients exhibited significant amelioration of anemia. Two iron-deficient patients did not respond to testosterone initially, but a satisfactory erythropoietic response followed additional iron replacement.

The anemia of renal failure is only partially ameliorated by long-term dialysis. Administration of relatively large doses of testosterone however, coupled with measures designed to increase the efficiency of dialysis and minimize blood loss, has reduced to 46 the number of transfusions required by 22 dialysis patients during a one-year period. Testosterone side effects included acne and, in one patient, evidence of hepatic dysfunction, which disappeared when the drug was withdrawn and later reinstituted at a lower dosage.

Future activities of the artificial kidney program

The Program will continue promising current research and development efforts and will pursue new ideas and approaches which appear feasible. The Institute is currently funding a number of studies aimed at the isolation and identification of unknown toxic factors which must be removed from the patient's blood, as well as metabolic wastes and other substances known to accumulate during kidney failure, such as urea, creatinine, uric acid, potassium, hydrogen ion, and water. Much of the future success in simplfying the treatment of patients with end-stage kidney disease will depend on developments in this area. The Program also intends to follow very closely clinical and technological developments abroad and, when promising, to enlarge upon them for the benefit of United States patients as well. This is particularly pertinent since developments in several Western European countries have been quite promising and their early and active introduction in the United States, and possible refinement (without waiting for the usual delay connected with spontaneous spread of new techniques) could provide highly beneficial to patients in the United States. For example, the Institute has adapted and helped to spread information about a special "selected low-protein" diet, first developed in Italy, that can delay the terminal phase of kidney failure in many cases.

Conferences, publications, and scientific communication

The Institute regularly organizes symposia and workshops on critical problems or opportunities in kidney disease research. In November 1970, a Workshop on Behavioral Bioassays in Uremia was held to help stimulate investigations on the effect of unknown toxic factors in uremia on the central nervous system, followed in January 1971 by a Workshop on Gastrointestinal Sorbents in Uremia. Abstracts of major papers presented at these workshops were contained in the programs, and the full manuscripts and discussions will be published and distributed broadly later in 1971.

In January 1971, the Fourth Annual Contractors' Conference of the Institute's Artificial Kidney-Chronic Uremia Program was attended by about 180 participants, key staff members who represented the contractors, and consultants to the Program and Institute staff. The three-day session involved extensive study of existing contract-funded research and development projects with emphasis on program progress and projected plans for the future. A considerable body of detailed and pertinent scientific and technical information was exchanged between the participants. As in previous years, this material will be published in the form of concise Proceedings to be widely distributed to workers in the relevant fields. The Proceedings of the previous annual conferences have become definitive publications on the state of the art in dialysis and it is anticipated that this and future such conferences will significantly assist attainment of the Artificial Kidney-Chronic Uremia Program's goals: optimal artificial kidney development, improved clinical methodology, and better patient rehabilitation.

A 30-minute color film "Diagnosis and Management in Chronic Kidney Disease," for the medical profession, was produced as part of the Artificial Kidney-Chronic Uremia Program's activities and is being widely distributed to teaching hospitals and county medical societies to advance professional education in chronic kidney disease. A previously produced 20-minute color film "Gift of Life," on the subject of home dialysis also is being widely distributed and was recently selected by the U.S. Information Agency for exhibiting abroad.

OUTLOOK

Research conducted and supported by the National Institute of Arthritis and Metabolic Diseases has added much to the understanding and treatment of kidney disease. Clearly this review of investigation and progress in the broad area of kidney disease, artificial kidneys, and renal transplantation, is not all-encompassing. Nonetheless, the variety and fruitfulness of the Institute's efforts and the stimulus to further investigation is apparent. Investigations such as those discussed in this report have increased our ability to cope with the problem of kidney failure. Additional new research efforts are called for in order that a more widespread and permanent control of kidney diseases can be achieved. A meaningful program to reduce kidney disease must include all of the various components—research, prevention, treatment, education—available in our armamentarium. Such a total program must be aimed at all the primary kidney diseases as well as at end-stage kidney failure. This combination, led by much-needed research, should yield maximal benefits in the number of lives saved today and the deaths prevented in the years to come.

ADVANCES IN KIDNEY TRANSPLANTATION

Mr. SMITH. What is the current status of kidney transplantation insofar as your Institute participates in this important activity?

Dr. WHEDON. As I mentioned briefly in my opening statement, there has been an important development in improving the matching of tissues in transplantation which will be particularly valuable for the use of cadaver kidneys. In 1968, an Institute grantee first devised a method of preserving isolated human cadaver kidneys for as long as 37 hours. Thus, time was gained for proper matching of cadaver kidneys which had become available and of potential recipients by tissue typing and for adequate preparation for surgery. Utilization of this kidney preserving device, the Beltzer Apparatus, now has permitted an important modification of standard tissue typing and cross-matching procedures to a point where cadaver kidney transplants can do as well as those from close relatives. Conventionally, only the white blood cells of the donor and potential recipients are tissue-typed and subsequently the best matching combination is selected. Under the new system, the recipient's white blood cells are typed and cross-matched

to the cadaver donor's kidney cells as well as white blood cells. Apparently there is antigen on the kidney cells not detected on white blood cells (leukocytes) during conventional tissue typing. Thus, many apparent "good" matches based on leukocyte-leukocyte typing alone can now be revealed as merely "fair" on the basis of the more complete double matching system, and poor outcome of cadaver transplants due to rejection can be more easily predicted and avoided.

Experiments by another grant-supported surgical team in Denver continue to indicate that antilymphocyte serum (ALS) and antilymphocyte globulin (ALG), a more purified fraction, can aid the body in accepting a new organ. The globulin tends to suppress the cellular reaction, the lymphocyte or white blood cell attack, largely responsible for damaging the transplanted organ. Usually prepared in horses or rabbits against pooled human donor lymphocytes, the serum is commonly used in conjunction with other immunosuppressive drugs to combat graft rejection. This team has been employing heterologous ALG with the immunosuppressant drugs azathioprine and prednisone in the management of several hundred heart, kidney, and liver transplant patients, with a consistently superior record of survival of the grafted organs.

PROGRESS AGAINST ARTHRITIS

Mr. Smith. What progress are you making in arthritis?

Dr. Whedon. As I mentioned to the committee last year, evidence is accumulating concerning the possibility that a transmissible, infectious agent is involved, directly or indirectly, in rheumatoid arthritis. A number of research findings point in this direction; for instance, when extracts of joint tissue of patients with rheumatoid arthritis are injected into mice the experimental animals develop a disorder very similar to rheumatoid arthritis. When tissue cultures of cells from rheumatoid arthritis afflicted joints are carried through several generations they show persistent abnormal cellular patterns, which again suggest a virus-originated change in genetic instructions.

Institute-supported investigators have recently found quite consistently virus-like particles which are visually indistinguishable from myxoviruses, in kidney tissue of patients with systemic lupus erythematosis, an inflammatory collagen disease related to rheumatoid arthritis. Although at this point these findings do not establish a vital causation for the disease, this is of distinct diagnostic importance and differentiates lupus nephritis from other kidney lesions.

Another microorganism developmentally somewhere between bacteria and viruses, the mycoplasma, has been implicated in recent years in the causation of rheumatoid arthritis-like joint lesions in various animals, and, of course, the implications for human rheumatoid arthritis cannot be ignored and must be followed up. Recently intramural investigators engaged in this work have succeeded in producing, in a uniform fashion, a polyarthritis in the joints of young swine by injecting mycoplasma organisms into the abdominal cavity of these experimental animals. We feel that this is a very promising beginning in creating a useful animal laboratory model which we never had before for studies related to rheumatoid arthritis.

With regard to the mechanisms which are directly involved in the joint destruction so characteristic of rheumatoid arthritis, I would like to mention that another Institute grantee at Harvard Medical School has found a specific enzyme which degrades the structural protein collagen in joint tissues of patients with rheumatoid arthritis, but not in normal subjects. The investigator is now examining the activity of this enzyme, collagenase, which may be responsible for the joint destruction characteristic of this disease.

An Institute grantee at the New York Medical College has shown in prolonged clinical trials that penicillamine may be of value in the treatment of rheumatoid arthritis patients with sustained disease activity. Prolonged penicillamine administration not only reduced rheumatoid factor titers, but other classes of abnormally elevated blood levels of immunoglobulins as well, suggesting that the drug may act by suppressing the abnormal immune response of rheumatoid arthritis. In an 8-year clinical study, a large percentage of patients displayed a significant reduction in subjective and objective signs of their disease, including diminished duration of morning stiffness and afternoon fatigue, decreases in joint tenderness and swelling of the joint lining and an increase in range of motion. Clinical improvement persisted in many cases 4 to 6 months after penicillamine was discontinued. Further study is now needed to delineate the precise mode of action of this agent.

Mr. Chairman, we have prepared a special report on the research accomplishments of this Institute in the field of arthritis and rheumatic diseases which describes these and many other developments in greater detail. With your permission we would like to submit this report for the committee's information.

(The information follows:)

ARTHRITIS, RHEUMATIC DISEASES, AND BONE DISORDERS

The arthritic disorders are the Nation's most prevalent, painful, crippling diseases, afflicting some 16,800,000 people, according to the U.S. Public Health Service's National Center for Health Statistics. The term arthritis, refers to inflammation and destruction of joints. Rheumatism, a more general term, usually refers to pain or impairment of function related to tissues outside the joints, such as muscles, tendons, bones, and nerves. About 100 disorders are listed under the combined heading of arthritis and rheumatism.

	1968	1969	1970	1971	1972
NIAMD research support for arthritis	$11,100,000	$11,746,000	$11,492,000	$12,095,000	$11,876,000

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

A vast amount of basic information on arthritis-related immunological, biochemical and physiological mechanisms has been assembled. Recently, for example, Institute researchers played a key role in the unraveling of the intricate structure of the parathyroid hormone, a regulator of bone metabolism, and in its synthesis as a man-made chemical that will contribute to the understanding of a number of bone disorders.

Elsewhere, at the New York University School of Medicine, an Institute grantee and his associates formed for the first time a man-made "lysosome" (a duplicate of naturally occurring intracellular enzyme packages), which was produced from commercially available purified lipids and enzymes. The synthetic lysosome will permit advanced investigations of the manner in which potentially tissue-degrading enzymes are released when natural lysosomes are ruptured and their contents released into joint cavities. The action of lysosomes in either protecting or destroying their environments thus may be approximated experimentally. This research is pertinent to rheumatoid inflammation phenomena, a major factor in arthritic damage.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis, a main target of Institute research, is a painful, potentially, crippling, inflammatory disorder affecting about four million people in the United States. Essentially a systemic disease that may involve entire organ systems or one or more joints, it may flare up in single or repeated episodes or persist as a chronic, degenerative disease.

While the primary cause of rheumatoid arthritis is still unknown, present research is endeavoring to discover whether an infectious process, or an autoimmune reaction, or possibly a combination of both processes are the mechanisms by which the disease develops. Institute grantees are continuing to gather data on the possible role of microbial organisms and viruses which have recently been recognized as potential pathogens in rheumatoid arthritis in man. To date, however, firm proof that infectious agents may cause this disorder remains elusive. Researchers are also examining the possibility that rheumatoid arthritis is initiated by an autoimmune reaction, in which the body reacts abnormally and destructively to materials (perhaps modified by infection) originating within the body's own tissues.

Search for an infectious or immunologic basis

In the report prepared last year, evidence was advanced for a transmissible agent in human rheumatoid arthritis. Citing underlying studies by Institute investigators and grantees, independent scientists of the University of California, Los Angeles, injected mice with tissue from human patients with rheumatoid arthritis. Not only did the mice acquire an arthritic disorder in which cellular changes resembled those commonly found in human rheumatoid arthritis, but they also transmitted it to their offspring. These, in turn, passed on the condition to the next generation of mice, and they, in turn, passed it on to a succeeding generation. This arthritis has now appeared consistently in several generations of experimental animals who never received injections of human rheumatoid material. Obviously, the experiment cannot be safely attempted in humans, in whom the search for specific agents causing rheumatoid arthritis continues.

Most recently, the Australia antigen (Au), a virus first isolated in Institute laboratories, has been linked with arthritic disease, according to grant-aided studies at the Robert B. Brigham Hospital in Boston. The Au agent is being investigated primarily as a hepatitis-associated virus, but the Boston researchers found it associated, in several patients, with a true arthritis—with clinical signs of joint inflammation, effusions, joint swelling, and redness, appearing very much like rheumatoid arthritis. In addition, these patients also had symptomatic or asymptomatic hepatitis. The condition associated with Au agent and hepatitis is relatively rare, however, and the investigators hypothesize that the individuals affected may display joint inflammation due to immune mechanisms rather than due to a direct viral invasion of joint tissues.

The pattern of inflammation, tissue breakdown, and gradual degenerative changes characteristic of many cases of rheumatoid arthritis resembles the pattern seen in infections of lower animals by the so-called "slow" viruses. These are now under study in a number of laboratories.

Another suspected group of infectious organisms, the mycoplasma, have only in modern times been recognized as pathogenic for humans. Mycoplasma from swine with arthritis will be further examined to determine how this infectious agent may induce pathological changes in joint tissues. A strain of *M. pulmonis* has been found by investigators of the National Institute of Allergy and Infectious Diseases to cause arthritis in mice and may provide a model for studying the arthritogenic properties of this group of microorganisms.

In another relevant study, National Institute of Dental Research scientists have found that rheumatoid factor, a protein found in the blood of patients with rheumatoid arthritis, can combine as part of a complex with herpes simplex virus. The latter is the common, so-called "cold sore" virus. The investigators demonstrated in tissue cultures of living cells that human rheumatoid factor combined with but did not neutralize the herpes simplex virus, leaving it capable, theoretically, of causing rheumatoid-type damage. Yet this complex containing infective virus would not be detected by ordinary tests for rheumatoid factor.

While various transmissible agents have been found in close association with rheumatoid arthritis, it still is not possible to state that any particular one of them is causative.

The hypothesis that rheumatoid arthritis is an immune disorder is based primarily on observations that violent immunological reactions within the body, possibly initiated by invading microbes or other foreign substances, can cause the type of inflammatory lesions observed in the disease. Iso-antibodies, mistakenly attacking components of the body's own tissues as though they were foreign invaders, are suspected of initiating the chain of events which ultimately results in rheumatoid damage. Infection-altered body cells might send the erroneous messages which set off elaboration of such iso-antibodies and autoimmune phenomena.

A number of basic studies seeking to clarify such mechanisms and their roles in rheumatoid arthritis are under way with support from the National Institute of Arthritis and Metabolic Diseases. Radioactive tracers are being employed in animal experiments to follow the pathways and observe the effects of iso-antibodies in the bloodstream. Drugs that suppress the immune response in humans are being tested for their efficacy against rheumatoid arthritis. Genetic influences on the immune make-up of various individuals also are being taken into consideration as possible pre-disposing factors in some cases of rheumatoid damage.

Metabolic disease hypothesis

While most investigators explore the possibilities that rheumatoid arthritis is an immune or an infectious disorder or a combination of both, one grant-assisted investigator at Downstate Medical Center, State University of New York, this year presented evidence to support his theory that this disease may be, at least in part, a metabolic derangement. His research is based on the discovery, made more than a decade ago and since confirmed by several investigators, that the blood of persons with rheumatoid arthritis contains subnormal concentrations of histidine, an amino acid and one of the building-blocks of protein. Several Institute laboratories at Bethesda are studying basic mechanisms by which histidine biosynthesis is controlled.

Treatment of rheumatoid arthritis

The New York grantee cited in the previous paragraph has treated 70 rheumatoid arthritis patients for periods averaging nine months with daily oral doses of L-histidine as large as six grams. His preliminary report notes modest but apparently significant improvement in three standard measurements of the disease's effects, with no detectable side effects due to the histidine. Patients showed general improvement in grip, walking gait, and in red-blood-cell sedimentation rates.

Because the causes of rheumatoid arthritis have not yet been determined and the disease mechanisms are not clear, the primary concern of the physician must be treatment rather than prevention. The main objectives of any treatment program are to reduce inflammation and pain, preserve function, and prevent deformity. Drug therapy is one important component of this overall plan. Individual responses to chemotherapy differ, and as the armamentarium of drugs developed through research increases so does the number of patients who can be benefited.

Aspirin remains the most generally used salicylate for reducing inflammation and controlling symptoms, but in the doses usually prescribed it can cause complications, including gastrointestinal bleeding. Investigators are searching for less toxic but equally effective salicylates. In Institute-aided research, a buffered and soluble form of aspirin given as a liquid was reported last year to reduce bleeding (in contrast to aspirin in solid form which can cause a local reaction which elicits bleeding on gastrointestinal surfaces), and other grant-assisted

studies recently showed that bleeding also may be diminished through use of an "alternate aspirin". The substance is a choline salt of salicylate that is available in both liquid and tablet form and which caused significantly less gastrointestinal bleeding than regular aspirin tablets in clinical trials.

As has been noted, the concept of rheumatoid arthritis as a disorder of immunity has led to the study of a number of drugs that suppress this biological reaction. One of these drugs, cyclophosphamide, has been under intensive trial because it is among the less toxic of the presently available immunosuppressive agents.

An Institute grantee at New York University, together with members of the Cooperating Clinics Committee of the American Rheumatism Association (a professional society of arthritis specialists), recently reported on controlled clinical trials of cyclophosphamide. While this drug may be of significant value in the treatment of patients with severe rheumatoid arthritis who are refractory to standard forms of therapy, its use in large doses was accompanied by a high rate of undesirable side effects. Additional studies will be undertaken to re-evaluate this potent drug in graduated dosages.

At New York Medical College, another Institute grantee has shown in prolonged clinical trials that pencillamine may be of value in the treatment of rheumatoid arthritis patients with sustained disease activity. Prolonged penicillamine administration not only reduced rheumatoid factor titers, but other classes of abnormally elevated blood levels of immuno-globulins as well, suggesting that the drug may act by suppressing the immune response. In an eight-year clinical study, a large percentage of patients displayed a significant (50 percent or better) reduction in subjective and objective signs of their disease, including diminished duration of morning stiffness and afternoon fatigue, decreases in joint tenderness and swelling of the joint lining and an increase in range of motion. Clinical improvement persisted in many cases four to six months after penicillamine was discontinued. Further study is now needed to delineate the precise mode of action of this agent.

Collagenase action studied

Future arthritis studies will also deal with the underlying mechanisms of joint destruction so characteristic of rheumatoid arthritis. In one past study by a grant-supported investigator at Harvard Medical School, a collagenase (collagen-degrading enzyme) which may be responsible for the articular destruction characteristic of this disease, was isolated in the synovial tissue of rheumatoid arthritis patients. The investigator is now examining the activity of this collagenase which was found in synovial fluid from 10 percent of patients with rheumatoid arthritis.

RESEARCH ON OTHER FORMS OF ARTHRITIS AND BONE DISEASE

While rheumatoid arthritis is one major form, arthritis specialists have divided the arthritic and rheumatic diseases into a dozen major categories. Each disorder is a distinct clinical entity, but all have in common similar symptoms, principally pain, swelling, disability or deformity in the joints or surrounding tissue. The main forms include arthritis of unknown cause (such as rheumatoid arthritis and ankylosing spondylitis); degenerative joint disease (osteoarthritis); connective tissue disorders, such as systemic lupus erythematosus; infectious arthritis; traumatic arthritis; and arthritis associated with biochemical abnormalities, such as gout.

Total hip replacement

Research is continuing on development of prosthetic devices for total hip replacement. Present materials, while effective for varying periods of time, are not permanent. As a result, replacement of the device may be necessary after several years. Grantees at the Johns Hopkins University School of Medicine, Baltimore, Maryland, are utilizing a new method for attachment of these devices to bone. Initial results appear promising, but long-range continuing studies will be necessary to evaluate this procedure properly, both as to duration of function of the device and the human response to these new non-biological materials.

New materials studied

Recently, interest has increased in the development of new materials for use as implants. Engineers, metallurgists, and orthopedists are working together

to develop and test new materials that more nearly mimic the properties of bone than do the present materials. Again, long-range studies will be necessary to properly evaluate tissue response of these materials. Ceramics, with controlled pore sizes, have been developed and are undergoing testing for tissue compatibility. One difficulty encountered with ceramics is their brittleness. Efforts to overcome this undesirable characteristic have been partially successful. Methods of binding ceramics to metals are being studied. If successful, such combinations of materials may provide the strength necessary for weight bearing as well as porosity which would permit tissue ingrowth through the ceramics outer layers.

Research on connective tissue disorders

One of the main areas of study relates to the abnormalities of connective tissue seen in systemic lupus erythematosus (SLE), rheumatoid arthritis, and a number of other disorders.

Systemic lupus erythematosus is a serious 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. Although the cause of SLE is not known, much evidence points, as in the case of rheumatoid arthritis, to a disorder of the body's immune mechanism which may or may not be tied to a previous infectious process. A strain of mice in whom an autoimmune disease (quite similar to lupus erythematosus in man) is genetically acquired will be employed by Institute investigators to study the mechanisms of tissue destruction characteristic of human SLE. The researchers have been able to induce massive production of destructive isoantibodies in the mice and to suppress this production capability with powerful drugs. More work will be required to determine whether this work is applicable to control of human diseases of an autoimmune nature.

Virus-like particles implicated

A grant-aided investigation at the University of California, Los Angeles, has demonstrated the presence of virus-like particles, morphologically indistinguishable from myxoviruses, in the affected renal tissue of 29 of 30 patients with SLE, at different stages of the disease, but not in any of 37 control patients with other renal diseases. The virus-like intracellular inclusions were detected in the glomerular endothelial cytoplasms of the SLE patients. There was no correlation between either the functional or histologic degree of involvement of the kidney by SLE and the presence of virus-like particles. These morphologic findings do not *establish* a viral causation for this connective-tissue disorder, but presence of the virus, reported in recent years by several investigators, is of diagnostic importance and differentiates lupus nephritis from other renal lesions.

These findings provide a basis for further studies directed toward positive identification of the SLE-associated particles, their possible significance in development of the disease, and/or their diagnostic import.

Other grantees at the University of Texas Southwestern Medical School, Dallas, have reported a statistically significant increase in antibody titers to myxoviruses, particularly parainfluenza 1 and measles, in patients with SLE.

Immunogenic mechanism

The basic mechanism of SLE is the focus of studies by staff scientists of the Institute at Bethesda. They hypothesize that the disorder may be triggered not by only one specific virus, but possibly by several different types. These viruses might serve to induce abnormal replication of nucleic acids in the host. Even quite ordinary viruses, such as reovirus, could become immunogenic in a suitably hyperreactive individual, whose extreme response could set off tissue-destructive "chemical warfare" within the body.

Treatment of Paget's disease

Several recent studies have indicated that porcine calcitonin (PCT) may be useful in the treatment of Paget's disease of bone, a chronic disease of the skeleton characterized by localized areas of bone destruction, increased formation of abnormal bone, increased blood circulation in the affected bones and (in cases of wide-spread, long-term involvement) congestive heart failure. Calcitonin is a polypeptide hormone produced by the C-cells of the thyroid gland which acts to

lower blood levels of calcium, apparently by inhibiting resorption of calcium from bone.

Preliminary investigation by Institute grantees of the use of *salmon* calcitonin (SCT) in the treatment of Paget's disease now has shown that SCT is far more potent than PCT. Minute doses markedly reduce excessive skeletal turnover with no evidence of toxicity or antibody formation, and it can be administered subcutaneously with great ease. These observations suggested the possibility of long-term treatment at home, much like the use of insulin therapy by diabetic patients. Further study will be needed to determine if larger SCT dosages administered more frequently can fully reverse the biochemical abnormalities of Paget's disease. Future studies of parathyroid hormone and of its biologically active molecular portion will allow investigators to examine its physiological role in the body in ways hitherto impossible.

Osteoporosis

Osteoporosis, a diffuse reduction in bone density, is a condition resulting from a combination of disuse or immobilization, calcium deficiency, hormonal imbalances, or senility. It is often found in elderly postmenopausal females, often results in vertebral abnormalities and/or frequent fractures of the hip and long bones. Grantees at several institutions are studying this disease through long-term data collections of individuals on controlled diets and patients with disuse or immobilization of limbs. Since osteoporosis is usually a disease of slow onset and long duration, and bone density decreases slowly, studies of this condition must continue over many years if the cause and possible methods of preventing, controlling, or slowing the process are to be accomplished.

Research on gouty arthritis

Gout is today one of the most controllable of the arthritic diseases and represents an excellent sample of the ultimate practicality of fundamental research in terms of direct health benefits. Institute scientists and Institute grant support played a major role in elucidation of the (primarily inherited) abnormal metabolism of uric acid and its precursors which underlies this disease and in the clinical trials of allopurinol a drug that helps prevent formation of sharp and painful needles of crystallized uric acid in tissues.

Elevated levels of uric acid in the body and tissues of gouty patients have been attributed to either excessive uric acid production or to diminished uric acid excretion by the kidney. While the uric acid overproducers have an obvious metabolic basis for their hyperuricemia and gout, little has been known about the mechanism for hyperuricemia associated with the so-called uric acid normoproducers. Now, grantees at the University of Wisconsin have demonstrated that the kidneys of the latter type patients do not excrete normal amounts of urate, suggesting that gout in this group of patients can be traced to the kidney excretion defect. Research now will be directed toward further elucidation of this rental abnormality.

Genetic basis for arthritis of the spine

In a grant-aided study of another type of arthritis, ankylosing spondylitis, investigators at the University of Texas Southwestern Medical School have teamed with scientists in New York to survey the influence of race (black or white) on this disease. Patients were located at four geographically separated Veterans Administration hosiptals. This arthritis disorder, which results in progressive rigidity of the spinal column and affects young men primarily, was found in the black patients with only 25 percent of the frequency it was found in whites. The percentage of white-derived genes found in black Americans is also about 25 percent, and ankylosing spondylitis has rarely been reported in black *Africans*. Consequently, the investigators suggest that a genetic factor may indeed be involved in the etiology of this disease, long regarded as familial in nature.

OUTLOOK

There is no question that the pain and disability of arthritic and rheumatic diseases have been lessened for many thousands of people as a result of the national research and training programs of the National Institute of Arthritis and Metabolic Diseases. The most encouraging evidence for the long run, however, is of year-by-year growth in understanding of the basic disease mechanisms

and of their interactions with the structures of essential biological systems. When the pieces fall into place, and we are entering a phase in which they already are beginning to do so, those who deliver health services will have the means for control and in many cases prevention of the arthritic and rheumatic diseases that are so prevalent today.

PROGRESS AGAINST DIABETES

Mr. SMITH. One of the diseases in which this committee is particularly interested is diabetes. What progress are you making in better understanding of this disease?

Dr. WHEDON. As you know, this heredity-related metabolic disease can be well controlled in patients in whom it emerged during the advanced adult years and even in its severe form when it strikes those of a younger age. Thus, today with proper treatment, most diabetics can lead a normal or near-normal life. Despite good control of clinical symptoms, however, and our ability to hold in check the abnormal blood sugar level, in too many cases the long-term complications of diabetes, primarily those affecting blood vessels, peripheral nerves, kidneys, and the eyes, still develop relentlessly.

Thus our research effort emphasizes not merely the development of still other drugs to treat diabetes or novel ways to supply insulin to the patient who needs it; to strike at the very fundamentals of the disease, in order to prevent its long-term complications, we must develop greater knowledge on a basic level concerning insulin and its role in the vital processes in the body, and concerning all other, heretofore unknown, metabolic abnormalities connected with the disease.

I am, therefore, pleased to mention several such studies of the last year which have greatly contributed to our understanding of diabetes and which constitute important steps forward in our mission to defuse, if you will, if not outrightly prevent, the disorder in individuals predisposed to it through inheritance. One such study by an institute-supported scientist at the University of Texas has suggested that a pancreatic hormone other than insulin, glucagon, may play an important role in diabetes. Glucagon, heretofore, has been viewed as playing a relatively minor role in the disease. These studies of the function of glucagon-secreting cells (alpha-cells) in the pancreas of normal and diabetic subjects have indicated that diabetes is characterized by a continuous state of relative or absolute glucagon excess. Because several actions of glucagon are antagonistic to those of insulin, the pancreatic hormone which facilitates normal carbohydrate utilization and storage, it is suggested that excess glucagon may exaggerate the metabolic consequences of insulin insufficiency, and may unfavorably influence diabetic control. Diabetes, therefore, may be a functtion of the level of glucagon and insulin, rather than of insulin alone. Thus, research must be directed at control of glucagon as well as at facilitation of greater insulin secretion.

In another fundamental study Institute scientists in Bethesda have now contributed significantly to our knowledge concerning the mechanism of action of insulin on the cell level. We know that insulin facilitates the transport of blood sugar and of other nutrients into body cells. This is one of its vital, indispensable roles. It was not previously

known, however, whether this hormone must actually enter the cell in order to exert its desirable action. Our studies in Bethesda have now shown that insulin, even when bound strongly to large particles which prevent it from actually diffusing inside cells, still interacts in some fashion with the cell membrane to stimulate blood sugar transport into the cell. Future research along similar basic lines will be devoted to various mechanisms of insulin-binding and insulin inactivation possibly active in diabetes.

Other studies related to the release of insulin from the special insulin producing cells (beta-cells) of the pancreas have now shown that not only glucose in the blood, but also amino acids, can act as a direct stimulus for the release of insulin from the pancreas.

Mr. Chairman, we have prepared a special report on research advances in the field of diabetes which describe these and many other findings in greater detail than it is possible to relate here.

(The information follows:)

DIABETES

Of all the metabolic diseases, diabetes, which affects millions of Americans, is probably the best known but hardly the best understood.

According to the American Diabetes Association, one American in 20 is either an actual or a potential diabetic. The Association estimates that there are more than four million known and undiagnosed diabetics in the U.S. population, and another five-and-one-half million are latent but potential diabetics who will develop the disorder later in their life-time, making diabetes a major public health problem.

Obligations for programs in diabetes

	1968	1969	1970	1971 estimate	1972 estimate
National Institutes of Health: National Institute of Arthritis and Metabolic Diseases	$7,542,000	$9,040,000	$3,052,000	$8,511,000	$8,347,000

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

A complicated disease, for which there is no known cure, diabetes ranks eighth on the list of diseases causing death in the United States. Diabetes has been known for some time to be a hereditary disorder. As a result of the body's inability to metabolize carbohydrates normally (which, in turn, is based on impaired production or activity of the hormone insulin), the diabetic is unable to convert dietary carbohydrates properly into the stored form, glycogen, or to utilize them normally for the energy required for body functions. Thus, the carbohydrates, in the form of glucose, accumulate in the blood and, because of their high concentration, overflow into the urine. As the disease progresses, abnormal carbohydrate metabolism becomes associated with a noticeable derangement in the metabolism of fats and proteins.

In its severe form (occurring more frequently in juvenile diabetes) the untreated disease rapidly progresses to a grave metabolic disorder, ketoacidosis, which may result in coma and death unless controlled by insulin administration and specific supportive therapy. When afflicted with its less severe form, the so-called "maturity-onset diabetes," patients may suffer from complications such as accelerated degeneration or "hardening" of the arteries, and thus, may have a 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. Despite good control of clinical symptoms,

however, and the usual ability to hold in check the abnormal blood sugar level, in too many cases the long-term complications of diabetes, primarily those affecting blood vessels, peripheral nerves, kidneys, and the eyes, develop relentlessly.

TOLBUTAMIDE STUDY

The most significant and far-reaching diabetes study in many years was concluded in 1970. It concerned the effects of tolbutamide (brand name: Orinase), an orally administered hypoglycemic agent (antidiabetes drug) which is used by an estimated 800,000 American diabetic patients.

The 10-year study, supported by the institute, was conducted by the University Group Diabetes Program (UGDP). It has revealed that tolbutamide is no more effective than diet alone in the treatment of mild, adult-onset diabetes, except insofar as it lowers blood glucose levels. Moreover, the drug was found to be less effective than diet, or diet and insulin, in reducing mortality from heart disease and related conditions in such patients.

The objective of the study was to ascertain the effectiveness of oral drug or insulin treatment in prevention, or long-term postponement, of the onset of the complications of diabetes (heart disease, kidney degeneration, blindness, and others) which make this disease such a serious disorder once they make their appearance. During the 10-year study period, instead of an anticipated advantage to oral drugs, approximately twice as many cardiovascular deaths occurred in the tolbutamide-treated group as in the other study groups of patients and this increased death rate was noted in a majority of the 12 clinics.

The investigators recommend that tolbutamide be used only in patients with symptomatic adult-onset diabetes who cannot be adequately controlled by diet alone or by diet and insulin. The Food and Drug Administration, after reviewing the results of this study with the aid of outside expert consultants, announced a similar conclusion, consonant with pronouncements of special study groups from the American Medical Association and the American Diabetes Association, that tolbutamide should be used only as a third line of defense against diabetes.

ROLE OF AMINO ACIDS

An institute-supported scientist at the Evanston (Ill.) Hospital, Dr. A. R. Colwell, Jr., has clarified the role played by amino acids in stimulating insulin secretion. Both protein ingestion and amino acid infusion are known to stmulate insulin secretion in man. This response has been attributed to an increased plasma amino acid concentration, but it has not been known whether amino acids exert a direct effect upon the insulin-producing cells of the pancreas, or whether the effect is mediated through some indirect mechanism.

Dr. Colwell's studies in dogs now have suggested that the insulin response associated with ingested or parenteral protein represents a direct effect of amino acids on the insulin-producing cells ("beta-cells") of the pancreas. His studies also suggest that the amino acid concentration in the pancreas may be as important as glucose concentration in the regulation of insulin secretion.

Previous evidence has favored the idea that glucose concentrations in the pancreas control insulin release. The present findings demonstrate the ability of amino acids to act independently (similarly to glucose) as a stimuls for insulin release, and suggest that both amino acids and glucose may provoke insulin secretion by a similar mechanism.

POSSIBLE ROLE OF GLUCAGON

In another, related study an Institute-supported scientist at the University of Texas has suggested that a pancreatic hormone other than insulin, glucagon, may play an important role in diabetes. Glucagon, heretofore, has been viewed as playing a relatively minor role in diabetes.

Dr. Roger Unger's studies of the function of glucagon-secreting cells ("alpha-cells") in the pancreas of normal and diabetic subjects have indicated that diabetes is characterized by a continuous state of relative or absolute glucagon excess. Because several actions of glucagon are antagonistic to those of insulin (the pancreatic hormone which facilitates normal carbohydrate utilization and

storage), it is suggested that excess glucagon may exaggerate the metabolic consequences of insulin insufficiency and unfavorably influence diabetic control.

The effect of large carbohydrate or protein meals upon plasma glucagon levels was compared in 14 nondiabetic subjects, in 12 patients with insulin-dependent, juvenile diabetes, and in 12 patients with insulin-independent, adult-onset diabetes. It was found that, in normal persons, plasma glucagon levels fall after carbohydrate ingestion and rise after protein ingestion, unless hyperglycemia is induced. In diabetic subjects, however, glucagon is not suppressed by carbohydrate and rises normally after protein, despite hyperglycemia. This is a strong indication that in the absence of adequate insulin secretion or activity (which characterizes the diabetic state), excess glucagon exaggerates such metabolic consequences of insulin deficiency as increased glucose production by the liver, and production of free fatty acids by fatty tissue. Diabetes, therefore, may be a function of the level of glucagon and insulin, rather than of insulin alone.

PIMA INDIAN STUDIES

In 1965 a team of Institute scientists discovered that the incidence of diabetes in the Pima Indians of Arizona is 10 to 15 times greater than that of the general American population. This finding was based primarily on tests which revealed abnormally high blood levels of glucose in nearly half of the members of the tribe. Some skeptics have suggested, however, that the abnormally high blood glucose levels observed in the Pimas were not actually true manifestations of classic diabetes.

The same team of investigators now has confirmed that the symptoms and signs of diabetes, including eye and kidney damage, are indeed correlated with the unusually high prevalence of glucose intolerance observed in the Pimas in the earlier study.

Epidemiologists conducted eye examinations on 1,495 Pima Indians without knowing which individuals had shown high blood sugar levels. When the results were tabulated, the group with high blood sugar levels was found to have nearly three times the frequency of abnormal eye changes as the low blood sugar group. Further epidemiological studies showed that the high blood sugar group of Indians also had a much higher frequency of kidney disease and more severe forms of this disease than others with low blood sugar test results.

In a related study the same team of scientists has disproved a medical theory of almost 40 years' standing: that there is a relationship between enlarged parotid glands and diabetes. The investigators found that such a relationship results mainly from the common association of both factors with obesity.

In seeking such an association among the Pima Indians, enlarged parotid glands were detected in 31 percent of 296 subjects whose diabetes status was unknown at the time. Subsequently, this condition was found to be more common among diabetic subjects than nondiabetic subjects. Because a correlation between parotid gland enlargement and obesity was noted, the data were further evaluated. It was then found that the association between parotid gland enlargement and diabetes vanished, whereas such as association with obesity emerged and was demonstrated. Further research showed that fatty infiltration may account for the observed enlargement of parotid glands. These findings are consistent with those of other scientists.

COMPLICATION OF DIABETES

Many patients with long-term diabetes develop complications such as "hardening" of the arteries, heart disease, kidney failure, and failing eyesight. Progressive damage to the retina develops in many persons whose diabetes begins in childhood and who have had the disorder 20 years or more. This condition, known as diabetic retinopathy, is the third leading cause of blindness in the United States.

The role that carbohydrate intolerance and associated abnormalities of insulin secretion or activity may play in the development of diabetic retinopathy is not known. Recent studies by Dr. Thomas J. Merimee of Boston University, however, have suggested that such metabolic abnormalities are "relatively impotent causes" of retinopathy in the absence of human growth hormone (HGH). Thus,

it would appear that HGH may play an important moderating role in the development of diabetic retinopathy.

The scientists compared the common metabolic abnormalities of sexual ateliotic dwarfs (who have an isolated deficiency of HGH) and of diabetic patients and found that they could not distinguish between these HGH-deficient dwarfs and diabetics on the basis of their insulin responses to several stimuli, the degree of their carbohydrate intolerance, or their blood lipid profiles. All of these parameters showed similar metabolic abberations. Nearly half (41 percent) of the diabetics exhibited significant pathological changes of the retina, however, whereas no retinal changes were observed in HGH-deficient dwarfs.

It was concluded that carbohydrate intolerance and blood lipid abnormalities *per se* do not play an important role in the development of retinopathy in the chronic absence of HGH. The investigators suggest that the evolution of diabetic retinopathy may occur only when the metabolic abnormalities of diabetes coexist with the ability to secrete HGH, but further study will be required to determine the validity of this hypothesis.

OUTLOOK

Continued advances against diabetes depend upon further knowledge of the disease and its complications; of genetic factors; of how insulin is made in the pancreas, how it is transported, how it does its work, and how and by what agents it is destroyed, neutralized or inactivated in the performance of its vital tasks. Progress in these areas, now under intensive scrutiny, should contribute substantially toward amelioration of diabetes and its consequences.

RESEARCH INTO GASTROINTESTINAL BLEEDING

Mr. SMITH. On page 162 you say "Gastrointestinal bleeding, which particularly affects older people appears to be increasing in our population as the incidence of ulcers and intake of alcohol and aspirin increases." Is there a direct correlation between the intake of alcohol and aspirin, and the incidence of ulcers?

Dr. WHEDON. No, Mr. Chairman, these are three separate items all related in some way to gastrointestinal bleeding. We mentioned gastrointestinal bleeding in our budget narrative in conjunction with a reseach advance which will permit us in the future to determine the site of gastrointestinal bleeding in a patient without subjecting him to overly complex and uncomfortable diagnotic procedures. We mentioned the intake of alcohol as a possible source of gastrointestinal bleeding because chronic alcoholics who develop cirrhosis of the liver eventually also may develop varicosities in the veins of the esophagus; these, in turn, often hemorrhage, leading to rapid blood loss into the gastrointestinal tract, and it is important to make a prompt and certain diagnosis of the specific site of the bleeding to be able to take effective steps to help the patient. We mentioned aspirin because it too can be a source of slight but quite consistent bleeding in the stomach, especially in people who consume many tablets every day. The sum total of such blood loss over a long period of time can be quite serious, especially in an older person, and here again a precise localization of the site of the bleeding and its differentiation from other sites and causes are important.

In answer to your question, Mr. Chairman, there is no direct correlation between the intake of alcohol and aspirin and the incidence of ulcers; these two substances are not the specific cause of peptic ulcers. On the other hand, they may well contribute to the establishment of

a peptic ulcer and, more specifically, once the ulcer is there, consumption of alcohol and constant use of aspirin will prevent its healing, not only through the direct chemical irritating actions of these substances but, in the case of alcohol, also through the stimulation of stomach acid which further erodes the ucler and prevents its healing.

Mr. Chairman, we have prepared a speeal report on research advances in the field of digestive diseases which describes in detail the advances of the past year. With your permission we would like to submit the report at this time for the committee's information.

(The information follows:)

SPECIAL REPORT: DIGESTIVE DISEASES*

Peptic ucler, regional iletitis, and diseases of the liver, gallbladder and pancreas—these are the numerous and diverse disorders which are traditionally included in the medical specialty of digestive diseases.

Although many ailments involving the gastrointestinal tract are poorly understood, they are among the most common illnesses in the country, ranking second only to diseases of the heart and circulation in the number of physician office visits or house calls. Peptic ulcer or peptic ulcer symptoms will strike about 10 percent of all adults in the United States at some time in their lives. Diseases of the stomach and intestines may afflict persons of any age, but most often affect those in the middle-aged groups at the peak of their most vigorous and productive periods, often causing prolonged and expensive hospitalization and countless social and emotional problems. Some diseases such as ulcerative colitis are of a chronic nature, patients being afflicted for years with their disorder and may have to undergo extensive and repeated treatments and surgery.

The National Institute of Arthritis and Metabolic Diseases (NIAMD) bears the responsibility for the Government's program of research in the field of digestive diseases. In an effort to facilitate increased attention to research and training in the field of diseases of the digestive tract, as well as nutrition, an Assistant Director for Digestive Diseases and Nutrition has recently been designated for the Institute.

Similarly emphasizing the importance of digestive diseases in the Institute's program, a gradual expansion is planned for the intramural Digestive and Hereditary Diseases Branch in which Institute scientists conduct clinical and laboratory investigations to determine abnormalities in structure and function of the esophagus, stomach, small and large intestines, pancreas and liver, and research on certain hereditary metablic diseases.

Through numerous grants to scientists at research centers across the country, a broad array of ailments of the digestive tract is undergoing investigation. Research progress has been achieved only through the most intensive and comprehensive laboratory experiments and clinical trials. The past year has seen the development of numerous important research findings, several of far-reaching importance.

RESEARCH DEVELOPMENTS

Cholesterol gallstone formation

A new concept of how cholesterol gallstones (the most prevalent type) are formed has emerged from recent studies and will be confirmed in experimental work with the Pima Indians of Arizona in whom Institute scientists have found the highest incidence of gallstones ever reported in the United States. Recent experimental results indicate that the formation of cholesterol gallstones is probably due to secretion by the liver cells of bile abnormally high in cholesterol in which the latter exists in a highly supersaturated state so that it will later precipitate out in the gallbladder. This important finding, which points to the liver as the origin of the disease rather than to the gallbladder itself, channels research

*Prepared February 1971 as background information for the Director, National Institute of Arthritis and Metabolic Diseases, Public Health Service, U.S. Department of Health, Education, and Welfare, in connection with the fiscal year 1972 appropriation hearings.

effort into a wholly new direction. Bile salts and lecithin are the primary solubilizing agents for cholesterol in bile. By supplying additonal bile acids, the composition of the bile might be changed toward normal. The extensive understanding of cholesterol and lecithin metabolism gained through much research aimed at the problem of atherosclerosis during the last decade can now be utilized in this area in an attempt to find ways to modify the composition of bile in gallstone-prone individuals.

Heartburn research

Heartburn, caused by reflux of acid stomach contents into the esophagus, is one of the most frequent complaints of gastrointestinal origin. More severe forms of this phenomenon occur in esiphagitis and hiatal hernia. Despite many published observations, how and why reflux occurs in these individuals and not in others, is largely unknown. Work performed by an Institute grantee is well along toward answering this question and, therefore, to offering some rational and effective, rather than merely empirical treatment of the condition. Studies by these investigators suggest that the important hormone gastrin, released by the stomach, is at least one factor which controls the baseline pressure of an important physiological structure, the lower esophageal sphincter, which normally acts as a one-way gateway between esophagus and stomach and which usually prevents stomach acid from flowing back into the esophagus. Patients who have frequent gastroesophageal reflux have lower baseline pressure in this structure than the normal group, perhaps because the sphincer is insufficiently responsive to gastrin or perhaps because insufficient gastrin is produced and released by the individual. If this conjecture proves to be correct, new avenues of rational therapy seem probable.

Gastrointestinal bleeding

Gastrointestinal bleeding, which particularly affects older people appears to be increasing in our population as the incidence of ulcers and intake of alcohol and aspirin increase. Diagnosis of the site of the bleeding is still difficult and, in a fair percentage of cases, uncertain. Barium meals, endoscopy and intubations each have their advocates and each is able to differentiate the bleeding site in majority of cases. If, however, a more certain and less traumatic or complicated procedure could be developed it would be a major advance. One of the Institute grantees is working on a new approach to localizing the bleeding site which would be rapid and relatively innocuous for the patient. Methane or radio-active xenon gas, instilled into the colon, is absorbed first and in highest concentrations by the blood supply to that region (portal) and, therefore, if the bleeding is from esophageal varices, the concentration of the gas in samples of blood recovered from the stomach will be high; if from gastric bleeding sites, it would be low.

Gastrin studies

Several years ago, Institute grantees in England synthesized gastrin, a hormone which stimulates secretion of gastric juice, and more recently another grantee showed that anti-gastrin antibodies produced in rabbits inhibited endogenous gastrin-mediated gastric acid secretion in rats. Since increased blood gastrin levels are correlated with gastroduodenal ulceration due to hypersecretion of gastric juice, this suggested the possibility of modifying through such novel approaches (development of immunologic antagonism to the hormone gastrin) excessive gastric acid secretion in disease states such as peptic ulcer.

Another grantee has shown that the hormone secretin prevented increased blood gastrin levels in animals and that subjects with duodenal ulcers secrete less secretin than do normal subjects in response to acid stimulation of the duodenum. This offers another possible approach (secretin supplementation) to attacking the ulcer problem through our recently much improved understanding of the basic physiological mechanisms involved.

A recently developed radioimmunoassay method, which enables one to measure minute amounts of gastrin, was applied by an Institute-supported grantee at the University of California, Los Angeles, to study the release and destination of this hormone. They determined that it is released into the bloodstream rapidly in response to food, and is significantly higher in the blood of duodenal ulcer patients than in normal subjects. For example, after a 1250-calories liquid test meal

the serum gastrin levels rose to an average peak of 148 picograms per ml. in normal subjects, and to 250 in ulcer patients.

Digestive disease in older people

In order to help gauge the problem of digestive disease in the geriatric population, a team of Institute-supported investigators from the University of California School of Medicine, Irvine, California, and the Long Beach Veterans Administration Hospital, studied a total of 1600 patients who had either vagotomy with drainage procedure or some type of gastric resection for non-canerous diseases of the upper gastrointestinal tract. Of these, 230 were over 60 years of age and 125 of them underwent surgery for bleeding. Ninety-one of the 125 had duodenal ulcers, 27 had gastric ulcers, four had gastritis, two had esophageal ulcers, and one had esophagitis.

The ratio of three duodenal ulcers to one gastric ulcer is similar to that found in younger patients, the investigators reported. The overall mortality rate of 21 percent in bleeding peptic ulcer indicates that this disease is a severe life-threatening situation. Survival, rather than long-term effects of the surgery, becomes more important and thus more radical surgical intervention seems indicated than has been conventionally deemed desirable in older patients. According to the investigators, the high mortality in this group of over-60 patients is related to the amount of bleeding, especially when there is a loss of over 2500 ml., and related to age, particularly among those over 75 years.

The stomach in PXE

Pseudoxanthoma elasticum (PXE)is a rare connective-tissue disorder which is inherited as an autosomal recessive trait. Five patients with PXE who had a history of upper-gastrointestinal tract bleeding were studied in order to determine if there are local gastric factors which might lead to hemorrhage. They were examined with a gastroscope at a time when they had not bled for at least one year. All five patients had linear or nodular, raised, submucosal lesions which were yellow in color and similar to the xanthomalike skin lesions seen in this disease. In addition, two patients had moderately severe gastritis.

In view of the high incidence of gastrointestinal bleeding and a presumed defect in the vascular component of clotting in this disease, the Institute supported researchers at Johns Hopkins Hospital suggest that all patients with PXE be examined by gastroscopy and treated intensively with antacids if gastritis exists.

Alcohol delays gastric emptying

The results of animal studies indicate quite consistently that alcohol interferes with gastric movement and evacuation. Alcohol was reported to reduce hunger contractions of the stomach in dogs, and to delay gastric emptying of glucose, fat and protein meals in the rat. The data obtained from human subjects are less consistent, and both interference with the emptying process and lack of any effect have been reported.

Institute-supported researchers at the Wood Veterans Administration Center and Marquette University School of Medicine investigated the problem of the gastric activity-alcohol relationship in an everyday situation: the effect of alcohol before dinner on the gastric emptying of a subsequent meal. A recently developed method, using radioactive chromium as a meal marker and external counting of radioactivity, was employed to measure the rate of gastric evacuation. It was found that ingestion of 4 oz. of whiskey delayed the gastric emptying of a subsequent meal by an average of 99 minutes.

Celiac disease

Celiac disease ("nontropical sprue") is characterized by fatty diarrhea, intestinal malabsorption, and dietary deficiency symptoms, all caused by an intestinal sensitivity to a polypeptide fraction (gliadin) of the cereal protein, gluten, in the diet.

An Institute-supported grantee at the University of Colorado Medical Center has recently reported that clinical findings of gluten-induced intestinal diseases are highly variable. Other coexisting disorders may cause malabsorption and can obscure and delay diagnosis and treatment.

The classic features of adult celiac disease were present in only eight of twenty-one patients studied from 1961–68. Individual case histories revealed that nearly all the patients demonstrated *some* of the classical features of malabsorption,

but mild and nonspecific gastrointestinal symptoms were misleading in some cases, and in others, secondary nutritional manifestations predominated. Since coexisting alternative explanations for malabsorption, including diabetes and gastric surgery, may obscure the diagnosis, a complete evaluation is necessary, the investigators reported.

Strict adherence to a gluten-free diet resulted in dramatic clinical, chemical and histologic improvement in some patients, although recovery sometimes required many months. Other patients were able to discontinue the diet without apparent adverse effects, confirming the work of other investigators.

Inflammatory bowel disease

The causative factors of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease are still unknown. From research carried on by several Institute grantees, however, immunological mechanisms seem to be strongly implicated. Thus, it has recently been reported that acute exacerbations of Crohn's disease responded favorably to systemic treatment of the patient with immunosuppressive agents. In other studies, granulomatous lesions (resembling the characteristic lesions of Crohn's disease) have been induced experimentally in animals by injecting small intestine and lmph node tissue homogenates from patients with Crohn's disease. These results point to the possibility of a transmissible agent in Crohn's disease. Further work is required to identify the nature of this agent and to provide a rational therapy for this disease based on this new hypothesis.

Therapy after gastrointestinal surgery

Other grant-supported investigators are studying new therapies to ameliorate the untoward after effects which sometimes occur as the result of extensive gastrointestinal surgery. For example, studies are continuing on the possible effectiveness of medium-chain triglycerides (special man-made fats which contain fatty acid chains considerably shorter than those ordinarily found in natural oils and fats) for patients with the "short bowel syndrome."

Massive resection of the small bowel for inflammatory bowel diease, or for other reasons, can create serious therapeutic problems. Typically, patients with a resultant "short bowl syndrome" develop severe diarrhea and lose excessive and, in some cases, life-threatening amounts of water and esseential electrolytes in their stools. No form of therapy has been completely satisfactory, until a grant-supported study this past year described use of a dietary regimen in which 50–75 percent of the long-chain (natural) fats are replaced with medium-chain trigylcerides, which previously had been shown by other Institute grantees to be of substantial value in managing various other fat malabsorption disorders. Such a regimen in patients with the short-bowel syndrome now has led to a gradual decrease in diarrhea and decline in fecal loss of water and electrolytes and to significant improvement in the patients' nutritional status on long-term follow-up.

LIVER DISEASE

The liver performs a multitude of complex biochemical tasks without which life cannot exist. The largest single organ in the human body, the liver functions, for example, as a "chemical filter" and clearing station for purification and detoxification of blood, as a storage house for certain nutrients (particularly carbohydrates, certain minerals, and vitamins), as a site of production of blood proteins, as a secretory gland which aids both digestion and the removal of wastes as well as myriads of other metabolic functions. Not surprising, an organ of such complexity is subject to a wide variety of injuries and disease states.

Hepatitis

The two major liver diseases, cirrhosis (on the increase in our adult population) and hepatitis (increasing at an alarming rate among our young population) are both crippling and potentially fatal diseases of great social and economic importance. A most rapidly moving field has been the finding of an association between the presence of a viral-like substance ("Australia antigen") and a type of hepatitis transmitted primarily through blood transfusions or by

contaminated needles. There is some evidence that fatal liver necrosis or cirrhosis occurs only in those cases of acute viral hepatitis in which the antigen is present. If further work establishes this, much apprehension, and costly medical care could be eliminated in the less hazardous cases. Further work may eventually permit the development of a vaccine effective against hepatitis or a therapeutically effective antibody preparation against Australia antigen.

Prednisone in liver disease

In a study of various drug regimens in the treatment of chronic active liver disease, Institute grantees at the Mayo Clinic have found prenisone to be clearly superior, either alone or in combination with azathiorpine to azathioprine treatment or nonspecific supportive treatment without use of either drug. The investigators examined 60 patients for up to a period of three years, and observed remissions in slightly more than half of the patients on either prednisone or the combination. Only in this group were there patients whose liver function and histology became normal enough for them to discontinue therapy.

Soft drink remedies cirrhotic intoxication

Patients with advanced cirrhosis of the liver frequently exhibit neurological symptoms similar to the signs of acute intoxication. Because of their inability to detoxify ammonia and related nitrogen compounds (the former through conversion, in the liver, to urea), they exhibit slurred speech, confusion, staggering gait, and have a tendence to lapse into coma. The usual treatment is a low-protein diet and neomycin to eliminate the intestinal bacterial flora which produces ammonia from nitrogen sources in the bowel.

Now, a grant-support investigator at Harvard University has produced a more acceptable, and possibly more effective remedy by developing a fig-flavored soft drink containing the rare sugar lactulose, which to date has been given to 20 patients prone to hepatic coma because of chronic liver impairment. Eleven responded well, six stopped therapy for various reasons, and three died. The scientist noted that these patients are often near the end of their lives from far-advanced cirrhosis and improvement is measured in weeks or months rather than years. The longest survivor has now been on lactulose treatment for 21 months.

In contrast to the usual dietary sugars, lactulose is not absorbed from the gastrointestinal tract into the bloodstream. Thus this unusual carbohydrate remains in the bowel and is available there for fermentation by intestinal bacteria. If lactulose is administered on a regular basis the bacterial population in the intestine changes in character from a primarily putrefactive one, which is largely responsible for the production of potentially toxic ammonia from various nitrogen sources, to a fermentative one, thus preventing much of the production of ammonia which is responsible for the symptoms of hepatic coma.

The presence and fermentation of lactulose in the intestine also cause a drop of pH in the bowel (renders contents more acid), which deters the absorption of ammonia.

The usual dose of the experimental lactulose-containing beverage is six to eight ounces, taken three times a day after meals. The greatest benefit from the treatment is that it keeps patients from lapsing into a coma that necessitates hospitalization and is potentially life-threatening.

OUTLOOK

Although this resume of research progress in digestive diseases encompasses but a small portion of the Institute-financed research in this extremely broad field, it demonstrates the diversity and productivity of the many investigations conducted and supported by the National Institute of Arthritis and Metabolic Diseases. 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 digestive disorders. While some of these advances have found immediate application at the bedside, others, of a more fundamental nature, are contributing to the broader base of research knowledge from which comes future progress in these disorders. Altogether, these findings give renewed hope for improved therapeutic modalities in the field of digestive diseases in the foreseeable future.

Mr. SMITH. Mr. Michel.

Mr. MICHEL. Thank you, Mr. Chairman.

ADJUSTMENTS IN RESEARCH GRANT FUNDING

I am not altogether sure I understand. On page 149 of the justification and then again on 170, noncompeting research grants go up by $3.7 million. But, then when you get down to decreases, research grants show a minus $2 million.

In summary, is it that the new ones are down but the old competing ones are increased?

Dr. WHEDON. That is correct. The allowance for support of noncompeting research grants, the grants for which we have made moral commitments which continue on into 1972 has been increased by $3,773,000.

Mr. MICHEL. Does that suggest these are extra good?

Dr. WHEDON. No. The judgment had been made at a prior time as to their merit with respect to being supportable. So this is merely to continue our moral commitment.

Mr. MICHEL. Then would it be correct to say this is to carry out the "moral obligation" we talk about?

Dr. WHEDON. Yes.

Mr. MICHEL. These are multiyear grants are they not?

Dr. MARSTON. No, sir, they are for 1 year because we are on an annual appropriation. But we review the needs of the applicant for subsequent years and indicate the amount of support that we would be prepared to give in subsequent years conditional on an administrative review of the needs and on congressional appropriations.

The problem we got into is that at the time the Expenditures and Revenue Control Act required a cutback in the regular grant programs, we acted on the assumption that this would be a 1-year emergency. So we negotiated reductions grant by grant at an average of between 10 and 15 percent reduction on the noncompeting continuations.

Actually, the grantees have been subjected to tight Federal funding for several years. What we have been doing every year is to negotiate downward the amount of money for each grant so that we can attempt to maintain the number of grants. Each year we have been going back and reducing the grants in almost arbitrary fashion.

I think this is an unworkable way to operate over a period of time. So we are trying to get ourselves out of the bind of making a decision on the level of support and then going back a year later and saying you actually will get 20 percent less. This creates a lot of problems for people trying to plan their research for more than a year at a time. So we made a decision to try to get out of that bind as far as the noncompeting continuation grants.

We continue to review them administratively, we continue to reduce the amount when there is a justification for reducing it, but we are getting away from this arbitrary need to go back and review and reduce the same grants year after year in an arbitrary fashion.

PROGRESS AGAINST CYSTIC FIBROSIS

Mr. MICHEL. Doctor, I was a little bit distressed to see no more discussion in your testimony with respect to cystic fibrosis. A few years ago for the first time we earmarked some money especially for this because we had been told at that time there had been some new breakthroughs we wanted to exploit.

I wonder if we could have for the record an updating of what progress we have made in this area. It was pretty striking testimony given a year or two ago. I would hope we are continuing that kind of progress, but it doesn't show as visibly as I thought it might in the testimony.

Dr. WHEDON. May I say, Mr. Michel, we do have a special report prepared on cystic fibrosis, and these are some specific items we shall mention that will, I hope, demonstrate to you that we are making progress in this area.

Mr. MICHEL. Let's have it displayed here in the record.

Dr. WHEDON. Our efforts in this important disease area have not slackened since the period you referred to, and I would like to illustrate progress in cystic fibrosis research with one or two examples of the findings of the past year. One such finding that may expalin the abnormal excretion of both viscous mucus and high salt concentration that characterize cystic fibrosis has been provided by an Institute grantee at the University of Nebraska. He has shown that the skin of children with cystic fibrosis is deficient in a specific lysosomal enzyme called beta-glucuronidase which is linked to metabolism of mucopolysaccharides, a group of complex carbohydrates, and of salt transport. He found that a significant decrease in beta-glucuronidase activity existed in the skin and sweat glands of patients with cystic fibrosis in contrast to normal children.

Other studies have suggested that this enzyme may be necessary for normal salt excretion and handling of mucopolysaccharides, and its diminished amount in cystic fibrosis may explain the impaired salt and mucosugar metabolism characteristic of this disorder.

Microscopic eyelash-like cilia present in the air passages in lungs of all mammals, including man, normally sweep moisture droplets, foreign particles and mucous collections from the lungs to the larger air passages from where they are coughed out. In previous years I have told the committee about studies which have indicated the presence of an abnormal factor in the serum of patients with cystic fibrosis that causes cessation of ciliary action in the bronchial mucosa of experimental animals. We suspect that this inhibition of bronchial ciliary action in man is one contributing factor to the characteristic obstruction of the air passages of the lung with mucus in cystic fibrosis.

This serum factor can be used in identifying cystic fibrosis patients and carriers of the disease, according to Institute-supported researchers at the University of Texas, who last year demonstrated inhibition of ciliary action in oyster gills with sera from cystic fibrosis patients and from their parents. The same investigators have now isolated from the sera of cystic fibrosis patients and asymptomatic carriers this in-

hibiting factor that may be the result of a gene mutation. Analysis of this factor indicates that it is a protein present in the gamma globulin fraction of the serum, which may be responsible for several metabolic defects in membrane transport, pulmonary function, and pancreatic enzyme secretion observed in cystic fibrosis patients. The analogous gamma globulin fraction in normal individuals did not contain this protein and, consequently, did not inhibit oyster ciliary action. The investigators hypothesize that this protein may act as an auto-antibody or a polycation which is destructive to membrane integrity and energy exchange.

We have prepared a detailed special report on these and other research advances on cystic fibrosis for the committee, and with your permission would like to submit it at this point.

(The information follows:)

Cystic Fibrosis

Cystic fibrosis (CF) is a grave disease of children and you adults caused by an inborn error of metabolism. The basic chemical defect is not yet fully understood, but it is known to be genetically transmitted. The Department of Health, Education, and Welfare's research activities in cystic fibrosis are centered in the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health; service activities of the Department related to this disease are centered in the Health Services and Mental Health Administration.

The research program on cystic fibrosis is carried out in the National Institute of Arthritis and Metabolic Diseases, a component of the National Institutes of Health, Bethesda, Md. The research conducted and supported by the Institute is aimed at specifically defining clinical manifestations and biochemical aberrations responsible for this inherited metabolic disorder. In addition to the research being conducted in the Bethesda laboratories, this Institute provides grant support to many cystic fibrosis research projects at medical centers and institutions across the country. Among promising new findings this past year is the demonstration that skin of patients with cystic fibrosis is deficient in a specific enzyme that is linked to salt secretion and mucopolysaccharide metabolism, both of which are abnormal in cystic fibrosis. This finding should help pinpoint the molecular defect in this metabolic disorder.

OBLIGATIONS FOR PROGRAMS IN CYSTIC FIBROSIS

	1968	1969	1970	1971 estimate	1972 estimate
National Institutes of Health: National Institute of Arthritis and Metabolic Diseases	$2,001,000	$2,588,000	$2,507,000	$2,645,000	$2,701,000
Health Services and Mental Health Administration: Maternal and Child Health Service	(1)	(1)	(1)	(1)	(1)
Total	2,001,000	2,588,000	2,507,000	2,645,000	2,701,000

[1] Not identifiable.

National Institutes of Health

National Institute of Arthritis and Metabolic Diseases

It is estimated that one baby in every 1,400 infants is born with an inherited metabolic disease called cystic fibrosis, or CF. It is characterized by malfunctioning exocrine glands which secrete abnormal fluid to internal and external body surfaces—the gastrointestinal and respiratory mucosal linings and the skin.

The basic metabolic disorder of exocrine secretion results in three principal clinical problems. The most serious complications involves the lungs. Nearly all cystic fibrosis patients develop progressive chronic lung disease. In cystic fibrosis, the mucus-producing glands fail to secrete normal, clear, free-flowing fluid. Instead they produce an abnormally thick, viscous mucus which tends to obstruct the ducts or openings of the glands and to accumulate in the organs in which it was produced. Thus, thick mucus obstructs the smaller air passages in the lung, causing labored breathing and a chronic, productive cough. In time, bacteria multiply in the accumulated secretions, and the child may fall victim to chronic bronchitis or pneumonia, a leading cause of death in these patients. Chronic lung changes may increase resistance to pulmonary blood flow and thus, may lead to an increased blood pressure in the lung; this can result in chronic heart strain and eventually in heart failure.

A second facet of the disease stems from the abnormal functioning of the mucus-secreting glands in other parts of the body. When the viscous mucus accumulates in the ducts of the pancreas, it interferes with the ability of this gland to supply digestive enzymes to the intestinal tract, thus leading to poor digestion and malabsorption of a number of nutrients. Depending on the severity of this complication, the patient may suffer from varying degrees of malnutrition—one of the major factors resulting in general underdevelopment, poor musculature, and retarded bone growth.

The third facet of the disease involves the production of sweat with a high salt content. Due to this defect, patients are unable to conserve salt and the very young are in danger of developing profound dehydration, or "heat exhaustion" in the summer months, which may lead to death.

Cystic fibrosis is inherited from parents who carry the genetic trait for the disorder (the parents themselves may be asymptomatic). When both parents carry the trait, the chances are one in four that cystic fibrosis will be manifested in the severe and classical form in the offspring. If only one parent carries the trait, it may be transmitted to the offspring; and although the child will be asymptomatic, the trait may in turn be inherited by his offspring. Thus, for every overt case, there is a large reservoir of hidden carriers, recently estimated at 2 to 5 percent of the general population. Clearly, since the genetic character of cystic fibrosis makes the disorder particularly pernicious, a method of identifying such carriers would be a major achievement for facilitating effective genetic counseling.

RESEARCH DEVELOPMENT AND TRENDS

The national Institute of Arthritis and Metabolic Diseases is deeply committed to a broad multidisciplinary research program on cystic fibrosis involving broad research grant support to scientists throughout the country as well as intramural research by Institute staff in Bethesda. Two aims are paramount: To define clinical manifestations and biochemical aberrations responsible for cystic fibrosis and to improve treatment methods to forestall the disease's serious complications. As yet there is no one hypothesis that can link the diverse observations made concerning the widespread abnormal behavior of the various exocrine glands. Encouraging research progress this past year, however, has helped narrow the field of speculation.

Enzyme deficiency may pinpoint molecular defect

A new finding that may explain the abnormal excretion of both viscous mucus and high salt concentration that characterize cystic fibrosis has been provided by an Institute grantee at the University of Nebraska. He has shown that the skin of children with cystic fibrosis is deficient in a specific lysomal enzyme called betaglucuronidase which is linked to mucopolysaccharide (a group of complex carbohydrates) metabolism and salt transport.

Skin biopsies were obtained from 15 patients with cystic fibrosis and 15 healthy children in the same age range. Fragments of epidermis, sweat glands, and dermis were isolated and assayed for the activities of several enzymes. Although the activity of many enzymes was found similar in normal children and in those with cystic fibrosis, a statistically significant decrease in betaglucuronidase activity existed in the epidermis and sweat glands of patients with cystic fibrosis.

Several other studies have suggested that betaglucuronidase may be a necessary component of the salt-secretion mechanism and may play a role in mucopoly-

saccharide metabolism. Other NIAMD grantees recently have shown that abnormal metachromatic material, presumably of mucopolysaccharide nature, accumulates in cultured skin fibroblasts from cystic fibrosis patients and carriers. (Metachromatic material fails to stain in a pattern similar to the surrounding material.) In view of the known connection between betaglucuronidase and mucopolysaccharide metabolism, the finding of decreased betaglucuronidase activity in cystic fibrosis may provide insight into the etiology of this disorder. Further study will be required to learn whether the observed decreased betaglucuronidase activity represents decreased enzyme synthesis, abnormal enzyme structure, or inhibition by some other substance.

One of the most important implications of these recent findings will lie in the results of subsequent investigations into the molecular defect of this metabolic disease. Up to now, clinical and chemical studies have indicated that cystic fibrosis is a generalized exocrine disorder. These new findings hint that the defect in cystic fibrosis is not limited to a single class of (exocrine secretory) cells but involves, among others, the body's connective tissue cells as well. Further biochemical analysis of the metachromatic cellular substance may prove to be a step forward in elucidating this theory.

Characterization of cystic fibrosis serum factor

Microscopic eyelash-like cilia present in the air passages in lungs of all mammals, including man, normally sweep moisture droplets, foreign particles and mucous collections from the lungs to the trachea and pharynx, from where they are coughed out. In recent years numerous studies have indicated the presence of an abnormal factor in the serum of patients with cystic fibrosis that causes cessation of ciliary action in the bronchial mucosa of several experimental animals. It is suspected that this inhibition of bronchial ciliary action in man is one contributing factor to the characteristic obstruction of the air passages of the lung with mucus in cystic fibrosis.

This serum factor can be used in identifying cystic fibrosis patients and carriers, according to Institute-supported researchers at the University of Texas Medical Branch in Galveston, who last year demonstrated inhibition of ciliary action in oyster gills with sera from cystic fibrosis patients and from their parents (carriers). When sera from the two control groups (normal and generally allergic individuals) were tested, oyster cilia movement persisted as long as 40 to 50 minutes after contact. By contrast, sera from cystic fibrosis patients produced cessation of ciliary movement within 30 minutes. None of the sera from cystic fibrosis patients and their parents permitted ciliary action for as long as did sera from the normals. Further, saliva from cystic fibrosis patients, but not from normal individuals, often inhibited ciliary action within 20 minutes.

The same investigators have now isolated from the sera of cystic fibrosis patients and heterozygotes (asymptomatic carriers) this inhibiting factor that may be the result of a gene mutation. Analysis of this factor indicates that it is a protein present in the gamma globulin fraction of the serum, which may be responsible for several metabolic defects in membrane transport, pulmonary function, and pancreatic enzyme secretion observed in cystic fibrosis patients. The analogous gamma globulin fraction in normal individuals did not contain this protein and, consequently, did not inhibit oyster ciliary action. The investigators hypothesize that this protein may act as an auto-antibody or a polycation which is destructive to membrane integrity and energy exchange.

At Duke University, Institute grantees demonstrated several years ago that an abnormal factor existed in sera taken from cystic fibrosis patients and their parents which inhibited ciliary synchrony in rabbit tracheal explants. Possibly, this factor is identical to the one inhibiting ciliary action in oyster gills.

Abnormal secretions in certain body systems

For many years, elevated electrolyte concentrations in exocrine gland secretions from cystic fibrosis patients have been recognized as playing important roles in the pathogenesis of the disease. Intensive studies are being conducted, therefore, to isolate the factors responsible for abnormal secretions. Through these efforts the inherited molecular defect which causes cystic fibrosis may be defined.

Previous studies by Institute grantees at the University of Wisconsin several years ago revealed elevated sodium concentrations in sweat and saliva from cystic fibrosis patients. Additionally, Institute scientists are designing new studies to

understand better the role of the autonomic nervous system in normal salivary gland secretion mechanisms because calcium concentrations in saliva of cystic fibrosis patients are also known to be high. Since this abnormally high concentration suggests a defect in calcium metabolism, these studies may define additional mechanisms that are distorted in cystic fibrosis.

Two years ago, Institute-supported investigators at the University of North Carolina described a marked decrease in sodium output from erythrocytes (red blood cells) of patients with cystic fibrosis, and a similar decrease in the red blood cells of their asymptomatic parents. At that time the researchers felt that the defect in sodium transport could be of value in detecting cystic fibrosis carriers, and therefore, should be useful in genetic studies.

Now two Institute researchers who have further examined the defect in erythrocyte sodium transport in cystic fibrosis patients have reported that decreased sodium is probably not related directly to the basic molecular defect and cannot be used as a genetic marker for the disease. The researchers analyzed sodium content and various components of sodium outflux in erythrocytes from 26 normal subjcets, 25 patients with cystic fibrosis, and 20 parents of such patients.

Their results differed from the past University of North Carolina study in that the fractional sodium outflux was diminished only in red blood cells from males and adolescent females with cystic fibrosis. This component was normal in erythrocytes from prepubertal females with cystic fibrosis and did not differ significantly between carriers of both sexes and the control group.

Since no abnormality in sodium transport in red blood cells from heterozygotes (carriers) were found, this component cannot be employed as a genetic marker. Furthermore, the investigators concluded, since heterozygotes and younger females with cystic fibrosis have normal erthyrocyte sodium outflux, the differences described are probably not related directly to the basic defect, but rather represent a secondary feature of the disease.

In refuting the genetic marker hypothesis, however, the researchers point out that specific variables, such as different sex hormone levels among patients and experimental procedures may account for the differences between their results and past findings.

The scientists speculate that the reduced sodium outflux in CF erythrocytes and the high sodium concentration of cystic fibrosis sweat may reflect a similar abnormality. With precise delineation of the sodium transport mechanism, insight may be provided into the saliva and sweat gland defects in cystic fibrosis and perhaps into the underlying abnormality as well.

TREATMENT

Early diagnosis and prompt institution of therapeutic regimens are of utmost importance both in forestalling or delaying development of such serious complications of cystic fibrosis as irreparable lung damage, and in reducing both morbidity and mortality rates of cystic fibrosis patients. Several significant advances in diagnostic and therapeutic techniques have been reported this year.

New diagnostic test

Measuring the amount of copper in nail clippings from newborn infants may provide a useful screening technique for cystic fibrosis, according to several investigators at Baylor College of Medicine and Texas A. & M. University. At the present time cystic fibrosis is diagnosed principally by the detection of excessive amounts of sodium in the sweat. Sweat-test facilities, however, are not always readily available, and results of such tests are not always conclusive.

In this study, infants' nails were trimmed with sterile surgical scissors and the resulting samples were irradiated with neutrons from a nuclear reactor. Using neutron activation analysis techniques the copper content was determined from the amount of annihilation radiation of the resulting copper isotope.

In 118 cystic fibrosis patients the copper content of nail clippings was 50 to 200 parts per million (p.p.m.). Nail clippings from about 250 normal adults contained 2 to 40 p.p.m. of copper, while clippings from 850 normal neonates showed a copper concentration similar to normal adults—2 to 30 p.p.m. Only 0.2 percent of healthy infants had a copper level above 50 p.p.m. of copper, whereas none of the cystic fibrosis subjects fell below that level.

The Texas researchers consider the copper assay method simpler, less costly, and more suitable for the mass screening of neonates than the sweat test. Locally, results are available within 48 hours, while the infant is still in the nursery. Using this method, large numbers of nail samples can be shipped by mail from broad geographic areas and great distances without danger of deterioration of the test samples, and can be tested centrally both rapidly and inexpensively.

Lung lavage

Since chronic obstructive lung disease is responsible for death in 90 percent of cystic fibrosis patients, control of pulmonary infection is a vital component of cystic fibrosis therapy. Conventional lung-clearance procedure involves postural drainage and chest thumping with cupped hands.

Recently, a more effective method of lung lavage, a process of washing mucus from the pulmonary passages of cystic fibrosis patients, has been employed by an Institute grantee at Duke University Medical Center. The new technique utilizes a bronchospirometry tube in periodic volume-controlled lung lavage. Over half of the 10 patients receiving lung lavage reported a decrease in viscosity and volume of sputum after lavage, as well as improved general well-being.

This technique is safe and simple when performed properly, although patients with severe impairment of pulmonary function are probably not good candidates for this therapy because of the widespread irreversible tissue damage already present. The investigators feel that periodic volume-controlled lung lavage may halt or significantly retard the "inexorable deterioration" of lung function in patients with cystic fibrosis.

Iron deficiency identified and corrected

In healthy babies, serum iron levels are usually high at birth, decrease until the child is around 6 months old, and then begin to rise again, stabilizing about age 4. Serum iron levels in cystic fibrosis patients follow the same general pattern, although most of these patients are deficient in iron when such a deficiency is looked for. This is a condition more physicians should identify, according to researchers at the Cystic Fibrosis Center of the Children's Hospital of Los Angeles who have recognized and corrected it with oral iron supplements.

They proposed that since cystic fibrosis patients have chronic pulmonary disease, resulting in impaired respiration, chronic hypoxia (lowered oxygen content in the blood) plays an important role in causing abnormal variations (excess) of red corpuscles in the blood. This results in a utilization of available iron at a faster than normal rate thereby causing depletion of available iron stores.

When iron levels in the sera of 151 patients with cystic fibrosis were studied, 87 percent of the patients were found to have serum iron levels that were one-half the normal value of 120 ugm/100 ml.

In general, this condition of iron deficiency is more easily determined by red blood cell morphology than by usual hemoglobin and hematocrit determinations. There was no close correlation between the general clinical condition of patients and their serum iron levels.

Patients were given ferrous sulfate supplements (1 to 4 mg./kg. per day) orally for 1 to 6 months. Iron given at the rate of 2 mg./kg. per day elicited the best response, but even the 1 mg./kg. per day treatment led to serum iron level increases in all patients who were not suffering from a concurrent lung infection. Identification and treatment of iron deficiency should be incorporated in all cystic fibrosis therapeutic regimens, according to these investigators.

Relief of intestinal obstruction

A nonoperative treatment for intestinal obstruction due to meconium ileus (intestinal inactivity due to impaction of a debris-like material in the bowel of newborn infants) has been used successfully in nine infants by investigators at Children's Hospital of Philadelphia. Meconium in patients with cystic fibrosis has less water than that of normal infants, and diminished pancreatic secretions allow the meconium to become so viscid as to be obstructive.

The new therapy consists of an enema with "Gastrografin" solution, a radiographic contrast medium, followed by parenteral fluid administration. This therapy can be used to obtain relief from obstruction in cases of meconium ileus not complicated by perforation, extreme twisting of the intestine, or peritonitis.

Surgery is indicated if these complications exist, usually as a consequence of the original obstruction.

Gastrografin is a 76-percent aqueous solution of sodium methyl-glucamine diatrizoate with 0.1 percent wetting agent added. This agent also contains finely bound iodine which makes it radiopaque. Because of its high osmolarity, Gastrografin, the investigators believe, draws fluid into the bowel from the circulation. This softens the meconium and provides fluid between the meconium and the bowel wall, thus facilitating bowel elimination.

The researchers summarized that in more than 50 percent of patients, in whom no complications existed intestinal decompression by single or repeated Gastrografin enemas appears to be a major advance in management.

Scientific communication and information

The Institute has consistently made efforts to communicate, effectively and promptly, diagnostic and therapeutic developments in cystic fibrosis to practicing physicians and research workers throughout the country. One particularly effective means of communication has been the new comprehensive scientific exhibit on cystic fibrosis presenting the latest research findings and therapeutic applications. This exhibit, along with detailed practical literature, has been brought to the attention of thousands of practitioners and research workers at medical meetings and conferences throughout the United States this past year. It has received many favorable comments.

A newly revised brochure on cystic fibrosis is being produced by the Institute in response to inquiries from the lay public. The illustrated publication explains in nontechnical language what is known about the disease, what treatment is available to patients with cystic fibrosis, and what efforts are being made by this Institute in research for both the cause and better management of the disorder.

OUTLOOK

For clinicians and research scientists alike, cystic fibrosis is a multifaceted disease which offers puzzling fragments, yet to be collated, for a full understanding of its basic mechanism. Recent promising findings in basic research, as well as new methods of diagnosis and treatment, have opened up new avenues for investigating cystic fibrosis, while bringing about a more optimistic outlook for patients with this disorder. Mainly as a result of research supported or carried out by the National Institute of Arthritis and Metabolic Diseases, the average life span of children afflicted with the disease has been increased considerably and the quality of their life has been improved. Now that a significant number of girls with the disease survive to childbearing age it has become even more important to develop reliable and simple tests to detect carriers of cystic fibrosis and to initiate active genetic counseling wherever indicated. Institute scientists and grantees fully expect to meet this and oher challenges posed by cystic fibrosis. Hopefully, this continued progress will lead to better management and eventual prevention of this grave disease.

HEALTH SERVICES AND MENTAL HEALTH ADMINISTRATION

MATERNAL AND CHILD HEALTH SERVICE

Forty-four State crippled children's agencies reported to the Maternal and Child Healh Service that they accepted an estimated 4,300 children with cystic fibrosis for diagnosis, treatment and continuing care in fiscal year 1970. Kentucky is the latest State which has added cystic fibrosis to their definition of a crippled child, thus making children with this diagnosis eligible for services under the crippled children's program of that State.

ADMINISTRATIVE REVIEW OF RESEARCH GRANTS

Mr. SMITH. Going back to your discussion of the continuing grants. If you don't review these grants, how do you know the same personnel are involved that were included in the original application and that they will not spin off some of the better people to make applications for new grants?

Dr. MARSTON. That is the reason for the administrative review we do have. If the team broke up or a man changed institutions or there is any reason to believe the estimates made by the review committees are inaccurate, we have no hesitation about renegotiating and reducing the grant.

Dr. WHEDON. In our Institute, for example, and I am sure a similar process is in use in the others, for each of our 11 areas of categorical responsibility we have a program director for grants. It is the responsibility of each of the 11 directors to know in intimate detail each one of the grants under his jurisdiction.

Mr. SMITH. Mr. Hull.

RELATIVE PRIORITY OF RESEARCH VS. TRAINING

Mr. HULL. Dr. Marston, yesterday morning I had some physicians in my office who were greatly disturbed over the reduction of training and fellowship grants. They felt it would be better to reduce other areas, even research, and have training continued at the same level.

What is your reaction to those thoughts?

Dr. MARSTON. The answer is that we have the whole training grant program under study and we have agreed that we will hold the dollars level until that study has been completed. That is the intention as far as the 1972 request before you.

Mr. HULL. Thank you.

Mr. SMITH. Mr. Shriver.

CUTTING THE COST OF KIDNEY DIALYSIS

Mr. SHRIVER. Dr. Whedon, kidney disease which requires continuous dialysis is difficult financially upon those who use it. Has there been any progress toward the development of improved dialysis methods during the past year or reduction in the cost?

Dr. WHEDON. Mr. Shriver, there definitely has. I mentioned very briefly in my statement just the main point.

More specifically, we now have the hollow fiber kidney which was first introduced I think about a year and a half ago. It is now in commercial production and ready for use. This disposable dialyzer unit kidney costs about $17. It can be used four or more times before it must be discarded. No blood pump is necessary. The amount of blood that has to be put into the instrument to prime it is only 70 milliliters. That is the equivalent of about 2½ ounces of blood. It is a presterilized unit. It's ease of use and reuse will enable many patients to shift from expensive hospital dialysis to much less expensive home dialysis.

So this I think will facilitate artificial kidney dialysis considerably in terms of expense and also in terms of saving time. A lot of expensive hospital labor has gone into the time of preparation of artificial kidneys for dialysis treatment.

In addition, during the past year there has been developed what we call the "envelope dialyzer," which is a set of presterilized, ready-to-use plastic membranes which can be used with the Kiil type of

artificial kidney, a type in rather common use. This particular set of membranes cannot be reused, but it costs only $6 and also will save much labor time. It is very small and is going to facilitate both home and hospital dialysis.

In addition, of course, in this program we pioneered interest in the study of the use of chemical absorbents in dialysis. If successful, this is going to shorten the time that a patient has to be on an artificial kidney, and make the dialysis much more efficient and cut costs of dialysate chemicals and of de-ionization of water. In addition to that, we are studying the importance of various special low protein diets as being beneficial in the maintenance of kidney failure patients, either by enabling less frequent dialysis or in some cases avoiding dialysis altogether.

Mr. SHRIVER. Thank you.

Mr. SMITH. Mrs. Reid.

SPURIOUS CURES OF ARTHRITIS

Mrs. REID (pointing at a copper bracelet). Doctor, first of all, my bracelet. What do you think of it?

Dr. WHEDON. Very attractive—and charming, Mrs. Reid [Laughter]. Actually, the current fad for wearing a charm against arthritis, while similar to many appeals to the occult in the past for other purposes, probably reflects the fact that arthritis is a complex set of many diseases. In many of its forms it has a tendency to wax and wane, to get worse and get better spontaneously, and it is inevitable that almost any treatment from cod liver oil—to oil the joints—to tomato juice or what have you, bee venom, for example, would be given credit by some as having been beneficial. These so-called cures have sometimes been given at a time when there is spontaneous remission. We never seem to hear about the failure after failure of all of these types of treatment. There has been, for example, in the past a great interest in the uranium mines in the Western States on the false assumption that the radiation would be helpful. This is part of the same pattern.

Mrs. REID. I suppose if I never have arthritis, no one will ever know whether it is because of this bracelet or because I am destined never to have it.

Dr. WHEDON. I would suggest that physicians who are concerned with what causes arthritis to develop have learned more and more each year and are making very significant progress. It is gradual but it is relentless. I would suggest that if you do ever have a twinge, you get advice as to the best physician to see and I am sure you will receive valuable help.

Mrs. REID. This is probably one of the reasons that something like a bracelet of this kind is really not beneficial because when someone feels the first twinges of arthritis, he may not go to a physician. I presume that would be one of the reasons.

EARLY TREATMENT OF ARTHRITIS

Dr. WHEDON. You raise an important point and that is that as we are coming to learn more and more, we are getting the message across to people that it is important to treat any form of arthritis as early as possible. Otherwise the patient may run into severe continuing disability. Joints will become more and more restricted in their motion, and crippling can occur which is not only unsightly but makes joints difficult to use.

Mr. MICHEL. Suppose a physician says to me, you are bound to get a few creaks as you get older, and you are not yet 50?

Dr. WHEDON. This reaction I am sure is part of the wide realization that osteoarthritis, the degenerative form of arthritis, is very widespread and is usually very gradual in its onset. Past the age of 60 nearly everyone has some degree of stiffening in the joints on this basis.

I suspect that if every case of mild pain or stiffness were to be treated, the doctors' offices would be inundated. So I wonder if perhaps the doctor may have been testing you as to how serious you felt your discomfort and disability was, and if you return to him with a vigorous complaint, I think you will get help.

RESEARCH OPPORTUNITIES IN ARTHRITIS AND DIABETES

Mrs. REID. Do you feel, Doctor, that research opportunities do exist at the present time that will permit significant progress to be made in the prevention and treatment of arthritis and diabetes by the implementation of carefully planned, collaborative efforts directed at these problems?

Dr. WHEDON. Yes, Mrs. Reid. Efforts along these lines are going on at the present time. I mentioned in my opening statement very briefly the cooperative clinical trial of 12 clinics for study of the possible benefit of one of the oral drugs to prevent the late complications of diabetes. Another such antidiabetes drug is under continuing study and the results probably will be published within the next year.

On arthritis there has been also a cooperative clinical trial on the usefulness in rheumatoid arthritis of a compound called cyclophosphamide which I mentioned, I believe, last year. That study has passed through its first phase which indicated in about 48 patients that the drug could be helpful and worth continued study. Now that cyclophosphamide cooperative study is in its second phase to determine the best dosages; this phase is most important because there have been indications of undesirable side effects in some patients. The plan is for patients to be treated with this compound for 16 months. They have now put 40 patients in the study and plan to go up to 150. I cite this detail as an example of one of the types of cooperative studies going on among several different arthritis university clinics.

These indeed will be other studies of this sort both in arthritis and diabetes and perhaps in other diseases as well. These cooperative studies require a great deal of careful effort and are expensive, but

many feel that they are the only way for conclusive determination of the effectivness and safety of important therapeutic drugs.

DEVELOPMENT OF AN ARTIFICIAL PANCREAS

Mrs. Reid. Has progress been made in regard to pancreas transplants to alleviate diabetes?

Dr. Whedon. There is some continuing interest along those lines but recently more on the possibility of an "artificial pancreas." There was a newspaper story by the Associated Press about a week ago about this. There are actually two or three different groups who are working on this possibility. This idea is not to transplant pancreatic tissue but to set up a mechanical pancreas, a mechanical system which could be worn by the patient all the time. The system would involve a sensor in the blood which would electronically indicate what the blood sugar level was and when it got too high, there would be a means of telling the reservoir of insulin which would be carried by the patient that it should deliver more insulin into the blood.

So, theoretically at least, this device would enable a patient to maintain his blood sugar at a proper level at all times no matter what physical or other stress would occur. This would obviate the daily injections of insulin through the skin, and all a patient would have to do would be to refill periodically the reservoir of insulin he was carrying around, perhaps every few weeks. This work at the present time is not being supported by the Institute. It is being supported by private funds.

I think we ought to put in a word of caution that I understand there are some difficulties. The principal difficulty is with the sensor which continuously tests for the level of blood sugar and with keeping it clear of blood clot formation because it has to sit in a vein all of the time. So it may take a few years, but the idea is an excellent one.

Mrs. Reid. Did you read the Associated Press article about the chemist laid off from the aerospace industry in California who provided the expertise which they say led to the breakthrough?

Dr. Whedon. That is the article I was referring to.

KIDNEY DIALYSIS COSTS

Mrs. Reid. In response to one of Mr. Shriver's questions, did I understand you to say that we now have an inexpensive kidney dialysis machine? Is this so?

Dr. Whedon. I spoke of two developments. One is the "hollow fiber kidney" which was introduced for experimental study about a year and a half ago. That is a new dializer, the most critical part of an artificial kidney machine, it does have to be used with a dialysis bath.

Mrs. Reid. Excuse me. How much is that?

Dr. Whedon. This unit costs about $17 and can be reused.

Mrs. Reid. How many times?

Dr. Whedon. About three or four times.

Mrs. Reid. Then you replace it completely and must pay the $17 again?

Dr. WHEDON. Then you replace it with a new unit after three or four times. In other words, you don't take the time to clean it out or resterilize it. It is simpler with the $17 unit level simply to replace it.

Mrs. REID. Is it small and compact?

Dr. WHEDON. It is about perhaps 12 inches long and I would say about 4 inches in diameter.

The other item I mentioned is an "envelope kidney" which is a set of membranes that can be used with one of our standard artificial kidneys, the Kiil unit. This can't be reused but it is very cheap, $6. This unit is advantageous in that it is all presterilized, and no one has to take the time and trouble to clean it and sterilize it. It is thus very useful in home dialysis which is much less expensive than dialysis in a hospital.

Mrs. REID. As I understand it, this takes the places of the same treatment that costs several hundred dollars?

Dr. WHEDON. When done in a hospital. Of course if one is on Kiil dialysis at home, one would have to buy a Kiil machine at the beginning of the treatments.

Mrs. REID. Which would cost how much approximately?

Dr. WHEDON. The Kiil machine costs between $700 and $1,000. Once you have paid that, you can use it over and over again for years.

Mrs. REID. Then this is a real breakthrough because patients were paying thousands of dollars for treatment were they not?

Dr. WHEDON. Yes. The overall annual home treatment costs in a situation like this would still be in the neighborhood of perhaps $4,000 to $10,000 a year. But this is a remarkable reduction from what it was just 3 or 4 years ago when we estimated that upwards of $20,000 a year, perhaps $35,000 or more would be required because most patients had to be dialyzed in the hospital.

With the advent of home dialysis which has taken place during the time we have had this NIAND artificial kidney program in effect, cost has been reduced to where now in the first year of home dialysis it is from $11,000 to $18,000 a year, including purchase of equipment and training of the patient or spouse. Then, in subsequent years it comes down to $4,000 to $9,000 depending on the type of equipment used.

Mrs. REID. But this is still out of range of the average person who must pay for such treatment.

Dr. WHEDON. May I ask Dr. Burton if he would give some detail on how the annual costs of artificial kidney treatment has been affected by our new developments.

Mrs. REID. Provide that for the record if you will.

Dr. WHEDON. Yes.

(The information follows:)

As you know from previous testimony of Dr. Whedon, dialysis conducted in the hospital is extremely expensive and out of the reach of most patients. The annual costs range from $25,000 to $35,000 and up. On the other hand, home dialysis, where the patient, with the aid of a close relative, conducts his own dialysis, costs only a fraction of the above. The first year including acquisition of the equipment and the very expensive hospital-based training of the patient will cost between $11,000 to $18,000 depending on the choice of the equipment and training cost; subsequent years, however, may cost only between $4,000 to $9,000, largely depending on the choice of equipment and occurrence of complications.

Many of the developments which our Institute's artificial kidney contract program have brought about have reduced the cost of dialysis for the patient either directly—and Dr. Whedon has already mentioned such examples—or through the fact that it makes possible effective, uncomplicated, and inexpensive home dialysis for a majority of patients who otherwise would not have been mechanically adept enough to conduct their own dialysis in the home without outside help. Dr. Whedon has already mentioned the new hollow fiber dialyzing unit which is not only a vast technical improvement over many previously available dialyzers but, because this "disposible" unit can actually be reused quite a few times before it is discarded, dialysis using it costs considerably less than dialysis with a disposable dialyzer unit which cannot be reused or the reuse of which is too complicated for most patients.

Development of the novel "envelope dialyzer" which is presterilized, ready-to-use, and easy to insert into the conventional Kiil artificial kidney greatly simplifies home dialysis with this apparatus to the point where many patients otherwise not suitable for home dialysis can conduct their own inexpensive Kiil dialysis in the home.

Peritoneal dialysis, the washing out of metabolic waste products from the abdominal cavity with numerous changes of very expensive sterile solutions for intravenous use, can now be done both in the hospital and in the home with the aid of a newly developed automated, closed-loop apparatus which prepares its own solutions extremely inexpensively. Incidentally, this type of dialysis is the only lifesaving maintenance treatment left for patients in whom the available locations for implanted blood vessel shunts for regular hemodialysis have been used up. In addition, this procedure can be safely carried out in the home after a relatively brief (and thus inexpensive) training period and even by patients who live alone.

Dr. Whedon has already mentioned a novel improvement of the conventional Kiil artificial kidney which now permits us to reduce the time span of Kiil dialysis in the hospital by one-third so it can be carried out within one single nursing shift, rather than two. The consequent cost savings are quite significant and result in major savings for this currently expensive method of treatment.

There are significant cost savings connected with the new experimental artificial kidneys which use novel sorbents and only about 2 liters of dialysate to dialyze patients. The elimination of relatively huge volumes of dialysate previously used (from 150 to 300 liters) promise to introduce significant cost savings as follows: (1) we avoid the expense of the large quality of chemicals which must be dissolved in large volumes of dialysate, (2) we do not have to treat the large volumes of tap water used in the conventional dialysis process with expensive deionizing columns or other methods of water purification like reverse osmosis, and (3) for the first time we can build portable artificial kidneys of the size of a television set. These, in turn, can be used for home dialysis even by the economically disadvantaged who live in substandard housing because they require no structural changes in the apartment, expensive plumbing alterations, or extra rooms set aside for the dialysis equipment.

Lastly, two of our research contractors working independently have demonstrated the possibility of maintaining selected patients with a combination of a special low protein diet and infrequently administered hemodialysis. Since ordinarily dialysis treatment is given three times weekly, increasing the interval between treatments which this new combination regimen makes possible, can indeed cut the overall yearly cost to a very significant degree.

Mrs. Reid. I hope this is an area where there could be something provided that would be less expensive, that we could look forward to this.

Dr. Whedon. I think it would be a fair statement that we are cutting the costs in half, but we still have a ways to go to reach an acceptable level of costs for the majority of the large number of patients with which we have to deal.

IMPROVING KIDNEY TRANSPLANT PROCEDURES

Mrs. REID. What is the present rejection factor in kidney transplants?

Dr. WHEDON. At the present time the 2-year survival of transplanted kidneys in close relatives is about 70 to 75 percent. To turn it around, the rejection rate is 25 to 30 percent. If the transplant is from an unrelated live donor or from a cadaver, the rejection rate is around 60 percent or a survival rate of 40 percent.

Survival rates will improve with improvement in organ preservation so that a kidney can be taken from a dead person promptly and well preserved for the time it takes to do proper matching of the tissues to reduce the likelihood of immunologic rejection, and with further developments along the lines I have mentioned in my statement, that is, that this past year there has been improvement in the system of tissue matching. Up until this year the matching has been done by setting up the patient's white blood cells against the cells from the donor. It has been a white cell to white cell matching. Now our grantees have found that by not only doing that, but by adding the matching between the patient's white cells and the cells of the donor kidney itself, this improves the quality of the matching a great deal. One can avoid transplanting a kidney which formerly would have been thought to be a proper match but now with the new system can be shown not to be as good.

So, I think we are going to do much better now and in the future with our matching so that when the transplant, it will be successful over a longer period of time.

Mrs. REID. That is encouraging.

Thank you, Doctor.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Amounts Available for Obligation

	1971	1972
Appropriation	$138,339,000	$135,433,000
Real transfers to:		
"Departmental Management"	-30,000	---
"Research Resources" (proposed transfer for increased pay costs)	-75,000	---
"John E. Fogarty International Center for Advanced Study in the Health Sciences" (proposed transfer for increased pay costs)	-54,000	---
"Division of Biologics Standards" (proposed transfer for increased pay costs)	-150,000	---
"St. Elizabeths Hospital" (proposed transfer for increased pay costs)	-74,000	---
Comparative transfers to:		
"Office of the Director"	-744,000	---
"National Eye Institute"	-69,000	---
"National Heart and Lung Institute"	-78,000	---
"Health Manpower"	-3,597,000	---
"Office of the Director"	-66,000	---
Comparative transfer from:		
"National Institute of Allergy and Infectious Diseases"	+1,023,000	---
Total, obligations	134,425,000	135,433,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
156	Research		$89,803,000		$91,491,000		+$1,688,000
	General research support grants		(8,123,000)		(7,243,000)		(-880,000)
	Scientific evaluation and planning		(20,000)		(20,000)		(--)
	Categorical clinical research centers		(1,380,000)		(1,380,000)		(--)
171	Fellowships		5,740,000		5,094,000		-646,000
174	Training		11,475,000		11,475,000		(--)
	Direct Operations:						
176	Laboratory and clinical research	491	17,727,000	491	17,958,000	--	+231,000
181	Collaborative research and development	21	5,953,000	21	5,477,000	--	-476,000
186	Biometry, epidemiology and field studies	31	921,000	31	949,000	--	+28,000
189	Review and approval of grants	63	2,410,000	63	2,572,000	--	+162,000
190	Program direction	21	396,000	21	417,000	--	+21,000
	Total obligations	627	134,425,000	627	135,433,000	--	+1,008,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	627	627	--
Full-time equivalent of all other positions	38	38	--
Average number of all employees	618	645	+27
Personnel compensation:			
Permanent positions	$9,151,000	$9,859,000	+$708,000
Positions other than permanent	198,000	183,000	-15,000
Other personnel compensation	53,000	86,000	+33,000
Subtotal, personnel compensation	9,402,000	10,128,000	+726,000
Personnel benefits	907,000	962,000	+55,000
Travel and transportation of persons	230,000	240,000	+10,000
Transportation of things	68,000	68,000	--
Rent, communications and utilities	230,000	240,000	+10,000
Printing and reproduction	180,000	189,000	+9,000
Other services:			
Project contracts	5,339,000	4,839,000	-500,000
Payment to NIH management fund	7,019,000	7,217,000	+198,000
Other	2,007,000	1,556,000	-451,000
Supplies and materials	1,540,000	1,550,000	+10,000
Equipment	485,000	384,000	-101,000
Grants, subsidies and contributions	107,018,000	108,060,000	+1,042,000
Total obligations by object	134,425,000	135,433,000	+1,008,000

Summary of Changes

1971 estimated obligations	$134,425,000
1972 estimated obligations	135,433,000
Net change	+1,008,000

	Base Pos.	Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase	—	---	--	+$394,000
2. Within-grade pay increases	--	---	--	+184,000
3. One extra day of pay in 1972	--	---	--	+37,000
4. F.T.S. rate increase	--	---	--	+10,000
5. Noncompeting research grants	--	$55,442,000	--	+3,773,000
B. Payment to "National Institutes of Health Management Fund" for centrally furnished services	--	6,840,000	--	+198,000
Total, increases	--	---	--	+4,596,000
Decreases:				
A. Program:				
1. Research grants	—	89,803,000	—	-2,085,000
2. Fellowships	--	5,740,000	—	-646,000
3. Laboratory and clinical research	491	11,955,000	—	-357,000
4. Collaborative research and development	21	5,889,000	—	-500,000
Total, decreases	—	---	--	-3,588,000
Total, net change				+1,008,000

Explanation of Changes

Built-in Increases--These increases will provide: $394,000 for annualization of the 1971 pay increase; $184,000 for within-grade pay increases in 1972; $37,000 for one extra day of pay in 1972; and $10,000 for increased costs in 1972 of using the Federal Telecommunications System.

Research grants--An increase of $3,773,000 for noncompeting grants and a decrease of $1,205,000 for new and competing renewal grants results in a net increase of $2,568,000 which will support 205 fewer grants than the 2,028 supported in 1971. A total of 1,823 grants will be supported in 1972. The request also includes a decrease of $880,000 for general research support grants, a program included in each NIH appropriation containing research grant projects, but administered separately by the Division of Research Resources.

Fellowships--The decrease of $646,000 will fund 63 fewer awards over the 1971 level of 343 for a total of 280.

Laboratory and clinical research--The decrease of $357,000 includes a reduction of $336,000 for non-recurring building renovations in 1971.

Collaborative research and development--The decrease of $500,000 in the Artificial Kidney Program will reduce the number of active contracts from approximately 65 in 1971 to 57 in 1972, a decrease of 8 contracts.

Significant Items in House and Senate

Appropriation Committee Reports

Item	
1971 House Report	
Clinical Research Studies at the Phoenix, Arizona, Indian Medical Center	
1. "The Committee...directs that at least the minimum staff requirements be made available for this important new clinical research approach."	1. Twenty four additional positions were made available to the Institute in 1971 for initial staffing requirements. Clinical studies on gallbladder disease were undertaken with the first staff additions. Studies on diabetes will be phased in when additional staff is employed.
1971 Senate Report	
Clinical Research Studies at the Phoenix, Arizona, Indian Medical Center	
1. "The Committee commends the National Institutes of Health and the Indian Health Service for their joint effort to undertake important clinical research among the Indian population of this country. The committee intends that some of the funds for the Institute be used for the first-year requirements and personnel for this unit."	1. Same as above.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation Requested
Public Health Service Act Section 301—Research and Investigation, in general	Indefinite	$135,433,000
Title IV, Part D—National Institute on Arthritis, Rheumatism and Metabolic Diseases	Indefinite	$135,433,000

PUBLIC HEALTH SERVICE ACT

The legislative authority which provides for the award of grants for research, research training, and fellowships is included in Section 301 of the Public Health Service Act.

The Public Health Service Act, Title IV, National Research Institutes, Part D, National Institute on Arthritis, Rheumatism, and Metabolic Diseases, National Institute on Neurological Diseases and Blindness, and other Institutes.—

"Sec. 431 (a) The Surgeon General shall establish in the Public Health Service an institute for research on arthritis, rheumatism, and metabolic diseases...."

"Sec. 433 (a) Where an institute has been established under this part, the Surgeon General shall carry out the purposes of section 301 with respect to the conduct and support of research relating to the disease or diseases to which the activities of the institute are directed, through such institute and in cooperation with the national advisory council established or expanded by reason of the establishment of such institute. In addition, the Surgeon General is authorized to provide training and instruction and establish and maintain traineeships and fellowships, in such institute and elsewhere, in matters relating to the diagnosis, prevention, and treatment of such disease or diseases with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he may deem necessary, and in addition, provide for such training, instruction, and traineeships and for such fellowships through grants to public and other nonprofit institutions."

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer to:		
Departmental Management	-$30,000	To establish the Facilities Engineering and Construction Agency.
Research Resources	-75,000	Proposed transfer for increased pay raise costs.
John E. Fogarty International Center for Advanced Study in the Health Sciences	-54,000	" " "
Division of Biologics Standards	-150,000	" " "
Comparative transfer to:		
Office of the Director	-744,000	To provide an equitable distribution of the Management Fund in 1972.
National Eye Institute	-69,000	" " "
National Heart and Lung Institute	-78,000	Transfer of regular research grants related to pulmonary diseases.
Health Manpower	-3,597,000	Transfer of institutional support funds to Health Manpower.
Office of the Director	-66,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director for establishing the Office of Contracts and Grants.
Comparative transfer from:		
National Institute of Allergy and Infectious Diseases	+1,023,000	Transfer of regular research grants for the malnutrition portion of the U.S.-Japan Program.

National Institute of Arthritis and Metabolic Diseases

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$ 68,740,000	$ 73,661,000	$ 90,000,000	$ 81,831,000
1963	91,921,000	98,721,000	105,721,000	103,388,000
1964	114,717,000	113,679,000	114,717,000	113,679,000
1965	113,369,000	113,344,000	113,544,000	113,344,000
1966	119,203,000	121,203,000	123,203,000	123,203,000
1967	129,908,000	133,687,000	135,687,000	135,687,000
1968	143,954,000	143,954,000	147,204,000	153,954,000
1969	151,718,000	141,287,000	147,287,000	143,888,000
1970	137,668,000	137,668,000	155,000,000	146,619,000
1971	132,152,000	138,339,000	140,339,000	138,339,000
1972	135,433,000			

Justification

National Institute of Arthritis and Metabolic Diseases

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	627	$10,309,000	627	$11,090,000	—	+$781,000
Other expenses.....	—	124,116,000	—	124,343,000	—	+227,000
Total.....	627	134,425,000	627	135,433,000	—	+1,008,000

General Statement

Established in 1950 under the provisions of Public Law 692, the National Institute of Arthritis and Metabolic Diseases received its first direct appropriation in 1952. For many years prior to 1950, laboratories which now constitute a part of this Institute were concerned with basic studies in chemistry, pathology, pharmacology, physiology, and nutrition. In 1947, they were grouped together into a division known as the Experimental Biology and Medicine Institute. These laboratories throughout their existence have had an outstanding record of accomplishment in fundamental research.

Over the years, the responsibilities of the National Institute of Arthritis and Metabolic Diseases have grown to encompass an unusually diverse area, including the broad spectrum of arthritic, rheumatic, and collagen (connective tissue) diseases; various metabolic disorders, such as diabetes; gastrointestinal diseases, such as peptic ulcer; endocrine malfunctions; dermatological conditions, such as psoriasis; diseases of blood, bone, liver, and kidney; and research in urology, nutrition, and orthopedic surgery.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Research projects	$80,280,000	$82,848,000	+$2,568,000
Special programs	9,523,000	8,643,000	-880,000
Total research grants	89,803,000	91,491,000	+1,688,000

Introduction

The National Institute of Arthritis and Metabolic Diseases seeks to control disease and promote health through research. Essential to this objective is a broad-scale fundamental scientific approach to the mysteries of health and illness and a marshaling and developing of results for research attacks on specific disease problems. To accomplish this objective, the Institute acquires new biomedical information in the main through scientists supported by about 2,000 research grants at some 400 institutions across the country.

Arthritis and Related Diseases

The arthritic and rheumatic disorders are the nation's most prevalent, painful, crippling diseases, afflicting some 16,800,000 people, according to the U. S. Public Health Service's National Center for Health Statistics. The term "arthritis" refers to inflammation and destruction of joints. Rheumatism, a more general term, usually refers to pain or impairment of function related to tissues outside the joints, such as muscles, tendons, bones, and nerves. About 100 disorders are listed under the combined heading of arthritis and rheumatism.

Rheumatoid arthritis, afflicting about 4 million people in the United States, is the most serious form of arthritis frequently seen by physicians. It is a painful, crippling, sometimes completely disabling disease that costs the nation dearly in diminished income and increased medical expenses. Only 25 years ago little could be done to alleviate the pain or slow the progression toward permanent joint deformity. Today, however, scores of anti-inflammatory or pain relieving drugs are available or under development and various methods of therapy and rehabilitation have improved the prognosis for the afflicted patient. The real hope, nevertheless, lies in understanding the fundamental cause or causes underlying this disease and in preventing the inflammation and degeneration of joints and surrounding tissues characteristic of rheumatoid arthritis.

While the primary cause of rheumatoid arthritis is still unknown, present research is endeavoring to discover whether an infectious process, an autoimmune reaction, or possibly a combination of both processes are the mechanisms by which the disease develops. Institute grantees are continuing to gather data on the possible role of microbial organisms and viruses which have recently been recognized as potential pathogens in rheumatoid arthritis in man. To date, however, firm proof that

infectious agents may cause this disorder remains elusive. Researchers are also examining the possibility that rheumatoid arthritis is initiated by an autoimmune reaction, in which the body reacts abnormally and destructively to materials (perhaps released by infection) originating within the body's own tissues.

Work by grant-supported investigators is providing physicians with a constantly growing armamentarium for the management of rheumatoid and other forms of arthritis. For example, a grantee has shown in prolonged clinical trials that penicillamine may be of value in the treatment of rheumatoid arthritis patients with sustained disease activity. Prolonged penicillamine administration not only reduced rheumatoid factor titers, but other classes of abnormally elevated blood levels of immunoglobulins as well, suggesting that the drug may act by suppressing the immune response. Further study is needed to delineate the precise mode of action of this agent.

Other grantees have shown in controlled clinical trials that the potent anti-cancer drug, cyclophosphamide, may be of significant value in the treatment of patients with severe rheumatoid arthritis who are refractory to standard forms of therapy. Use of the drug in large doses, however, was accompanied by a high rate of undesirable side effects, and additional studies will be undertaken to re-evaluate this potent drug in moderated dosages.

Like rheumatoid arthritis, systemic lupus erythematosus (SLE) is one of a group of connective tissue disorders. Connective tissue, comprised mainly of collagen fibers and a glue-like basic matrix called "ground substance," makes up a major part of the body tissues and is essential for its structure and function. SLE is manifested by various disorders in the structure and activity of the skin, joints, blood vessels, and internal organs. It is an insidious, inflammatory disease of considerable gravity. The disorder most often affects people in the 20–40 year age group, particularly young women.

Although the cause of SLE is not known, much evidence points, as in the case of rheumatoid arthritis, to a disorder of the body's immune mechanism which may or may not be tied to a previous infectious process. A grantee of the Institute has detected virus-like particles in the affected kidney tissue of 29 of 30 patients with systemic lupus erythematosus. These morphologic findings do not establish a viral etiology for this connective tissue disorder, but presence of the virus-like particle is of diagnostic importance and tends to differentiate lupus nephritis from other kidney lesions. The findings provide a basis for further studies directed toward positive identification of such particles, their possible etiologic significance, and/or their diagnostic import.

Lupus nephritis is a term used to describe the renal involvement that may complicate systemic lupus erythematosus. Recent studies have revealed that there is a great variation in the clinical and pathologic manifestations of lupus nephritis; it may appear benign, gradually progressive, or rapidly progressive and fatal.

Orthopedics

Orthopedics is that area of medicine and surgery concerned with the musculoskeletal system. Research in orthopedics supported by the Institute is primarily concerned with disorders of the skeletal system in adults.

Research is also directed toward studies of the overlying soft tissues in diseases such as scoliosis (curvature of the spine). Scientists are currently searching for an animal model of this disease that is comparable to the human form. Development of a model should enhance research in this area since biochemical, histological, histochemical and ultrastructural studies could be easily done on muscles, ligaments, cartilage, and bone, tissues presently not readily available.

Osteoporosis, a diffuse reduction in bone density, is a condition resulting from a combination of disuse or immobilization, calcium deficiency, hormonal imbalances, or senility. It is often found in elderly postmenopausal females, often results in vertebral abnormalities and/or frequent fractures of the hip and long bones. Grantees are studying this disease through long-term data collections of individuals on controlled diets and patients with disuse or immobilization of limbs. Since osteoporosis is usually a disease of slow onset and long duration, and bone density decreases slowly, studies of this condition must continue over many years if the cause and possible methods of preventing, controlling, or slowing the process are to be accomplished.

Research is continuing on development of prosthetic devices for total hip replacement. Present materials, while effective for varying periods of time, are not permanent. As a result, replacement of the device may be necessary after several years. Grantees are utilizing a new method for attachment of these devices to bone. Initial results appear promising, but long-range continuing studies will be necessary to evaluate this procedure properly, both as to duration of function of the device and the human response to these new non-biological materials.

Recently, interest has increased in the development of new materials for use as implants. Engineers, metallurgists, and orthopedists are working together to develop and test new materials that more nearly mimic the properties of bone than do the present materials. Again, long-range studies will be necessary to properly evaluate tissue response of these materials. Ceramics, with controlled pore sizes, have been developed and are undergoing testing for tissue compatability. One difficulty encountered with ceramics is their brittleness. Efforts to overcome this undesirable characteristic have been partially successful. Methods of binding ceramics to metals are being studied. If successful, those materials may provide the strength necessary for weight bearing as well as porosity which would permit tissue ingrowth through the ceramics' outer layers.

Diabetes

According to the best estimates there are, at present, approximately four million diabetic people in this country. Moreover, another five million of our present population are expected to develop the disease during their lifetime. Factors contributing to the growing prevalence of the disease include the soaring population, increased longevity for diabetics due to improved maintenance care and the rise in obesity which seems to stimulate emergence of frank diabetes in genetically predisposed individuals. Since more diabetics will be living longer and may possibly have more children, an increasing number of their offspring will have it and pass it on.

A complicated disease, for which there is no known cure, diabetes ranks seventh on the list of diseases causing death in the United States. Diabetes has been known for some time to be in part a hereditary disorder. As a result of the body's inability to metabolize carbohydrates normally, the diabetic is unable to convert carbohydrates properly into the stored

62-645 O - 71 - pt. 3 - 41

form, glycogen, or to properly utilize them for the energy required for normal body functions. The carbohydrates, in the form of glucose, accumulate in the blood and overflow into the urine. As the disease progresses, abnormal carbohydrate metabolism becomes associated with a noticeable derangement in the metabolism of fats and proteins and with changes in the cardiovascular system.

The oral anti-diabetic drugs continue to be a prime area of interest for the Institute. A ten-year study of the effects of anti-diabetic drugs conducted by 12 leading medical centers (University Group Diabetes Program or "UGDP") with research grant support from the Institute, has been reported recently and has raised questions concerning the use of the oral hypoglycemic agent tolbutamide (brand name Orinase) in the control of diabetes and its sequelae. The conclusions of the investigation, based on the results obtained in this long-term well-controlled study, were that: "The findings of this study indicate that the combination of diet and tolbutamide therapy is no more effective than diet alone in prolonging life. Moreover, the findings suggest that tolbutamide and diet may be less effective than diet alone or than diet and insulin at least insofar as cardiovascular mortality is concerned." This ten-year study has also resulted in an announced consensus of diabetes study groups representing the American Medical Association, the American Diabetes Association, and the Food and Drug Administration, that this oral hypoglycemic agent should be used only in diabetics with adult onset diabetes in whom the disorder cannot be controlled by diet alone or by diet plus insulin. This shows the importance of clinical research which pursues the definition of the practical utility and ultimate value to patients of new treatments as more basic biomedical information is generated. Study of another oral anti-diabetic drug, phenformin (DBI), now in its eighth year, is being continued by the University Group with support from the Institute.

Insulin

Many diabetes investigators today believe that determination of the precise mode of action of insulin, how it is produced and released by the pancreas and how it does its vital work in human tissues, is essential to clarifying the cause or causes of diabetes, and to preventing or controlling the complications of the disease.

Both protein ingestion and amino acid infusion are known to stimulate insulin secretion in man. This response has been attributed to an increased plasma amino acid concentration, but it has not been known whether amino acids exert a direct effect upon the insulin-producing cells of the pancreas, or whether the effect is mediated through some indirect mechanism. A grantee of the Institute has shown this past year that amino acids, like glucose, exert a direct secretion-stimulating effect on the insulin-producing cells of the pancreas, suggesting that pancreatic blood-amino acid concentrations play an important role in control of insulin secretion.

In other grant-supported research, a scientist has reported on his studies of pancreatic alpha-cell function in normal and diabetic subjects. His research indicates that diabetes is characterized not only by impaired insulin secretion and action, but also by a continuous state of relative or absolute excess of the blood sugar level-enhancing hormone glucagon which is produced in the alpha-cells of the pancreas (in contrast to pancreatic beta-cells which produce and secrete the blood sugar decreasing hormone insulin). Because several actions of glucagon are antagonistic to those of insulin, it is suggested that excess glucagon may exaggerate the metabolic consequences of insulin insufficiency and may unfavorably influence diabetic control. Further study will be required to determine the mechanism of the alpha-cell dysfunction in diabetes.

Prevention or effective control of diabetes requires additional work in many areas not yet adequately investigated. Some of these are: genetic studies in experimental animals to identify a genetic marker for predicting the disease; better measurements of vascular complications and study of the biological events leading to these lethal changes, more work on the factors affecting pancreatic islet cell differentiation; and more work on the actions of insulin and glucagon at the molecular level.

Other Inherited Diseases of Metabolism

Recognition of the other hereditary metabolic diseases, as well as understanding of the mechanisms by which they produce discomfort and dysfunction, has increased immensely over the past half century. Further emphasis needs to be placed on early recognition of these "inborn errors of metabolism" inasmuch as improved medical management can delay the onset of complications and can even permit a longer survival in some instances. Institute and Institute-supported scientists have been particularly productive this past year in their studies of this group of diseases, one of which is cystic fibrosis (CF).

Cystic fibrosis is an inherited generalized metabolic disorder characterized by an abnormality in the products of certain types of glands which secrete fluid to external body surfaces, the lungs and the gastrointestinal tract. The abnormalities which are found in these secretions seem to be responsible for the symptoms and signs that plague the patient.

The principal clinical problems relate to the basic metabolic disorder of external gland secretion. The first of these results from the production of sweat with a high salt content. Due to this defect many patients are unable to conserve salt, especially in hot weather, and are in constant danger of developing profound dehydration, which may lead to death.

A second, and considerably more serious facet of the disease stems from the abnormal functioning of the mucus-secreting glands of the body. In cystic fibrosis, these glands fail to secrete normal, free-flowing fluid. Instead, they tend to produce an abnormally thick, sticky mucus which obstructs the ducts or openings of the glands of the pancreas, a defect which results in impaired digestion.

The third and most important complication involves the lung. Nearly all cystic fibrosis patients develop chronic lung disease at some time during their illness. Thick mucus obstructs the finer air passages in the lung, causing labored breathing and chronic cough. In time bacteria multiply in the accumulated secretions, and the child develops chronic bronchitis or pneumonia. The latter infection is the leading cause of death in these patients.

Among the studies which warrant continued support is one by a grantee who has examined an abnormal factor in the serum of cystic fibrosis patients. Several studies have indicated that the presence of this abnormal factor causes interruption of normal ciliary action in the bronchial mucosa of several experimental animals. The same investigators have now isolated the ciliary inhibiting factor from the sera of cystic fibrosis patients and heterozygotes and identified some of its chemical characteristics.

Another grantee has shown that the skin of patients with cystic fibrosis is deficient in beta glucuronidase, an enzyme linked to salt secretion and mucopolysaccharide metabolism, both of which are abnormal in cystic fibrosis. Further study will be required to learn if such

decreased activity represents decreased synthesis of this enzyme, abnormal enzyme structure, or inhibition of the enzyme by some other substance.

Although diabetes and cystic fibrosis are the most widely known of the inherited metabolic diseases, there are many other such disorders for which the Institute serves as the focus of research support. Among these are phenylketonuria, Wilson's disease, galactosemia, alcaptonuria, histodinemia, homocystinuria, familial Mediterranean fever, the various glycogen storage diseases, congenital nonhemolytic jaundice, and many others. Many of these and other metabolic diseases are known to result from an enzyme deficiency. Of the therapeutic approaches to diseases due to hereditary enzyme deficiency, induction or transfer of enzyme activity is in many ways the most attractive.

Metabolic and Endocrine Disorders (unrelated to genetics)

Endocrinology

Endocrinology concerns itself with the study of the endocrine glands and their secretions, the hormones, and with the effect of these secretions on the metabolism and physiology of man. Thus, research in the field of endocrinology is considered one of the most important areas of Institute concern.

For many years endocrinologists were concerned with the clinical conditions resulting from under or over-production of the endocrine glands. In recent years, however, the importance of the hormones as a control factor in the metabolism, growth and reproduction of the whole body and particularly of the individual cells has become more and more evident.

Studies by an intramural scientist and an Institute grantee resulted in the successful synthesis of the active portion of the parathyroid hormone and its influence on the control of calcium metabolism. Two groups of scientists working independently on this puzzling problem reported, almost simultaneously, the complete 84 amino acid sequence that makes up the hormone. One group includes the above-mentioned Institute grantee and an intramural investigator, and the other an intramural scientist of the National Heart and Lung Institute and his associates. The synthesis of an active fragment of this hormone comes after more than 45 years of investigation in many laboratories and has important implications both for better understanding of the biochemical operation of other hormones and of the diagnosis and treatment of a number of human disorders, including hyperparathyroidism, kidney stones, and metabolic bone disease.

An outstanding feat of biomedical research in this area by two groups of scientists working independently of each other came this past year when reproducible, biologically active hypothalamic hormone, thyrotropin- releasing hormone (TRH) was synthesized. Synthesis of this first biologically active hypothalamic hormone opens the way to regulation of several important bio-endocrine functions, possibly including ovulation.

Another very important recent advance made by an Institute grantee is the synthesis of pituitary growth hormone by Dr. C.H. Li and his associates. Dr. Li has been working for several years on the purification of anterior pituitary hormones and on the determination of their physical properties and chemical structure. The successful treatment of many endocrine diseases will ultimately depend on this type of research and the Institute has been instrumental in helping sponsor centers capable of producing such efforts.

Gastroenterology

Gastroenterology is a field of enormous scope, in terms of the number of people affected by disease. Encompassing all the diseases of the digestive tract, which may range from peptic ulcer or liver disease to ulcerative colitis, it is an area of medicine perhaps second only to heart disease in the frequency of physician house and office visits required. Any classification of disorders of the gastrointestinal system includes, in addition to the gastrointestinal tract itself, related organs such as the liver, gallbladder, and pancreas.

Several years ago, Institute grantees in England synthesized gastrin, a hormone which stimulates secretion of gastric juice and more recently another grantee showed that anti-gastrin antibodies produced in rabbits inhibited endogenous gastrin-mediated gastric acid secretion in rats. Since increased blood gastrin levels are correlated with gastro-duodenal ulceration associated with hypersecretion of gastric juice, this suggested the possibility of modifying through such novel approaches excessive gastric acid secretion in disease states such as peptic ulcer. Another grantee has shown that secretin prevented increased blood gastrin in animals and that subjects with duodenal ulcers secrete less of this hormone than do normal subjects, in response to acid. This offers another possible approach to attacking the ulcer problem through an understanding of the basic physiological mechanisms involved and deserves further support.

The two major liver diseases, cirrhosis (on the increase in our adult population) and hepatitis (increasing at an alarming rate among our young population) are both crippling and fatal diseases of great social and economic importance. A most rapidly moving field has been the finding of an association between the presence of a viral-like particle (Australia antigen) and a type of hepatitis transmitted primarily through blood transfusions or by contaminated needles. There is some evidence that fatal liver necrosis or cirrhosis occurs only in those cases of acute viral hepatitis in which the antigen is present. If further work establishes this, much apprehension, and costly medical care could be eliminated in the less hazardous cases. Further work may permit the development of a vaccine effective against hepatitis or a therapeutically effective antibody for Australia antigen.

Gastrointestinal bleeding, which particularly affects older people appears to be increasing in our population as the incidence of ulcers and intake of alcohol and aspirin increases. Diagnosis of the site of the bleeding is still difficult and, in a fair percentage of cases, uncertain. Barium meals, endoscopy and intubations each have their advocates and each is able to differentiate the majority of cases. However, if a more certain and less traumatic procedure could be developed it would be a major advance. One of the Institute grantees is working on a new approach to diagnosis which would be rapid and relatively innocuous for the patient. Methane or radio-active xenon gas, instilled into the colon, is absorbed first and in highest concentrations by the blood supply to that region (portal) and, therefore, if the bleeding is from esophageal varices, the concentration of the gas in samples of blood recovered from the stomach will be high; if from gastric bleeding sites, low.

Heartburn, caused by reflux of acid stomach contents into the esophagus, is probably the most frequent complaint of gastrointestinal origin. More severe forms of this phenomenon occur in esophagitis and hiatal hernia. Despite many published observations, how and why reflux occurs in these individuals and not in others, is largely unknown. Work performed by an Institute grantee is well along toward answering this question and, therefore,

to offering some rational and effective, rather than merely empirical treatment of the condition. Studies by these investigators suggest that the important hormone, gastrin, released by the stomach, is at least one factor which controls the baseline pressure of an important physiological structure, the lower esophageal sphincter, which normally prevents stomach acid from entering the esophagus. Patients who have frequent gastro-esophageal reflux have lower baseline pressure in this structure than the normal group, perhaps because the sphincter is insufficiently responsive to gastrin or perhaps because insufficient gastrin is released. If this conjecture proves to be correct, new avenues of rational therapy seem probable.

A new concept of how cholesterol gallstones (the most prevalent type) are formed has emerged from recent studies and will be confirmed in experimental work with the Pima Indians of Arizona. The formation of cholesterol gallstones may be due to the secretion by the liver cells of an abnormal bile in which the cholesterol exists in a highly supersaturated state which later precipitates out in the gallbladder. This important finding, which points to the liver as the origin of the disease rather than to the gallbladder itself, channels research effort into a wholly new direction. Bile salts and lecithin are the primary solubilizing agents for cholesterol in bile. By feeding bile acids, the composition of the bile may be changed toward normal. The extensive understanding of cholesterol and lecithin metabolism gained through much research aimed at the problem of atherosclerosis can be directed to find other ways to modify the abnormal bile.

Kidney and Urologic Disease

Among the leading causes of kidney disease are: hypersensitivity disorders involving an overreaction of the immune system and its misdirection against the body's own kidney tissues; infections; circulatory disorders, such as high blood pressure; developmental anomalies; obstructive conditions in which blockage of urine flow results in back-pressure damage to the kidneys, usually with accompanying infection; and other contributing conditions.

A common characteristic of almost all kidney diseases is their tendency to progress eventually to a common end-stage of irreversible kidney failure characterized by uremia. Uremia is the composite of signs and symptoms resulting from the loss of the kidney's functions of removing metabolic wastes from the body and of regulating the internal chemistry of the body. Two main types of kidney failure can be distinquished, acute (and possibly reversible) kidney failure and chronic progressive renal insufficiency. In acute kidney failure, the kidneys are damaged by an acute insult or attack, are shut down rapidly, and the symptoms of uremia develop soon. The damage may be reversible after a short period, and the kidneys may heal and regain normal function.

Chronic kidney failure, however, 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. Unlike the majority of chronic diseases, kidney diseases are particularly likely to cause death to patients in the middle, productive years. The social and economic impact of kidney diseases, therefore, is far out of proportion to what one would expect from simple analysis of the bare statistics.

The development of two dramatic therapeutic approaches to end-stage kidney diseases, chronic kidney hemodialysis and kidney transplantation, has thrust the renal disease problem into the public eye and led to a proliferation of activities directed toward reducing morbidity and mortality. This past year, scientists supported by the Institute have reported on many research findings which shed light on some of the causes and manifestations of chronic renal failure, and which merit continued support.

Kidney transplantation is still a developing treatment modality, but with continued research it should be noted that transplantation depends upon maintenance of the kidney failure patient with the aid of hemodialysis (use of artificial kidneys) until he is ready for an operation and until a suitable donor kidney is available. Dialysis is also used post-operatively as a temporary kidney-sparing measure, and, in case of transplant failure, as a life-saving maintenance method.

The surgical techniques for transplanting kidneys have in large part been developed and are constantly being refined. The body, however, ordinarily defends itself against a "foreign" transplanted organ by elaborating specific antibodies to that graft and by other cellular defense processes. In a series of complex events not at all well defined, the foreign transplanted organ is attacked and may ultimately become functionless. Treatment with special drugs which suppress the host's immune response to transplanted foreign organs of a different tissue "type" (analogous to the well-known, mutually-incompatible blood types) can abort such an attack temporarily. In the long run, however, only organs of identical tissue composition (obtained from an identical twin) or of closely matching antigenic composition bear the promise of prolonged, dependable function in the host.

Thus it has become increasingly apparent that improvement in kidney transplantation and organ transplantation as a whole will depend on additional knowledge of human tissue immunology. Sophisticated methods must be developed for close immunologic matching of donor and recipient tissues. In addition new methodology must be sought for effective long-term preservation of donor organs so that at all times a sufficient number of pre-"typed" (tissue typed) organs with different antigenic composition is available for transplantation into (matching) patients who need them.

Considerable progress continues in the area of kidney transplantation, which integrally include advances in organ preservation and immunosuppression. In the former field, for example, a grantee of the Institute has shown that tissue matching involving both leukocytes and kidney cells improves the survival rate of transplanted human cadaver kidneys. In 1968, an Institute grantee first devised a method of preserving isolated human cadaver kidneys for as long as 37 hours. Thus, time was gained for proper matching of cadaver kidneys which had become available and recipients by tissue typing and for adequate preparation for surgery. Utilization of this kidney preserving device (The "Beltzer Apparatus") now has permitted an important modification of standard phenotyping and cross-matching procedures to a point where optimally matched cadaver kidney transplants may do as well as those from "A" matched (on the Terasaki matching scale) siblings. Conventionally, only the leukocytes of the donor and potential recipients are tissue-typed and subsequently the best matching combination is selected. Under the new system, the recipient's leukocytes are typed and cross-matched to the cadaver donor's kidney cells as well as leukocytes. Apparently there is antigen on the kidney cells not detected on

leukocytes during conventional phenotyping. Thus, many apparent "good" matches based on leukocyte-leukocyte typing alone can now be revealed as merely "fair" on the basis of the more complete double matching system, and poor outcome of cadaver transplants due to rejection can be more easily predicted and avoided.

Nutrition

Nutrition has become a major national issue, and the practical application of the science of nutrition holds immediate interest and concern for all population groups. Despite the wide reduction of frank nutritonal deficiency diseases in this country, the margin of safety is not large. Improved methods of determining nutritional status and revised criteria for normal nutritional status have contributed to a new emphasis on the definition and diagnosis of malnutrition. Through application of new principles and laboratory techniques learned in recent years from studies of intermediary metabolism, many supported by this Institute, the evaluation of nutritional status in the absence of overt disease is no longer dependent on ill-defined lesions and symptoms or the subjective judgment of physicians. These advances in knowledge now form the basis for exacting nutrition surveys conducted to discover pockets of malnutrition in vulnerable population groups in the United States. They will also be necessary in many developing countries in order to deal more effectively with endemic malnutrition.

The Institute's research grants program in nutrition can be divided into two groupings: physiology of normal nutrition and nutritional disorders. Projects dealing with physiologic processes of normal nutrition involve body composition, digestion and absorption of nutrients in the gastrointestional tract; appetite regulation and food intake; the biochemistry and physiologic role of nutrients; and their fate in the body; quantitative requirements of proteins and amino acids, carbohydrates, fats and fatty acids, minerals, trace elements, vitamins, and fluids and electrolytes; interrelationships between different nutrients and between nutrients and hormones, and nutrients and enzymes; and the relationship of the intestinal flora to nutrition.

Research in abnormal nutrition involves discovery and definition of deficiency states, nutrient toxicity, obesity, malabsorption of specific nutrients, and the relationship of diet to specific disease entities, such as celiac disease and others. Another major subdivision of these research grants relates to nutrition in specific diseases or stress states, such as in diabetes, bone and joint disease, liver disease, gastrointestinal disease, infectious diseases, disorders of immunity, anemia, endocrine disorders, gallbladder disease, inborn errors of metabolism, skin disorders, kidney disease and urolithiasis, and stress (including surgery, trauma, wound healing and environmental extremes).

A number of outstanding research findings by grant-supported investigators will be followed up carefully during the next fiscal year. These include work on the biologically active form of vitamin D, 25-hydroxycholecalciferol. In earlier studies the grantee investigators had isolated the major biologically active form of vitamin D3, 25-hydroxycholecalciferol (25-HCC), had identified the liver as the site of vitamin D3 conversion to 25-HCC, and had shown that the metabolite is markedly more effective than the conventional form of the vitamin in preventing or treating rickets in animals. This past year, they have shown that patients with vitamin D-resistant rickets (who do not respond to conventional treatment with vitamin D3) respond symptomatically, chemically, and radiographically to high doses of 25-HCC with no evidence of toxicity. Their findings suggest that 25-HCC will prove to be a safe, effective treatment for vitamin D-resistant rickets.

Another grantee has demonstrated the feasibility and effectiveness of one-time parenteral administration of iodized oil, in lieu of ingestion of iodized salt, in the treatment and prevention of endemic goiter in isolated population groups. Endemic goiter continues to be a significant health problem in many areas of the world, including certain remote sections of Ecuador and Peru, where iodized salt is unknown and where attempts of introduction of such salt among the poor Indian population have been promising. Spurred by earlier successful field trials by other scientists in New Guinea, a pilot program using iodized poppy seed oil has been instituted in several rural communities in Ecuador and Peru. Results after approximately two years of study have indicated the feasibility and effectiveness of such a prophylactic program. There has been a sharp reduction in the incidence of goiter, and goiter-associated cretinism has not appeared among progeny of treated populations. Such a procedure is technically simple, free of serious risk, and is recommended for endemic goiter regions where salt-iodization programs have not yet been implemented. Several more years of observation, however, are needed to assess the full impact of the program in this and related health areas.

Metabolic studies conducted earlier by other investigators in Peru supported by the Institute suggested that malnourished infants and children at risk might thrive on a diet containing cottonseed flour (CSF) as the only source of protein. Prolonged feeding trials now have established that properly processed CSF, at adequate levels of intake, can serve as the main or sole source of protein for rapidly growing infants and children at least for short period of time. It is expected that these studies will be continued, as well as research on the recent finding that hair root analysis for protein content is a simple, sensitive, and clinically useful means of determining the degree of protein malnutrition. This new procedure is more objective than estimate of hair root diameter, which may vary for several reasons; in fact, low hair root protein values were often found in malnourished patients with deceptively normal ranges of serum protein levels.

Research supported in large part through the U.S.-Japan Cooperative Medical Science Program has added important new knowledge regarding severe protein calorie malnutrition (marasmus and Kwashiorkor), the carefully controlled metabolic procedures required to effectively treat malnourished infants and children; interrelationships between nutrition and infectious diseases; nutritional anemias; use of low-cost food supplements in developing countries; occurrence of toxic aflatoxins in foods; and methods for genetic improvement of protein quality and content of cereal grains.

The dietary treatment of gastrointestinal diseases and other clinical disorders has been based, in large part, upon empiricism and tradition. Recent emphasis on the unproved value, ineffectiveness and potential harm of many therapeutic diets reveals the deplorable gap between recent advances in scientifically based nutrition knowledge and diet therapy. Well planned research into the role of foods in gastrointestional disorders and the formation of meaningful, palatable, nutritionally adequate diets based upon sound nutritional knowledge will improve treatment of diseases of the digestive system, kidney, pancreas, and heart.

Obesity interferes with optimal health and longevity in over 20 per cent of adults in the U.S.A. It enhances emergence of frank diabetes in adults predisposed to the disease through inheritance. It aggravates cardiovascular disease and osteoarthritis and increases the liability to hypertension, atherosclerosis, hernia, and gallbladder

disease in persons of all socio-economic levels and ethnic origins. Studies of intake of calories in excess of energy requirements as a cause of obesity should be augmented by research on the metabolic aberrations of lipid metabolism, morphogenesis of adipose tissue cells, psychogenic and other factors regulating appetite, endocrine dysfunctions, hereditary influences, specific effects of individual nutrients and of overall dietary variations, effect of periodicity of eating, evaluation of body composition, and the effects of gastrointestinal short-circuiting as a treatment.

Hematology

One of the most important stimuli in hematology research is the continuing need for defining the metabolic mechanism responsible for anemia, one of the most prevalent disorders of man. Hemoglobinopathies, mineral, hormone and enzyme deficiencies, hemolysis due to pathologic immune mechanisms, and drug sensitivity, the major etiologic entities involved in anemias, will all be under intensive investigation during the next fiscal year.

Hemoglobin variants of animals and man will continue to be elucidated and the exact structure and composition of their molecules will be defined. Drawing on this biochemical background, the structural-functional relationships of abnormal hemoglobins producing such human diseases as sickle cell anemia, thalassemia and other hereditary hemoglobinopathies will be studied.

A most promising treatment for sickle cell anemia will be further explored by Institute grantees during the coming year. The method, so far tried in a limited number of patients, consists of intravenous injections of high concentrations of urea in invert sugar. Preliminary findings indicate the injections block and reverse the sickling of cells, resulting in rapid abortion of acute sickling crises. The treatment is based on the pioneering work of an Institute scientist, whose study is covered in the Intramural Laboratory and Clinical Research portion of this document.

Two other noteworthy findings reported during the past fiscal year will be pursued further during this coming year. One involves the effects of aspirin on bleeding time in hemophilia. In previous research, grantee investigators had shown that the mean bleeding time of five minutes in normal subjects is prolonged to 9-1/2 minutes after ingestion of aspirin. This study now has been extended to patients with the clotting disorders hemophilia A and B, PTA deficiency ("Factor XI deficiency") and von Willebrand's disease, and it has been shown that moderate doses of aspirin may considerably lengthen the bleeding time of patients with severe hemophilia A and B. Further study will be required to learn why responses to aspirin vary from normal to excessive bleeding times in patients with severe hemophilia. The chief implication of the study is the potential therapeutic hazard which aspirin may hold for some patients with major blood clotting disorders.

Another grantee has provided new information concerning the production of antihemophilic factor by the spleen. Two years ago an Institute grantee had produced abundant quantities of anti-hemophilic factor (AHF) by perfusing pig spleens with human hemophilic blood. Subsequently, he reported preliminary success in "curing" true canine hemophilia A through transplantation, into these dogs, of spleens from normal dogs. Despite these successes, controversy still existed as to whether the spleen actually synthesizes, or merely stores,

AHF. The present grantee has now shown conclusively that the normal spleen is a source of de novo synthesis of AHF. These results indicate that transplantation of normal spleens into patients with hemophilia should be given further consideration as a possible method of re-establishment of AHF synthesis in the patient, and, consequently, as a cure effective for as long as the transplanted organ remains functional.

New information concerning the regulation of the production of white blood cells has been obtained and should add to the general concepts of the control of all cell production. A substance has been isolated by a grantee from incubated human blood cells that has been found to stimulate bone marrow cells grown in culture to produce different cell types. This substance could have therapeutic value in serving as an important regulatory mechanism in various disorders of blood cell growth.

Since the characterization of hemoglobin S led to its implication as the genetic cause of sickle cell disease, little real progress has been made in finding a cure for the disease. Supportive therapy has improved considerably as medical techniques have developed. Use of antibiotics, blood transfusions and the improved general level of care have played their part but as with many diseases of an inherited cause a direct attack on the aberrant genes has not been possible. A research project currently supported by the Institute through studies showing that fetal hemoglobin appears to protect the red cell from the sickling effects of hemoglobin S, could provide the necessary steps to genetic management of not only sickle cell disease but other genetic blood diseases as well.

Environmental problems affect the general level of health and present new and challenging diagnostic problems to medicine. The development of a new, sensitive screening test for lead poisoning has been developed by a grantee as an outgrowth of work on the metabolism of abnormal red cells. Utilizing measurements of the enzyme aminolevulinic acid dehydratase (ALA-D), a versatile test for lead that promises to be of value in measuring copper levels (apparently increased in women taking birth control pills) and mercury levels as well, has been developed.

Dermatology

Diseases of the skin are not limited to disorders that are merely unsightly or disfiguring. Many diseases of the integument are of a considerably more serious nature; they can be chronically disabling as in allergic hand eczema seen in the home and throughout industry; they may become life threatening and some like pemphigus vulgaris and malignant melanoma are generally fatal.

Dermatologic research is no longer of an empirical nature. In response to a developing medical specialty that is manifesting expanded and more sophisticated research activities, Institute-supported research in dermatology has been focused upon further elucidation of basic cutaneous metabolism and function. It is thus designed to gain better insight into the underlying causes of various skin diseases. As a result of support of studies of basic mechanisms of disease, investigators have been able to place additional emphasis upon clinical studies, and a number of new approaches are emerging for the management of such chronic disorders as psoriasis, eczematoid dermatitis, acne and pemphigus vulgaris.

Few diseases of the skin are more frustrating for both the patient and his physician than psoriasis, a disease estimated to affect more than four million Americans. Although the thickened, reddish patches of skin

covered with multiple layers of white scales are not painful, the lesions are extremely disfiguring and can have a profound psychologic effect upon the afflicted individual. Although the etiology of psoriasis is unknown all information points to a too rapid epidermal growth as being the final tissue event that accounts for the major clinical expression of this disease, i.e. the formation of scales. All evidence suggests that adequate control of epidermal cell replication can satisfactorily control the cutaneous lesion.

In addition to basic studies in psoriasis, this coming year grantee scientists will study further the use of the potent cytotoxic drug, methotrexate, which is effective in treating psoriasis, to learn more about the suspected liver toxicity side effect of this agent. The effectiveness of methotrexate in intractable psoriasis however has stimulated the interest of grantees to seek methods to diminish or avoid the hepato-toxicity and other side effects of this drug. In response to the rapid expansion of both scientific and public interest in psoriasis, the Institute will support a workshop on psoriasis research in the fall of 1971 to hasten the interchange of information and new research ideas. Along with studies of the proliferative diseases of the skin, electron microscopic research of keratinizing tissues will include studies of the formation and fate of differentiation products of the epidermis. This will be done by auto-radiographic studies of epidermis, and by means of a new technique developed by grantees for processing skin cultures for electron microscopic investigations.

Research Grants Program Analysis

Fields	1971 Estimate	1972 Estimate	Increase or Decrease
1. Arthritis	$ 8,319,000	$ 8,575,000	+$256,000
2. Dermatology	1,910,000	1,969,000	+59,000
3. Diabetes	5,613,000	5,786,000	+173,000
4. Endocrinology	12,179,000	12,554,000	+375,000
5. Gastroenterology	9,516,000	9,810,000	+294,000
6. Hematology	6,782,000	7,072,000	+290,000
7. Metabolism	20,154,000	20,776,000	+622,000
8. Nutrition	5,657,000	5,800,000	+143,000
9. Orthopedics	3,602,000	3,713,000	+111,000
10. Urology and kidney diseases	7,928,000	8,173,000	+245,000
11. Subtotal 1/	81,660,000	84,228,000	+2,568,000
12. General research support grants	8,123,000	7,243,000	-880,000
13. Scientific evaluation and planning	20,000	20,000	---
14. Total obligations	89,803,000	91,491,000	+1,688,000

1/ Includes $1,380,000 in 1971 and $1,380,000 in 1972 budgeted for Categorical Clinical Research Centers.

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting continuations	1,380	$55,442,000	1,311	$59,215,000	-69	+$3,773,000
2. Competing projects	410	16,572,000	340	16,799,000	-70	+227,000
3. New	238	7,478,000	172	6,284,000	-66	-1,194,000
4. Supplementals	(116)	788,000	(81)	550,000	(-35)	-238,000
5. Subtotal regular program	2,028	80,280,000	1,823	82,848,000	-205	+2,568,000
6. General research support grants.		8,123,000		7,243,000		-880,000
7. Scientific evaluations		20,000		20,000		---
8. Categorical clinical research centers		1,380,000		1,380,000		---
9. Total research grants	2,028	89,803,000	1,823	91,491,000	-205	+1,688,000

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Fellowships.....	$5,740,000	$5,094,000	-$646,000

Fellowships continue to represent a critical instrument in the overall goal of the Institute in aiding the development of biomedical research personnel needed to support the many categorical areas of its responsibility. The various components of the Fellowships program serve to meet varied needs by supporting research training at different stages of career development, as well as individuals with a variety of doctoral backgrounds, M.D., Ph.D., or D.V.M.

The NIH postdoctoral fellowships provides support to individuals in clinical or basic science departments in virtually any institution found appropriate on review. The preponderance of postdoctoral fellowships in the Institute are awarded to post-Ph.D. individuals, typically to support their second research endeavors. Their thesis work for the Ph.D. provided the opportunity for their first research endeavor under the sponsorship of faculty members. This postdoctoral fellowship provides an opportunity allowing him a greater measure of choice of research direction and provides a key step in allowing his development into the independent investigator whose capabilities are so critical to institutions participating in both research and training in the various categorical fields of interest of this Institute. It also provides a means to attract young scientific personnel into these categorical fields themselves. The postdoctoral fellowship thus contributes to a balanced effort by attracting basic scientists to the categorical responsibilities of the Institute.

Special Fellowships are an instrument adapted to the needs of more senior personnel, complementing the Institute's postdoctoral and training grant programs. It has more flexible stipend arrangements and serves for extension of work begun under postdoctoral fellowship or training grant support, and sabbatical leave or "retooling" experience for established faculty members.

The Research Career Development Award (RCDA) supports individuals who have already passed the step of being selected for faculty membership at an institution of higher learning. It provides faculty support for the infrequent but significant young investigator who should be given special opportunity to develop his research potential while serving as a faculty member. This is a joint endeavor between the Institute and the institution at which the RCDA recipient is appointed which assures the candidate of the requisite protected time, appropriate working relationships, and the necessary facilities. Provision of support via this instrument provides the opportunity for developing investigators to reach their full potential within an environment that includes patient care service and teaching. Selection of awardees emphasizes the quality of research, the developmental plan, the institutional setting, and assures an effective role in American medicine for the ablest of emerging investigators.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting.....	186	$3,799,000	178	$3,854,000	-8	+$55,000
b. Competing.....	12	135,000	12	138,000	--	+3,000
2. Supplementals.....	--	---	--	---	--	---
3. New.....	145	1,806,000	90	1,102,000	-55	-704,000
4. Total fellowships.....	343	5,740,000	280	5,094,000	-63	-646,000

Fellowships (by type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Postdoctoral.....	107	$888,000	82	$697,000	-25	-$191,000
2. Special.....	93	1,076,000	72	881,000	-21	-195,000
3. Research career:						
a. Career.....	26	779,000	26	826,000	--	+47,000
b. Developmental.....	117	2,997,000	100	2,690,000	-17	-307,000
4. Total fellowships.....	343	5,740,000	280	5,094,000	-63	-646,000

Fellowships Program Analysis

Fields	1971 Estimate	1972 Estimate	Increase or Decrease
1. Arthritis.....	$ 496,000	$ 440,000	-$56,000
2. Dermatology.....	155,000	138,000	-17,000
3. Diabetes.....	476,000	422,000	-54,000
4. Endocrinology.....	1,215,000	1,078,000	-137,000
5. Gastroenterology.....	591,000	525,000	-66,000
6. Hematology.....	766,000	680,000	-86,000
7. Metabolism.....	1,103,000	978,000	-125,000
8. Nutrition.....	324,000	287,000	-37,000
9. Orthopedics.....	60,000	54,000	-6,000
10. Urology.....	554,000	492,000	-62,000
11. Total obligations.....	5,740,000	5,094,000	-646,000

Training Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Training Grants.....	$11,475,000	$11,475,000	--

The Institute's Training Grants Program, together with Fellowships, is evidence of its concern for the chronic shortage of qualified personnel in the fields of clinical investigation and research training. Aimed toward career development in investigation and teaching, the program is centered in the clinical departments of medical schools throughout the country. The Institute bears responsibility for arthritis, dermatology, diabetes, endocrinology, gastroenterology, hematology, metabolism, nutrition, orthopedics, urology and renal diseases, and related areas.

The Institute's training grants serve both post-Ph.D. and post-M.D. training, but are peculiarly suited to the latter in providing for research training that builds on and reinforces the trainees' clinical skills. Most commonly this support is for the first sustained participation in investigation by the trainee. The traineeship is typically the time at which choice of a specific field of medicine or surgery is made. It allows a ready transition from the physician's involvement in clinical training to a research training effort and often reflects much exposure and discussion between the applicant and the faculty under whom the trainee's research will be accomplished. This opportunity enables the physician to become thoroughly enmeshed in research which will challenge fully his imagination and capabilities and will lead him toward a definitive career choice. The trainee may function initially in the role of minor participation as "a pair of hands" in a team effort, then progress through various stages until he reaches the full potential of his development as a researcher capable of formulating clinical questions in basic terms and developing strategies for their solution.

Such training programs and the activities of the trainees organizationally are within departments that serve a very wide and important range of teaching and patient care service functions. This combination of varied involvement in research training in a wide variety of professional roles in differing institutions results in a very diversified yield that is sensitive to the changing national needs for research, teaching, and patient care. Training grants thus provide the opportunity for recent medical graduates to develop their potential as teachers and investigators on a "learning-by-doing" basis; preceptors can recruit and develop according to the needs of their disciplines and institutions; and the Institute complements detailed arrangements for individual training programs to fit with broader overall plans responsive to the needs of the categorical fields for which it has responsibility.

In summary, the Institute training and fellowships programs took their starting impetus from concern for manpower needs of the Institute research programs. Their manpower yield today spans a wide range of personnel presenting research experience as part of their qualifications. At a time of rapid change, these programs can and are responding to national research and health care needs.

Distribution of Training Grants

		1971 Estimate		1972 Estimate		Increase or Decrease	
		No.	Amount	No.	Amount	No.	Amount
1.	Continuations:						
	a. Noncompeting.....	214	$9,130,000	195	$8,880,000	-19	-$250,000
	b. Competing.....	34	1,581,000	40	1,886,000	+6	+305,000
2.	Supplementals.....	(12)	233,000	(10)	210,000	(-2)	-23,000
3.	New.....	16	471,000	14	439,000	-2	-32,000
4.	Scientific evaluation.	(1)	60,000	(1)	60,000	--	---
5.	Total training grants.	264	11,475,000	249	11,475,000	-15	---

Training Grants (by type of program)

		1971 Estimate		1972 Estimate		Increase or Decrease	
		No.	Amount	No.	Amount	No.	Amount
1.	Graduate.....	264	$11,415,000	249	$11,415,000	-15	---
2.	Scientific evaluation.	(1)	60,000	(1)	60,000	--	---
3.	Total training grants.	264	11,475,000	249	11,475,000	-15	---

Laboratory and Clinical Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	491	$8,326,000	491	$8,804,000	--	+$478,000
Other expenses.....	--	9,401,000	--	9,154,000	--	-247,000
Total.....	491	17,727,000	491	17,958,000		+231,000

Introduction

The Institute bears responsibility for a broad array of chronic disabling diseases--a wider, more diversified range of illnesses than covered by any of the other Institutes of the National Institutes of Health. Research activities, in addition to studies of the various arthritic diseases, include the study of a broad spectrum of heredity-linked metabolic diseases such as diabetes and cystic fibrosis, gastroenterology, hematology, endocrine disorders and mineral metabolism. Underlying these clinical studies is extensive fundamental research in biochemistry, pathology, histochemistry, chemistry, physical, chemical and molecular biology, nutrition, pharmacology, and toxicology.

The major objectives of the Institute's intramural program are to develop more complete information about fundamental chemical and physiological mechanisms on a cellular level as well as in the organism as a whole, and to employ such knowledge to discover the mechanism by which diseases develop. Of equal importance are studies to discover improved methods of therapy and prevention of disease.

A clinical research unit attached to the new Phoenix Indian Medical Center of the Indian Health Service has been activated. This unit has space for 25 beds, a metabolic kitchen, 5 laboratories, and the necessary supporting facilities. The unit will conduct clinical studies on a wide variety of diseases in the American Indian and Eskimo populations served by the Indian Health Service. Special emphasis will be given initially to gallbladder disease and diabetes where the particular population under study provides promising opportunities because of the high prevalence of these disorders among the Indians.

Arthritis and Rheumatism

Arthritis and rheumatoid diseases, such as rheumatoid arthritis, osteoarthritis, and gout, afflict more than 16 million people in the United States and are estimated to affect adversely the economy by nearly $4 billion annually. Arthritis specialists have divided the arthritic and rheumatic diseases into a dozen major categories. Each disorder is a distinct clinical entity, but all have in common similar symptoms, principally pain, swelling, disability or deformity in the joints or surrounding tissue.

In rheumatoid arthritis, the most crippling and painful form of arthritis, Institute investigators are studying a possible infectious process in this disease. Mycoplasma from swine with arthritis will be further examined to

determine how this infectious agent may induce pathological changes in joint tissues. In the treatment of rheumatoid arthritis, this coming year intramural investigators will continue to scrutinize closely an anti-cancer agent, cyclophosphamide. Although preliminary results have been promising, scientists are anxious to learn more about the mechanism of action of the drug and how to deal with its potent side effects which may place limitations on its more widespread use.

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. Although the cause of SLE is not known, much evidence points, as in the case of rheumatoid arthritis, to a disorder of the body's immune mechanism which may or may not be tied to a previous infectious process. A strain of mice in whom an autoimmune disease (quite similar to lupus erythematosus in man) is genetically acquired will be employed by Institute investigators to study the mechanisms of tissue destruction characteristic of human SLE. The researchers have been able to induce massive production of destructive isoantibodies in the mice and to suppress this production capability with powerful drugs. More work will be required to determine whether this work is applicable to control of human diseases of an autoimmune nature.

Other studies in arthritic disorders during the forthcoming fiscal year will range from molecular phenomena to the natural history of human disease or animal models of human disease.

Diabetes and Other Metabolic Diseases

Diabetes has the dubious distinction of being the best known metabolic disease, of ranking seventh in the list of diseases causing death in the United States, and of affecting currently more than four million Americans, with an additional five million or more individuals now living who will develop the disease during their lifetime. The most obvious defect in diabetes is the body's inability to utilize carbohydrates normally for energy expenditure and storage. A primary goal in Institute diabetes research is understanding the basic impairment of insulin activity, a complete knowledge of which would uncover some of the riddles now surrounding diabetes. Studies during the forthcoming year will center on the physiology of insulin, and how this hormone exerts its influence on cell membranes.

Cystic fibrosis is a grave disease of children and young adults caused by an inborn error of metabolism. The basic chemical defect is not yet fully understood, but it is known to be genetically transmitted. Estimates of the incidence of cystic fibrosis in the population today range as high as 1 in 1,400 live births. As a cause of death in children under 15 years, cystic fibrosis outranks many of the better known diseases such as poliomyelitis, rheumatic fever, and diabetes, and now that it is being diagnosed with increasing frequency throughout the world, it is recognized as a serious public health problem.

Institute researchers will continue clinical studies of this disorder, with additional basic studies in such disciplines as biochemistry, genetics, and molecular biology. Efforts will be geared toward uncovering the specific basic biochemical aberrations of this disease in expectation that in this way improved detection, control and therapy will result. For example, since the components of external secretions play such important roles in the pathogenesis of cystic fibrosis, intensive studies will be conducted to isolate the abnormal factors in such exocrine gland secretions as saliva.

Calcium concentration in saliva also is known to be abnormally high in cystic fibrosis patients, suggesting a defect in calcium metabolism. Little is known, however, about the mechanisms of calcium transport into salivary glands or the manner in which it is stored. Institute scientists will undertake new studies to understand better the role of the autonomic nervous system in normal salivary gland secretion mechanisms. These studies may define the mechanisms that are distorted in cystic fibrosis.

Endocrinology

Endocrine disorders, such as hyper-and hypothyroidism, growth retardation and osteoporosis, are known to strike many Americans. One main thrust in endocrinology is to learn the precise mechanisms by which hormones influence metabolism. Recent findings are leading to a better understanding of disorders of the parathyroid gland, such as hyperparathyroidism. This disease, marked by an oversecretion of the parathyroid hormone, causes decalcification of bone, an abnormally high blood calcium level and can lead to kidney stones, bone cysts, and other problems. Institute scientists have resolved an argument going on for many years as to whether the major effect of parathyroid hormone is on the kidney or on bone. They have found that the hormone activates the enzyme adenyl cyclase in both bone and kidney target cells and the resulting increased formation of cyclic adenosine monophosphate is responsible for both renal and skeletal effects. This potent substance is found in many tissues and appears to be the agent that mediates many hormonal effects. Furthermore, they have found that the newly synthesized 34 amino acid fragment is active in both kidney and bone. Up until now, pure parathyroid hormone has been in short supply and availability of the synthetic product will be useful in further studies in basic research and possibly clinically as well. Indeed it might be possible to synthesize a parathyroid hormone congener more active than the natural product.

In more clinically-directed research, Institute scientists will pursue their preliminary findings regarding the administration of thyroxine. The scientists have shown that weekly administration of thyroxine, a synthetic thyroid hormone, is a safe and effective means of controlling hypothyroidism in young patients without cardiovascular disease.

Prior to this discovery, it had been generally accepted that treatment of hypothyroidism required replacement of thyroid hormone in daily amounts adequate for maintaining normal metabolism. With the knowledge that some hypothyroid patients neglect to take their medication regularly, and that a single large dose of thyroxine has no untoward effects, the Institute clinicians had explored the possibility of managing hypothyroidism through once-a-week administration of thyroxine. Results of two important thyroid function tests were comparable in patients on the daily and weekly thyroxine regimens. All patients showed complete suppression of radioactive iodine uptake by the thyroid gland one week after the single dose of thyroxine. All patients remained symptom free during the one to three month period on weekly thyroxine therapy, the medication was well tolerated, and several patients expressed a preference for the intermittent therapy.

Among other planned endocrine research by the Institute, studies will be continued of the pituitary, thyroid, parathyroid and adrenal glands, their respective hormones, and the roles they play in the normal and abnormal physiology of the body.

Gastroenterology

There are numerous diseases of the gastrointestinal tract and its associated organs about which much remains to be learned, including diseases of the liver, gallbladder and pancreas. The diversity and magnitude of gastrointestinal disorders combine to place these diseases in a high position among the chronic afflictions affecting man.

The newly-established Digestive and Hereditary Diseases Branch will continue to conduct clinical and laboratory investigations to determine abnormalities in structure and function of the esophagus, stomach, small and large intestines, pancreas and liver, and research on certain hereditary metabolic diseases.

Work will be directed at an understanding of human disease and its treatment in terms of underlying derangements in the body's chemistry. Because the digestive tract lends itself particularly well to the pursuit of this goal and permits a ready extension of animal studies into man, this organ system is a primary focus of the Institute's clinical activities. In addition, since the inborn errors of metabolism constitute a direct clinical reflection of a chemical derangement, and since the inborn errors frequently affect segments of the digestive system, the Institute is also engaged in studies of such disorders.

Hematology

Hematology represents an important part of the Institute's research. The sum total of Americans afflicted with the killing and disabling disorders of the blood, excluding heart and vascular disease and circulatory problems, but including the anemias, sickle cell disease, and blood clotting disorders such as hemophilia, is considerable, being estimated at more than one million cases in this country. Among Institute research goals is a definition of the specific defects in the various blood disorders, as well as knowledge of the precise steps in normal and abnormal blood clotting mechanisms, with application of resulting findings to improved diagnosis and therapy.

In hemophilia research, Institute hematologists have been studying the role of Factor VIII (one of the blood coagulation factors) in the treatment and prevention of the hemorrhages that occur in hemophilic patients. It is known that spontaneous bleeding episodes and hemorrhages following surgery or trauma in patients with hemophilia can be treated readily with the potent Factor VIII concentrates now available. Little is known, however, about long-term prophylactic therapy to prevent recurrence of bleeding episodes. Now, however, Institute scientists have reported that prophylactic treatment of four hemophilic patients for as long as two years with Factor VIII-rich cryoprecipitate was found to decrease significantly the number of spontaneous hemorrhages. Further work is planned of this prophylactic regimen.

The basic research of an Institute scientist has provided clinicians with a possible new treatment for sickle cell anemia. This disorder is a major health problem for Negroes, occurring in about one in 500 births. Thus, for the Negro population, it is more common than the better known hereditary diseases such as phenylketonuria or cystic fibrosis.

Grantee investigators devised the first specific test to detect both homozygous and heterozygous hemoglobin S (the abnormal erythrocyte sickling component), which subsequently provided the key to the new therapy. The test was based on the observation of the Institute scientist that reduced hemoglobin S systems have a negative temperature coefficient of aggregation, due to the presence of abnormal hydrophobic bonds. The

scientist had demonstrated that under conditions of lowered oxygen tension, bonding occurs between alpha and beta hemoglobin chains in sickling-prone erythrocytes. The resultant bound chains aggregate in the form of erythrocyte-deforming, elongated rods. He also showed that cooling weakens the hydrophobic bonds and tends to counteract sickling and speculated that other physical or chemical mechanisms which break abnormal hydrophobic bonds could provide the basis for national therapeutic innovations.

Correspondingly, clinicians at the Blodgett Memorial Hospital in Grand Rapids, Michigan, aimed their therapeutic strategy at in vivo attack on the abnormal hydrophobic bonds. Urea was used since it was recently recognized as capable of breaking hydrophobic bonds, and, in conjunction with invert sugar, had already been proven non-toxic through other therapeutic uses in controlling cerebral edema. Additional research demonstrated, in vitro, that urea dissolved in invert sugar solution desickled sickled erythrocytes and prevented further bond formation in susceptible cells. This new treatment is reported to have aborted the sickle cell crises in patients in severe pain who received urea in invert sugar intravenously, but further studies are needed to confirm these observations.

The net increase of $231,000 includes a decrease of $257,000 for non-recurring building renovations in 1971, offset by increases of $299,000 for annualization of the 1971 pay increase, $135,000 for within-grade pay increases, $31,000 for one extra day of pay in 1972, $10,000 for increased costs in 1972 of using the Federal Telecommunications System, and $113,000 for payment to the National Institutes of Health management fund for centrally furnished services.

Collaborative Research and Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	21	$334,000	21	$354,000	--	+$20,000
Other expenses.....	--	5,619,000		5,123,000	--	-496,000
Total.....	21	5,953,000	21	5,477,000	--	-476,000

The mission of the Institute and the versatile role it must play in pursuit of its goals has evolved other programmatic modes of approach to problems which fall within its province of responsibility. When the need becomes evident for a major new development, such as new organ preservation techniques or new, effective drugs to counteract the body's rejection barrier, it is usually impractical and inefficient to reassign to new directions intramural scientists who have specialized and are engaged in an ongoing orderly and productive research program. It is likewise seldom that competent and high caliber outside scientists will be willing to drop their studies of long standing in favor of a new problem which has become of special programmatic interest to the Institute. In attempting to meet special needs, then, where the kind and content of the work required is clear, direct collaboration is sought with special scientific talent or resources, usually already engaged and competent in closely related efforts and techniques, to further the accomplishment of the specific goal. Thus a third type of Institute activity has evolved through the years which encompasses features borrowed both from the extramural and intramural research approach, which is financed by direct operations funds of the Institute in contrast to extramural funds, and which makes use of the contract mechanism to finance its activities; this is the "collaborative" approach to attainment of Institute goals.

Artificial Kidney Program

In the United States today an estimated 55,000 individuals die each year as a result of irreversible kidney failure. The diseases which originally initiate the chain of events which terminates with advanced kidney failure vary considerably in nature. They may be primary kidney diseases like glomerulonephritis. In other instances progressive kidney damage may be induced by long-standing high blood pressure or diabetes, or kidney infection, and kidney damage may be initiated by obstructions such as kidney stones or hypertrophy of the prostate in aged males. Regardless of the original disease, serious progressive kidney damage leads to a common final pathway, end-stage kidney disease, followed by fatal irreversible kidney failure. It was estimated, based on recent experience, that about 7,500 patients of the yearly 55,000 individuals with end-stage kidney disease would possess the necessary medical and psychological prerequisites necessary for successful long-term dialysis treatment.

The problem of perpetual maintenance of patients with artificial kidneys is complicated by the fact that the cost of currently available techniques is too high, both in terms of money and qualified manpower, to permit widespread patient treatment. Also, patients maintained with the aid of artificial kidneys continue to display a number of undesirable symptoms related either to the underlying disease or to the treatment.

The artificial kidney will not be discarded. Many chronically uremic patients are not medically or psychologically suitable candidates for transplantation. Furthermore, patients who are suitable candidates will have to be sustained with an artificial kidney until they are well enough to have a transplantation operation and until a suitable, antigenically matching donor kidney can be found for them. Also they may have to be placed on an artificial kidney after transplantation if the donated kidney does not function properly for a time or is rejected.

Activities

At present about 65 carefully selected research and development projects are in existence, financed by contract funds. These contracts were placed with universities, nonprofit research laboratories and industrial concerns, and constitute a broad-spectrum approach to the problems of highest priority. Several projects each are focused on the problem areas mentioned above and to related investigations which promise to make the treatment of end-stage kidney disease less expensive and more effective, including development of special adsorbents for uremic toxins, evaluation of special protein-restricted diets in the maintenance of uremic patients to reduce the frequency of dialysis treatments required, and the maintenance of a national registry of all patients who are currently being maintained with the aid of dialysis.

Accomplishments

Among recent achievements is the development of a new generation of compact artificial kidneys, the so-called "hollow fiber dialyzers." The first of these has been started in commercial production after having proven extremely effective and relatively simple and inexpensive in trial use. Similar compact dialyzers of slightly different design are in the process of development.

Another innovation is the presterilized, disposable "envelope kidney" that saves many hours of preparation time in home dialysis. Developed for use with the conventional Kiil artificial kidney machine, the envelope kidney is essentially a presterilized sealed sandwich of Cuprophan PT-150 membranes supported externally by a fiber screen. The envelope is pre-tested for leaks, and blood ports for attachment to the patient's circulation are included within the sealed package.

Preliminary clinical results from trials of the envelope kidney have been excellent, with no adverse reactions, and with blood purification performance as good as or better than with standard membranes in the Kiil apparatus. At this point, no road blocks are foreseen to commercial production and routine use of the envelope kidney.

Another contractor has shown in preliminary investigations that dihydrotachysterol arrests the hyperparathyroid bone disease that characteristically accompanies chronic kidney failure and chronic hemodialysis. Hyperparathyroid bone disease, manifested by hypercalcemia, calcification of soft tissue, and decalcification of bone, is a

well-recognized accompaniment of renal failure and chronic hemodialysis. Although the condition usually responds to parathyroidectomy, it has been difficult to manage medically because uremic patients characteristically develop vitamin D resistance with attendant impaired intestinal calcium absorption.

Dihydrotachysterol, a compound structurally similar to vitamin D, but differing markedly in its biological action, now has been found capable of arresting the hyperparathyroid bone disease seen in patients on long-term dialysis. Marked improvement was observed in all six patients treated in preliminary studies, suggesting that remission of such bone disease is possible by medical means without resort to parathyroidectomy.

Future Activities of the Artificial Kidney Program

The Program will continue all promising current research and development efforts and will pursue any new ideas and approaches which appear feasible. The Institute is currently funding a number of studies aimed at isolation and identification of unknown toxic factors which must be removed from the patients' blood, in addition to metabolic wastes and other substances known to accumulate during kidney failure, such as urea, creatinine, uric acid, potassium, hydrogen ion, and water. In this regard the program is actively pursuing the lead of the origins and effects of guanidinosuccinic acidemia and of methylguanidine in uremia. Studies, supported by this program, have shown that both substances are elevated in uremics, and have a pathophysiologic correlate to uremic symptoms. Searches will also be pursued for other toxicants possibly involved in the uremic syndrome. Much of the future success in simplifying the treatment of patients with end-stage kidney disease depends on developments in these areas. The Program also intends to follow very closely clinical and technological developments abroad and, when promising, to enlarge upon them for the benefit of United States patients as well. This is particularly pertinent since developments in several Western European countries have been quite promising, and their early and active introduction in the United States, and possible refinement, (without waiting for the usual delay connected with spontaneous spread of new techniques) could prove highly beneficial to patients in the United States.

Hormone Developmental Research Program

In recent years, gradually increasing knowledge has revealed the intricate regulatory relationship between hormones and enzymes in most biochemical processes. Alteration of this relationship undoubtedly underlies the functional derangement in many diseases of the blood, bone, liver and intestinal tract. There are numerous examples of areas in protein hormone research which if stimulated and strengthened by direct, concerted efforts would yield valuable results directly applicable to diagnosis and patient care in addition to filling gaps in fundamental and clinical endocrine research. At present, pending future expansion, the Institute's hormone developmental research program is comprised of three contracts.

Program Plan for 1971 and 1972

Current Activities: The Institute has contracted for the operation of the National Pituitary Agency to increase and improve the collection of human pituitary glands and to provide for the distribution of purified HGH to qualified research scientists. The NPA contract provides for the

collection of human pituitary glands, fractionation of their major hormones, and distribution of HGH and other pure fractions to selected investigators for research purposes. At present, HGH can only be administered to patients in conjunction with clinical research studies because it is impossible to collect enough human pituitary glands to obtain sufficient HGH for treatment for all of the children suffering from hypopituitary dwarfism in the United States.

Another contract provides access for American investigators to the Steroid Reference Collection of the British Medical Research Council. This collection which includes literally hundreds of reference samples of steroids of highest purity is the only resource of this kind in the world. Investigators in the United States, including grantees of the Institute, require access to such a collection to facilitate and expedite their research since there is no counterpart in the United States to many of these standards.

The other project in this program provides for the collection of rat pituitary glands on a large scale and for their extraction and fractionation to yield purified standardized pituitary hormones: growth hormone, lactogenic hormone, follicle stimulating hormone, and luteinizing hormone. These purified hormones are being made available to qualified, interested investigators with the aid of a specially constituted group of outside scientific consultants. This project which had been strongly endorsed by investigators in endocrinology provides a much needed source of purified pituitary hormones for bioassy and chemical studies which have been held back to date for lack of the purified hormone fractions.

Scientific Communications

A continuing problem confronting individual physicians and research scientists today is the difficulty of keeping up with rapidly developing fields of knowledge directly or indirectly related to their work. The Institute, through its Office of Scientific Communications, will continue to provide current-awareness ("alerting") publications and other similar materials in areas within its purview, conduct retrospective literature searches, initiate conferences and workshops and publish their proceedings in order to provide the widest possible dissemination of up-to-date research information. The Institute will also conduct other activities related to scientific communication, such as the production of a limited number of specialized motion pictures and development of thesauri in carefully selected areas where the state of knowledge is less than optimal.

The Institute issues, on a regular basis, five current-awareness publications in major disease areas important to its mission. Currently published on a monthly basis are: ARTHRITIS AND RHEUMATIC DISEASES ABSTRACTS, DIABETES LITERATURE INDEX, and GASTROENTEROLOGY ABSTRACTS AND CITATIONS. In addition, ENDOCRINOLOGY INDEX is published on a bimonthly basis, and ARTIFICIAL KIDNEY BIBLIOGRAPHY is being published on a quarterly basis.

Each of these publications covers the entire scientific literature related to the subject matter (diabetes, gastroenterology, etc.) from throughout the world regardless of the original language. The response to these publications by investigators and medical school staffs has been very enthusiastic, and their need and usefulness have been clearly documented.

The net decrease of $476,000 includes a program decrease in the Artificial Kidney Program of $500,000, offset by increases of $10,000 for annualization of the 1971 pay increase, $9,000 for within-grade pay increases, $1,000 for one extra day of pay in 1972, and $4,000 for payment to the National Institutes of Health management fund for centrally furnished services. The decrease of $500,000 in the Artificial Kidney Program will reduce the number of active contracts from approximately 65 in 1971 to 57 in 1972, a decrease of 8 contracts.

Biometry, Epidemiology and Field Studies

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	31	$365,000	31	$541,000	--	+$176,000
Other expenses.....	--	556,000	--	408,000	--	-148,000
Total.....	31	921,000	31	949,000	--	+28,000

Epidemiology, the study of population and disease, is recognized by medical scientists as indispensable to the advancement of biomedical knowledge. In essence it deals with the relationships of the various factors which determine the frequencies or distributions of a disease.

The Epidemiology and Field Studies Branch is presently conducting studies to aid in determining the etiology of diabetes mellitus, cholelithiasis, various arthritides, and goiter. A number of these studies have been undertaken in American Indian populations because the characteristics of some of these make them especially suitable for investigation by epidemiologic methods.

The Southwestern Field Studies Section is located in Phoenix, Arizona, in order to be in geographic proximity to a number of American Indian reservations, and, in particular to the Gila River Reservation, where baseline studies relating to diabetes mellitus, gallbladder disease, and arthritis are being conducted.

Program Plans

The Southwestern Field Studies Section initiated a long-term program in 1965 in which the development of manifestations of diabetes, arthritis, and gallbladder disease in selected population groups are being studied and evaluated. Various factors, including hereditary, environmental, dietary, and anthropological aspects that may have a bearing on the frequency and severity of these diseases are and will be investigated. Selected findings are being contrasted with similar studies performed on other populations with different characteristics or environments.

There is a continuing professional and collaborative liaison with the Institute's clinical research program at the new Phoenix Indian Medical Center, and staff members are engaged in studies on gallbladder disease and diabetes at that new research facility.

Diabetes Mellitus

Diabetes mellitus and its vascular complications have been shown to occur at least ten times as commonly among the Gila River Indians as in the United States population as a whole. As diabetes mellitus is a very significant cause of morbidity and mortality in the United States, a major effort is being made by the Southwestern Field Studies Section to gain a detailed understanding of the distribution of this disorder and its complications in the Gila River Indian Community.

methods of genetic analysis to detect the simple patterns of inheritance, utilizing the bimodal distribution of the glucose tolerance levels, have been developed. The hypothesis that diabetes mellitus is inherited as a simple recessive trait will be tested, but at the present time inadequate numbers of family units have been examined in which the offspring are of sufficient age to have developed diabetes.

The study of the geographic distribution of diabetes among American Indian populations will also continue. Additional data from the Southwestern Field Studies Section and other investigators indicate that there is wide inter-tribal variation in the prevalence of the disease. Other ongoing studies of diabetes are designed to explore the nature and inter-relationships of carbohydrate intolerance to the renal, retinal, and non-specific vascular complications of diabetes in the Gila River Indians. It is hoped that an understanding of the variation and extent of such complications will be obtained which might lead to the development of methods of prophylaxis.

Gallbladder Disease

The Southwestern Field Studies Section has recently completed the second phase of a study on the prevalence of cholelithiasis on the Gila River Reservation. Following the demonstration of a high frequency of symptomatic gallstone disease two years ago, subjects without clinical evidence of the disease have been examined by cholecystogram. It has now been shown that asymptomatic cholelithiasis is extremely common, especially in young adult females. The study has shown that the majority of Pima Indian females develop cholelithiasis between the ages of twenty to thirty years. Hence, females within the 15-25 year age group are at very high risk of developing gallstones within a short time. The identification of such a group will enable a critical analysis of possible precipitating factors. The group is also one in which more detailed studies are indicated.

Rheumatoid Arthritis

The presence of rheumatoid factor is a characteristic of subjects with rheumatoid arthritis, yet in natural populations many subjects may be shown to have the factor, but have no overt evidence of arthritis. Gila River Indian subjects with "false positive" tests for rheumatoid factor and an age-sex matched control group have been serially examined to determine the incidence of arthritis in the two groups. A six-fold difference in the incidence of probable and definite rheumatoid arthritis has been shown, indicating that the presence of rheumatoid factor is of predictive value. This suggests that an understanding of the reasons for the development of rheumatoid factor may be a vital clue in determining the etiology of sero-positive rheumatoid arthritis. In an attempt to gain insight into this process, the distribution of rheumatoid factor and the search for related phenomena will be extended to all Gila River Indians aged five years and over.

Metabolic Diseases Epidemiology Unit

The Metabolic Diseases Epidemiology Unit has previously demonstrated that simple goiter occurred in areas with polluted water supplies and was not inevitably associated with a low iodine intake. Following these observations, efforts have been made to identify goitrogens in the environment, and, in particular, in polluted water, from areas with a high prevalence of goiter, using the rat as an experimental animal.

The influence of clostridium perfringens, an anaerobic bacterium found in soil and sewage, as an antithyroid substance has been examined, and under certain defined circumstances, this bacterium has been shown to produce an exotoxin with goitrogenic properties. Laboratory studies are being conducted on other bacteria which are common contaminants of polluted water and soil. It is hoped that these studies will lead to clarification of a hitherto not investigated, novel causative mechanism for endemic goiter, which does not involve the classical theory of dietary iodine deficiency, and which is amenable to control through environmental improvement.

The increase of $28,000 includes $15,000 for annualization of the 1971 pay increase, $7,000 for within-grade pay increases, $1,000 for one extra day of pay in 1972, and $5,000 for payment to the National Institute of Health management fund for centrally furnished services.

Review and Approval of Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	63	$971,000	63	$1,061,000	--	+$90,000
Other expenses.....	--	1,439,000	--	1,511,000	--	+72,000
Total.....	63	2,410,000	63	2,572,000	--	+162,000

This activity involves professional and supporting personnel who are responsible for the administration of the Institute's several grants activities. They assist in the planning and development of programs in research, training, and fellowships that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; review and evaluation of research and training grant applications for presentation to the National Advisory Arthritis Council; required Council staff assistance; liaison with applicants, grantees, other components of NIH and the Department, advisory bodies, and interested organizations; continuous surveillance of scientific activities and progress; and recording and reporting of fiscal and scientific information relevant to all transactions.

The increase of $162,000 results from increases of $61,000 for annualization of the 1971 pay increase, $26,000 for within-grade pay increases, $3,000 for one extra day of pay in 1972 and $72,000 for payment to the National Institutes of Health management fund for centrally furnished services.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	21	$313,000	21	$330,000	--	+$17,000
Other expenses.....	--	83,000	--	87,000	--	+4,000
Total.....	21	396,000	21	417,000	--	+21,000

This activity is comprised of the Institute Director, his immediate staff and administrative management and service personnel who are responsible for the general direction, coordination and administration of the total Institute activities.

The increase of $21,000 includes $9,000 for annualization of the 1971 pay increase, $7,000 for within-grade pay increases, $1,000 for one extra day of pay in 1972, and $4,000 for payment to the National Institutes of Health management fund for centrally furnished services.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Program Purpose and Accomplishments

Activity: Research Grants (Public Health Service Act Title IV Part D)

1971	1972	
Amount	Authorization	Budget Estimate Amount
$89,803,000	Indefinite	$91,491,000

Purpose: This program provides support for clinical and basic research in an unusually broad spectrum of diseases and disciplines including arthritic, rheumatic, and collagen (connective tissue) diseases; various metabolic disorders, such as diabetes; gastrointestinal diseases, such as peptic ulcer; endocrine malfunctions; dermatological conditions, such as psoriasis; diseases of blood, bone, liver, and kidney; and research in urology, nutrition, and orthopedic surgery.

Explanation: Applications from individual investigators at educational and non-profit institutions are reviewed and ranked on the basis of the qualifications of the investigator and the merit of the proposed project by panels of outstanding experts in specific fields. Within the funds available, the Institute makes grant awards in the order of these priority scores.

Accomplishments in 1971: In 1971, an estimated 2,028 research projects will be supported at over 400 institutions throughout the nation. This represents about 35% of those applications approved by the panels of experts.

Objectives for 1972: The Institute will continue to attempt to maintain a balanced program across the broad areas of its responsibility. It is estimated that the funds to become available will support 1,823 research projects or 205 fewer than in 1971.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Program Purpose and Accomplishments

Activity: Fellowships (Public Health Service Act Title IV Part D)

1971 Amount	1972 Authorization	1972 Budget Estimate Amount
$5,740,000	Indefinite	$5,094,000

Purpose: The increasing complexity and specialization in biomedical research demand a highly skilled reserve of scientific manpower. To increase the number and effectiveness of individuals in research and related academic fields, the Institute will continue its three-pronged Fellowship program designed to develop the full investigative potential of the young scientific community. The program includes Special Fellowships, Postdoctoral Fellowships, and the Research Development Awards.

Explanation: Postdoctoral fellowships provide support directly to selected individuals and may be applied at clinical or basic science departments of any institution in the United States. This award may be directed toward a unique line of investigation and, as such, may provide the groundwork for future fields of research.

Placing emphasis on individuals with broader biomedical backgrounds, special fellowships are awarded, for the most part, to young men and women in advanced research and techniques training who have not yet established a permanent affiliation with an academic institution. However, recipients also include established investigators on leave from their positions to pursue special studies.

Young scientists who have displayed exceptional investigative ability in their postdoctoral training are candidates for the Research Development Award. Designed to develop full professional potential, the award provides salary support for a limited number of years to encourage careers in health-related independent research.

Accomplishments in 1971: It is estimated that in 1971, 343 fellowships will be supported in ten major fields for which this Institute is responsible.

Objectives for 1972: Approximately 280 fellowships will be supported. This is 63 fewer than in 1971 and results from a budget reduction of $464,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Program Purpose and Accomplishments

Activity: Training Grants (Public Health Service Act Title IV Part D)

1971	1972	
Amount	Authorization	Budget Estimate Amount
$11,475,000	Indefinite	$11,475,000

Purpose: The Institute's Training Grants Program is evidence of its concern for the chronic shortage of qualified personnel in the fields of clinical investigation and research training. Aimed toward career development in investigation and teaching, the program is centered in the clinical departments of medical schools throughout the country.

Explanation: Applications are submitted by and awards made to the directors of the training programs rather than to individual trainees. These grants provide for the support of the research environment within the department as well as for stipend support for trainees selected by the program director.

Accomplishments in 1971: During 1971 approximately 264 training grants with about 678 trainees will be supported.

Objectives for 1972: In 1972, funds expected to become available will support an estimated 249 training grants or 15 fewer than in 1971.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Program Purpose and Accomplishments

Activity: Laboratory and Clinical Research (Public Health Service Act Title IV Part D)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
491	$17,727,000	Indefinite	491	$17,958,000

Purpose: 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; and diseases of the blood and bone.

Explanation: The total intramural 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 constitutes the foundation of knowledge pertinent to any of the above disease categories. The fundamental scientific disciplines include chemistry, biochemistry, enzymology, molecular biology, anatomy, histology, pathology, physiology, medicinal chemistry, pharmacology, and genetics.

Accomplishments in 1971: Significant gains were made in the field of endocrinology where the determination of the complete structure of the parathyroid hormone has been determined and has led to its successful synthesis. In the field of hematology, the so-called Australia antigen in the blood has been related to both serum and infectious hepatitis. A possible new treatment for sickle cell anemia has resulted from basic research studies by an Institute investigator.

Objectives for 1972: Projects underway in 1971 will be continued but no major new projects are planned. The program decrease of $357,000 includes reductions of $347,000 for non-recurring building renovations in 1971 and $10,000 in the Office of Information as part of a government-wide policy to reduce public relations activities.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Program Purpose and Accomplishments

Activity: Collaborative Research and Development (Public Health Service Act Title IV Part D)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
21	$5,953,000	Indefinite	21	$5,477,000

Purpose: This activity is designed to make use of the research and development contract as a mechanism to meet special needs where the kind and content of the work required is clear and direct collaboration is sought with specific scientific talent or resources to pursue specific goals. The use of research contracts permits a coordinated, focused, developmental effort to reduce the lag period between development of basic research information and its practical application to human welfare.

Explanation: Three separate programs are conducted within this activity. The Artificial Kidney Chronic Uremia Program is focused upon improvement of repeated hemodialysis for patients with permanently impaired kidney function and upon making this therapeutic modality less expensive and more effective. The Endocrine and Diabetes Hormone Developmental Program currently supports the collection, fractionation and distribution of rare, pure hormonal fractions to selected investigators for research purposes. The Scientific Communications Program provides current-awareness publications and other similar materials, conducts retrospective literature searches and initiates conferences and workshops and publishes their proceedings in order to provide up-to-date research information to individual physicians and research scientists.

Accomplishments in 1971: Among the achievements of the last year were the development of a new generation of compact artificial kidneys, the so-called "hollow fiber dialyzers". The first of these has been introduced into commercial production after having proven extremely effective and relatively simple and inexpensive in use. A new "envelope dialyzer" has been developed which decreases significantly the set-up time in home dialysis and eliminates the need for complicated sterilization of dialyzers by the patient. The new dialyzers have been very successful in clinical testing and will become available commercially in March 1971.

A new selfcontained automatic peritoneal dialysis system has been developed and has been tested clinically. This new system, which will permit hospital center or home peritoneal dialysis, will soon see commercial production.

Objectives for 1972: A decrease of $500,000 in the Artificial Kidney Program will reduce the number of active contracts from 65 in 1971 to 57 in 1972, a decrease of 8 contracts.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Program Purpose and Accomplishments

Activity: Biometry, Epidemiology, and Field Studies (Public Health Service Act Title IV Part D)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
31	$921,000	Indefinite	31	$949,000

Purpose: Epidemiology, the study of population and disease, is recognized by medical scientists as indispensable to the advancement of biomedical knowledge. In essence it deals with the relationships of the various factors which determine the frequencies or distributions of a disease.

Explanation: The Institute's Southwestern Field Studies Section, located in Phoenix, Arizona, initiated a long-term program in 1965 in which the development of manifestations of diabetes, arthritis, and gallbladder disease in selected population groups are being studied and evaluated. Various factors, including hereditary, environmental, dietary, and anthropological aspects that may have a bearing on the frequency and severity of these diseases will be investigated. Selected fundings are being contrasted with similar studies performed on other populations with different characteristics or environment.

Accomplishments in 1971: Intensive studies of the Pima Indians of the Gila River Reservation, who have been found by Institute investigators to have a diabetes incidence 10 to 15 times greater than that of the country in general, have now made possible a valid separation of individuals with high blood sugar levels into those truly diabetic or latent diabetic, and others in whom high blood sugar levels are merely an expression of attendant obesity. This is a major step forward in investigations of the genetic and all possible environmental factors which could determine the emergence of frank diabetes in such a population.

It has also been shown that the majority of Pima females develop gallstones before the age of 30. Thus, the 15- to 25-year age group can now be selected as a study group known to be at very high risk of developing gallstones within a relatively short time. This will permit a statistically valid critical analysis of factors precipitating gallstone formation--a disorder which affects literally millions of Americans.

Objectives for 1972: Epidemiological research on the conditions noted above will continue. Obesity and diabetes rates will be studied and compared among the Pimas and other Indian tribes in Arizona. Collaborative studies at the Institute's clinical research unit in Phoenix will be undertaken and will include gallbladder disease, diabetes, and digestive diseases.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Program Purpose and Accomplishments

Activity: Review and Approval of Grants (Public Health Service Act Title IV Part D)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
63	$2,410,000	Indefinite	63	$2,572,000

Purpose: This activity covers the centrally furnished services from the National Institutes of Health management fund and the direct costs of staff and outside advisors engaged in the administration of the Institute's several granting activities.

Explanation: The staff participates in the planning and development of programs in research, training, and fellowships that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; reviews and evaluates research and training grant applications for presentation to the National Advisory Arthritis Council; furnishes required Council staff assistance; maintains liaison with applicants, grantees, other components of NIH and the Department, advisory bodies, and interested organizations, maintains continuous surveillance of scientific activities and progress; and records and reports fiscal and scientific information relevant to all transactions.

Accomplishments in 1971: During 1971 the staff reviewed approximately 3,391 grants for scientific merit and program relevance and maintained surveillance over 2,635 grants.

Objectives for 1972: In 1972, a continuing effort will be made to strengthen the liaison and surveillance activities in order to obtain maximum benefit from the available grant funds.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Metabolic Diseases

Program Purpose and Accomplishments

Activity: Program Direction (Public Health Service Act Title IV Part D)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
21	$396,000	Indefinite	21	$417,000

Purpose: This activity is comprised of the Institute Director, his immediate staff and administrative management and service personnel who are responsible for the general direction, coordination and administration of the total Institute activities.

WEDNESDAY, MAY 5, 1971.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE

WITNESSES

DR. EDWARD F. MacNICHOL, JR., DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ELDON L. EAGLES, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE
ECKART WIPF, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE
ROBERT L. SITHENS, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

National Institute of Neurological Diseases and Stroke

Object Classification (in thousands of dollars)

Identification code 09-30-0886-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	7,595	8,310	8,460
11.3	Positions other than permanent	275	300	325
11.5	Other personnel compensation	187	206	215
	Total personnel compensation	8,057	8,816	9,000
12.1	Personnel benefits: Civilian employees	760	823	837
21.0	Travel and transportation of persons	403	418	399
22.0	Transportation of things	125	130	124
23.0	Rent, communications, and utilities	342	354	338
24.0	Printing and reproduction	165	171	163
25.0	Other services	13,214	14,751	10,892
26.0	Supplies and materials	1,270	1,315	1,256
31.0	Equipment	350	362	346
41.0	Grants, subsidies, and contributions	72,480	75,884	72,143
	Subtotal	97,166	103,024	95,498
95.0	Quarters and subsistence	−2	−2	−2
99.0	Total obligations	97,164	103,022	95,496

Personnel Summary

	1970 actual	1971 est.	1972 est.
Total number of permanent positions	588	608	608
Full-time equivalent of other positions	55	52	52
Average number of all employees	620	633	633
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0886-0-1-651	1970 actual	1971 est.	1972 est.
Program by activities:			
1. Grants:			
(a) Research	54,710	58,802	58,092
(b) Fellowships	2,713	2,782	2,595
(c) Training	14,204	14,300	11,456
Total grants	71,627	75,884	72,143
2. Direct operations:			
(a) Laboratory and clinical research	10,260	11,668	9,696
(b) Collaborative research and development	9,100	9,440	7,451
(c) Biometry, epidemiology, and field studies	3,094	3,324	3,371
(d) Review and approval of grants	2,208	2,194	2,265
(e) Program direction	525	512	570
Total, direct operations	25,187	27,138	23,353

Program and Financing (in thousands of dollars)

Identification code 09-30-0886-0-1-651		1970 actual	1971 est.	1972 est.
	Total program costs, funded [1]	96,814	103,022	95,496
	Change in selected resources [2]	350	.....	.....
10	Total obligations	97,164	103,022	95,496
	Financing:			
25	Unobligated balance lapsing	101	3,629	.....
	Budget authority	**97,265**	**106,651**	**95,496**
	Budget authority:			
40	Appropriation	106,978	105,807	95,496
40	Portion withdrawn (Public Law 91-204, sec. 410)	−6,576	.....	.....
40	Pay increase (Public Law 91-305)	387	.....	.....
41	Transferred to other accounts	−3,524	−17	.....
43	Appropriation (adjusted)	97,265	105,790	95,496
46.10	Proposed transfer wage-board pay increases	.....	131	.....
46.20	Proposed transfer for civilian pay act increases	.....	640	.....
46.30	Proposed transfer for military pay increases	.....	90	.....
	Relation of obligations to outlays:			
71	Obligations incurred, net	97,164	103,022	95,496
72	Obligated balance, start of year	72,532	55,539	51,124
74	Obligated balance, end of year	−55,539	−51,124	−47,309
77	Adjustments in expired accounts	−1,791	.....	.....
90	Outlays, excluding pay increase supplemental	112,366	106,610	99,277
91.10	Outlays from wage-board supplemental	.....	126	5
91.20	Outlays from civilian pay act supplemental	.....	615	25
91.30	Outlays from military pay act supplemental	.....	86	4

[1] Includes capital outlay as follows: 1970, $435 thousand; 1971, $500 thousand; 1972, $550 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $31,804 thousand; 1970, $24,089 thousand; 1971, $24,089 thousand; 1972, $24,089 thousand.

NOTES

Includes $445 thousand in 1971 and $490 thousand in 1972 for activities previously financed from: Research resources, 1970, $411 thousand.

Excludes $1,159 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	*1971*
National Eye Institute	1,947	1,088
Office of the Secretary	4	4
Office of the Director	72	67

Excludes $2,844 thousand in 1972 for activities transferred to: Health manpower, 1970, $2,844 thousand; 1971, $2,844 thousand.

INTRODUCTION OF DR. MAC NICHOL AND ASSOCIATES

Mr. FLOOD. We continue with the National Institutes of Health, and we now have the National Institute of Neurological Diseases and Stroke. The presentation will be made by Dr. MacNichol, Jr., the Director. We have a biographical sketch for you.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCHES

Name: Edward F. MacNichol, Jr.
Position: Director, National Institute of Neurological Diseases and Stroke.
Birthplace and date: Toledo, Ohio, October 24, 1918.
Education: Princeton University (Physics), A.B., June 1941. University of Pennsylvania, 1946–49; the Johns Hopkins University (Biophysics), Ph. D., June 1952.
Experience:
Present: Director, National Institute of Neurological Diseases and Stroke.
1952–68: Instructor to professor, Department of Biophysics, the Johns Hopkins University.
1957: Visiting professor, Venezuelan Institute for Scientific Research.
1941–46: Staff member, Radiation Laboratory, Massachusetts Institute of Technology.
1964: Summer Investigations, Marine Biological Laboratory, Woods Hole, Mass.
Association membership:
Member, American Association for the Advancement of Science.
Member, American Physical Society.
Member, American Physiological Society.
Member, Biophysical Society.
Fellow, Institute of Electrical and Electronics Engineers, Inc.
Member, Society of Neuroscience.
Member, New York Academy of Sciences.
Special awards and citations:
Morlock award of the Institute of Electrical and Electronics Engineers, Inc.. 1965.
Army-Navy certificate of appreciation for work done at MIT Radiation Laboratory, 1948.
1946–48 predoctoral fellowship, American Cancer Society.
Publications: Over 30 scientific and technical publications on the electrophysiology of vertebrate and invertebrate eyes and on the measurement of pigment in single vertebrate photoreceptors.

Name: Eldon Lewis Eagles.
Position: Deputy Director, National Institute of Neurological Diseases and Stroke.
Birthplace and date: Moncton, New Brunswick, Canada, March 9, 1911 (U.S. citizen since 1961).
Education:
M.D., C.M., Dalhousie University, Halifax, Nova Scotia, 1936.
D.P.H., University of Toronto, 1940.
Dr. P.H., The Johns Hopkins University School of Hygiene and Public Health, 1958.
Experience:
Deputy director, National Institute of Neurological Diseases and Stroke, National Institutes of Health, 1970 to present.
Assistant director, NINDS/NIH, 1964–1970.
Associate Research Professor of Maternal and Child Health, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pa., 1960–64.
Research associate, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pa., 1957–60.

Director of studies, Subcommittee on Medical Sciences and Facilities for Handicapped Children, Committee on Medical Care, The Maryland State Planning Commission, Baltimore, Md., 1956–57.

Director, child and maternal health and communicable disease control, Nova Scotia Department of Public Health, Halifax, Nova Scotia, 1954–56.

Divisional medical health officer, Department of Public Health, Nova Scotia, 1940–54.

General practice of medicine and surgery at Port Maitland, Yarmouth County, Nova Scotia, 1936–39.

Association memberships:

Phi Rho Sigma.

Nova Scotia Medical Society (vice president 1938–39).

American Public Health Association (Fellow 1951 to present).

American Speech and Hearing Association (Fellow 1964 to present).

American Association for the Advancement of Science (Fellow 1960 to present).

Special awards citations, or publications:

Sigma XI.

Among some 30 papers and monographs: Human communication: The Public Health Aspects of Hearing, Language, and Speech Disorders, Eagles, E. L., Hardy, William G., Catlin, Francis I., NINDS Monograph No. 7, 1968.

Hearing Sensitivity and Ear Disease in Children: A Prospective Study, Eagles, E. L., Wishik, S. M., Doerfler, L. G., Monograph The Laryngoscope, 1967.

Name: Eckart Wipf.

Position: Executive Officer, National Institute of Neurological Diseases and Stroke.

Birthplace and date: Freeman, S.Dak.; April 18, 1917.

Education: University of South Dakota, A.B., 1939. University of Minnesota, M.A. (Public Administration), 1947. National Institute of Public Affairs, Washington, D.C. 1946.

Experience:

Present: Executive officer, National Institute of Neurological Diseases and Stroke.

1951–55: Classification officer, Personnel Management Branch, NIH.

1948–50: Position classifier and personnel assistant, Personnel Management Branch, NIH.

1946–48: Administrative assistant, Veterans Administration, St. Paul, Minn.

1941–44: U.S. Army Air Corps.

1939–41: Public High School Teacher, Colome, S.Dak.

Honors and awards: Rockefeller Scholarship to National Institute of Public Affairs, 1946.

Mr. FLOOD. Who is with you?

Dr. MACNICHOL. Mr. Wipf, our executive officer, and next to him, Mr. Sithens, my financial officer, and Dr. Eagles, the Deputy Director of the Institute.

Mr. FLOOD. If any of these people testify, we would like a biographical sketch to follow yours.

I see you have a prepared statement, doctor. How do you wish to proceed?

Dr. MACNICHOL. May I read it?

Mr. FLOOD. Yes.

GENERAL STATEMENT

Dr. MACNICHOL. Mr. Chairman and members of the committee. It is my privilege to appear before you in behalf of the National Institute of Neurological Diseases and Stroke.

The diseases that the Institute seeks to eliminate are important both because of number of people they kill, stroke being the third most prevalent cause of death, and because these diseases severely handicap their victims often for an entire lifetime.

The financial burden to the victims' families and to the community, and the prolonged anguish that these crippling diseases cause are unusually great.

PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

Parkinson's disease is a vivid example of a long-term neurologic disability. It afflicts more than 1 mililon of our citizens. Many of them lapse into a state of living death in which, though mentally alert, they are almost unable to communicate or to make purposeful movements. Last year we reported to you the remarkable success of research that has led to the use of levodopa for parkinson's patients. A year ago the drug had not yet been released to the public. Now that clinical trials have been completed, levodopa is available to all who need it, though treatment to be effective must be skillfully supervised. Three of our large treatment centers have reported that over 70 percent of patients with parkinson's disease are benefited by levodopa; about 25 percent spectacularly so. Thus if all who are afflicted obtain treatment, about 700,000 sufferers will be able to lead much more normal lives, and of these perhaps 200,000 will appear to be almost completely cured.

Does levodopa arrest the progress of the disease or merely control the symptoms? Long-term followup studies are seeking answers to this and other questions affecting levodopa therapy.

This drug has an importance beyond being the first effective agent against parkinsonism. Fundamental studies seeking to determine how it produces its effects are beginning to give us an understanding of the basic processes underlying parkinsonism and releated diseases. New interest in all movement disorders has now been generated.

Mr. FLOOD. What do you mean by movement disorders?

Dr. MACNICHOL. Involuntary movement, paralysis due to central nervous causes.

The Institute has initiated, through grants, a number of new projects aimed at opening up unexplored territories in the chemistry, physiology, and pharmacology of the brain. One of these projects is at Brookhaven National Laboratory and is headed by Dr. George C. Cotzias who pioneered in the effective use of levodopa. With Institute support he is now trying it on patients who have related disorders such as dystonia and Wilson's disease.

Other Institute-supported scientists are attempting to develop new drugs which will prove still more effective and have less severe side effects than levodopa, and are testing enzyme inhibitors that decrease the amount of levodopa required to produce therapeutic effects. These could markedly cut the cost and increase the effectiveness of treatment.

NATURE AND TREATMENT OF STROKE

Strokes kill over 200,000 people a year in this country.

Mr. FLOOD. What is dystonia?

Dr. MacNichol. Dystonia is where due to unbalanced input of the nervous systems, there are turnings——

Mr. Flood. Unbalanced input of the nervous system?

Dr. MacNichol. Input from the muscles. The head will be on one side or the neck is twisted.

Mr. Flood. What is Wilson's disease? Put in the record a brief description of these two disorders.

(The information follows:)

Dystonia is a rare nervous disorder—it is believed to have a hereditary aspect—in which the patient experiences slow, strong, sustained, twisting, turning and writhing movements of the body muscles. While there is no paralysis, the contractions may interfere with purposeful movement and spasms may be so powerful that the patient cannot relax the affected muscles.

Wilson's disease appears in young people, usually between 11–25 years of age. Due to an inborn defect in the body's inability to break down copper, the disease allows a build up of this element in tissues and leads to damage to the liver and nervous system.

Mr. Flood. What is stroke?

Dr. MacNichol. A stroke is some interference with the blood supply of the brain, either the bursting of a blood vessel or the blocking of a blood vessel.

Mr. Flood. Proceed.

Dr. MacNichol. Another 2 million are disabled in varying degrees, many so severely that they are unable to walk or talk and must be cared for in hospitals or nursing homes. The cost of caring for surviving stroke victims is estimated at $4 billion per year.

For a number of years with the support and encouragement of this committee the problem of preventing stroke and of minimizing its effects has been approached jointly with the National Heart and Lung Institute. Together we have worked with the Veterans' Administration and the regional medical programs of the Health Service and Mental Health Administration, sponsored research, held meetings to exchange information and plan research, and supported stroke clinical research centers. These organizations have cooperated with the American Neurological Association in establishing a Committee for Stroke Facilities. Steady progress is being made. Recently a careful study by the Veterans' Administration dramatically confirmed the suspicion that if blood pressure is controlled by regular drug therapy in people who are otherwise hypertensive, the chances of their having strokes are decreased.

The National Heart and Lung Institute has recently announced a program to evaluate the effects of antihypertensive therapy upon a large and varied segment of the population. This is a followup to a most promising pilot study made by the Veterans' Administration.

An NINDS grantee in St. Louis has just begun a study of the use of urokinase, a thrombolytic agent that dissolves blood clots, in stroke patients.

Improved techniques have steadily increased the success of surgery of the arteries of the head and neck. Recently grantees have reported removal of clots from very small blood vessels and the grafting of small blood vessels using microsurgical techniques. When these techniques are perfected they will greatly benefit the correction of aneurysms, which may occur in younger persons.

There are now 17 Institute-supported clinical stroke research centers in hospitals and universities. Most of these have coordinated clinical and basic research programs.

An urgent problem is the improvement of acute stroke care, since 70 to 80 percent of deaths of stroke victims occur within the first 10 days. Accordingly NINDS has launched a pilot study of acute stroke care. Recent findings in our laboratories of Perinatal Physiology and Surgical Neurology have shown that the brain can survive regional losses of circulation for longer than had been previously believed. This finding leads to the hope that stroke may be overcome if circulation can be quickly restored in the affected areas.

Better instrumentation must be developed for monitoring the acute stroke victim and for the diagnosis of incipient stroke. At a recent meeting sponsored by NINDS and NHLI many new possibilities were considered for improved measurement of cerebral blood flow. Among the most promising were the use of ultra-sound and nuclear magnetic resonance. Research on these methods is proceeding actively.

Grantees at two different medical centers have recently reported success in shortening the time required for two important diagnostic techniques for critically ill stroke patients. The gas inhalation technique has been shortened from the usual 30 minutes to 11. Also, a new cerebral angiographic technique cut in half the time required to conduct multiple vessel studies. In this technique, called the femoral approach, dye is injected through a catheter which is threaded from an artery in the leg all the way to the head. This technique minimizes patient discomfort and eliminates the need for general anesthesia. It has been reported highly satisfactory in over 200 patients.

Incidence and Treatment of Head and Spinal Cord Injuries

Head and spinal cord injuries have become a major health problem due to increases in automobile and sporting accidents. Over 70 percent of auto accident victims suffer head injury, resulting in many cases in permanent paralysis, impaired mental function, and epileptic seizures.

Institute scientists have shown that whiplash injuries resulting from rapid rotation of the head are more frequently produced and may have as severe effects as skull fractures. Whiplash often produces a tearing of the brain tissue and also rupture of the blood vessels inside the covering of the brain producing effects similar to stroke.

Mr. Flood. What is a whiplash?

Dr. MacNichol. Whiplash is the rapid rotation of the head such as that which occurs when the prizefighter hits another prizefighter on the chin and his head is rapidly rotated or a car is hit from behind and a person's head goes like this (snaps backward). Essentially the head rotates and the brain stands still producing a tearing action.

Mr. Flood. These new headrests are a help then on motor cars?

Dr. MacNichol. When they are properly designed.

Mr. Michel. Your response suggests they are not all properly designed.

Dr. MacNichol. I only know what I read in the papers on this.

Mr. Flood. Proceed.

Dr. MacNichol. Our scientists have not only contributed to the understanding of this type of accident but also have obtained information needed for improvement of safety devices such as helmets and headrests.

Over 100,000 persons in the Nation are paralyzed in the arms, legs or both due to spinal cord injury. In many cases the nerve fibers running down the spinal cord are not severed by the accident, but die slowly due to compression by swelling and by interference with the blood supply. Thus if the swelling and vascular damage can be minimized the victims can recover. Therefore increased research upon the acute phase of spinal cord injury is urgently needed. Indeed, the subcommittees of both the House and Senate have urged the Institute to move forward in this area.

The management of acute spinal cord injury is much more advanced in some European centers than in our country.

During 1971 the Institute funded two research centers for research and treatment of acute spinal cord injury. We are currently reviewing applications for six research grants for studies of the feasibility of establishing additional comprehensive research programs directed toward effective care of acute spinal cord injury. In 1973 we expect to make two or three of these centers fully operational.

In addition we are supporting programs of basic research on the mechanism of nerve growth and regeneration, the understanding of which may lead to a more successful treatment for spinal cord injury.

RESEARCH INTO DELAYED EFFECTS OF VIRUSES

The delayed effects of virus infection have been shown in recent years to be responsible for an increasing number of diseases. Recently Institute scientists showed that subacute sclerosing panencephalitis, a rare but inevitably fatal disease of children, is due to a virus indistinguishable from measles. This virus is activated by yet unknown factors after having lain dormant in the body for a prolonged period. Possibly multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis, parkinsonism and a variety of degenerative diseases of the nervous system may be caused by slowly acting virus infections. Some of these diseases strike young adults and produce increasing disability resulting in death after many years. Other neurological ailments render the aged incapable of caring for themselves over long periods of time.

Since 1957 the Institute's slow virus program has succeeded in transmitting two human neurological diseases to chimpanzees and from them to three species of smaller monkeys, proving without question that we are dealing with an infectious agent. Attempts are now underway to purify and isolate this agent so that means may be found to combat it.

HEREDITARY METABOLIC DISEASES

Inborn errors of metabolism identify a large group of hereditary diseases in which enzymes that cause important biochemical reactions in the body are missing.

During the past few years a group of diseases called the lipidoses have been studied intensively by our intramural scientists and grantees. In the victims of these diseases certain kinds of fatty materials accumulate, particularly in the brain, because the enzymes that normally cause them to break down are lacking. Our scientists have now identified the missing enzymes in six of these diseases, the best known of which is Tay-Sachs disease, and developed tests for carriers.

Mr. FLOOD. What is Tay-Sachs disease?

Dr. MACNICHOL. It is a disease in which certain kinds of fats accumulate in the brain. It is a hereditary disease that is most prevalent in a certain segment of the East European population. The children that have this usually die in the first few years of life. By a technique known as amniocentesis, the unborn fetus can be tested and if shown to have the disease, pregnancy can be terminated. Thus carriers of these diseases can have normal children and avoid having affected offspring.

COLLABORATIVE PERINATAL PROJECT

The collaborative perinatal project was started by NINDS over a decade ago, before there was an Institute at NIH with a primary interest in child health. Because many disorders of children such as cerebral palsy, epilepsy, mental retardation, and deafness affect the nervous system and appear to be caused by adverse factors present during pregnancy and birth, a group of farsighted medical scientists and administrators decided to do an extensive study of 58,000 pregnant women with periodic tests of their offspring through age 8 to determine the causes of abnormal development. Fourteen institutions have cooperated in this most ambitious undertaking which operates under the guidance of a central committee and 11 task forces composed of outstanding medical scientists. The more than 50,000 children in the project have been examined through age 4; 75 percent have had 7-year and 65 percent 8-year examinations.

The data collected are now undergoing intensive analyses. Some important correlations have already been established such as those between maternal weight gain, birth weight, and prematurity; and between prematurity and mental retardation. As a result some important obstetrical practices are being reviewed and new ones introduced which are sure to decrease the proportion of defective children born into the population each year. In addition to the "Core" studies made by NINDS and the collaborating institutions the data from the project are being used by investigators supported by other organizations such as the National Institute of Child Health and Human Development, the National Heart and Lung Institute, and the Office of Education.

Due to the time, effort, and cost involved (over $100 million have already been spent on the project) it is unlikely that anything like it will be repeated in the foreseeable future. Thus it is urgent that the maximum possible use be made of the data.

Through the use of these data in the ongoing analysis, it is expected that important additional insights will be gained about pregnancy factors associated with brain damage of childhood including minimal brain dysfunction and learning deficits.

BASIC NEUROSCIENCE RESEARCH

Basic research in neuroscience continues to be an essential part of both our intramural and extramural programs. Intensive directed programs in nuclear energy and space exploration appeared to be feasible at the time they were conceived and could be reasonably planed because of the advanced state of physical science upon which they were based. We do not yet have this base in bioscience on which to build revolutionary programs aimed at eradicating neurological and communicative disorders. Consequently, we must continue to support substantial efforts toward understanding the basic properties of the cells of which the nervous system is composed. The mechanisms directing their orderly growth, the ways in which they interact, the infectious agents that destroy them, and the body's defenses against these agents, are some of the important subjects needing much more investigation. Without new basic knowledge we would soon run out of ideas; further advances in the fight against neurological and communicative disorders would be greatly retarded.

In conclusion, Mr. Chairman, the budget request for 1972 is $96,521,000 as compared to the 1971 operating level of $99,482,000.

I have a number of special reports on items of particular interest which I will be glad to submit for the record if the committee wishes.

PROPOSED BUDGET CUT IN FISCAL YEAR 1972

Mr. FLOOD. Doctor, you are about as bad off as the Institute of Arthritis and Metabolic Diseases. The only program increases or decreases you have is a list of six minuses. Take a look at the bottom of page 204. You have this cryptic note: "All of the program decreases result from the need to provide funds for special scientific initiative programs." What in the world does that mean? You never wrote that.

Dr. MACNICHOL. That means certain new activities the Department and NIH decided were more important and needed to be pushed this year. And in order to push these initiatives and at the same time not contribute to inflation, and increasing the total budget, some appropriations had to be reduced.

Mr. FLOOD. That is a pretty fair statement.

RESEARCH ON LEVODOPA

Last year you talked a lot about "L-dopa." I gather from the justification that has been changed to levodopa. What is the significance of the change?

Dr. MACNICHOL. This simply is the generic term that the Food and Drug Administration has assigned to this particular drug. We are following what is now the established practice.

Mr. FLOOD. In our report of last year we indicated very clearly our hopes that you would make every effort to follow up your research on levodopa and Parkinson's disease.

What progress have you made since last year? We made quite a point of it.

Dr. MacNichol. Yes. We have a special report on Parkinson's disease if you would like to have it.

Mr. Flood. Suppose you give us a brief oral statement now.

Dr. MacNichol. Essentially there are a number of substances called enzyme inhibitors, which allow less levodopa to break down in the body so that more of it eventually gets into the brain and does its work. This allows a smaller effective dose of levodopa and apparently causes fewer side effects like nausea and vomiting.

Two of the drug firms have different inhibitors which are being tested at the present time. These look quite promising but are still controversial.

The use of levodopa has stimulated a great deal of research into just what causes Parkinson's disease, and what is the metabolic defect in the central nervous system which is overcome by the use of this compound?

SIDE EFFECTS OF LEVODOPA

Mr. Flood. What bad side effects have you had from the treatment with levodopa? We have read about it off and on during recent months. Within the last year especially.

Dr. MacNichol. There are changes in blood pressure which can be quite serious and these can be either up or down, also, nausea and vomiting which occur particularly if the dose of drug is built up too rapidly. I think one of the things that has happened since the drug has been readily available is that it hasn't been given under adequate supervision and the dosage has been built up too rapidly in some cases.

Mr. Flood. At one time it was very difficult for anybody suffering from Parkinsonism to obtain this drug. All of a sudden, as I understand, it became quite easy for them to get it. Is that a contributory factor to the sudden outbreak of fallout of bad side effects?

Dr. MacNichol. We knew about the side effects. They were recognized during the early experiments but one of the things that these investigators and particularly Dr. George Cotzias learned to do, has been to control the side effects and make them minimal by very carefully controlling the dose.

Mr. Flood. We have the impression that anybody, and I can understand why, suffering from Parkinson's disease would grasp anything and be willing to take a chance, a 100 to 1 shot. They don't care about warnings. How could they be worse, so they take a chance on anything?

Dr. MacNichol. They will take a chance on it. On the other hand if they are seriously nauseated, they tend not to take their drug. It is a question of balancing the benefit of the drug against the unpleasantness of the side effect.

The other thing that happens is that after the drug has controlled the parkinsonism for some months, some patients begin to have other difficulties which are involuntary movements. They grimace and do various other things not within their control. It doesn't bother the patient much but apparently the people who watch them think this is bad.

Mr. Flood. The average family physician diagnosing this condition can prescribe these drugs now, and they can be bought at the corner drugstore?

Dr. MacNichol. I understand that is true. The levadopa is quite widely available now and it will be a problem of educating the family physician to give it at an optimal dosage and to increase and decrease it by the right amount when various side effects are produced. They will have to be able to recognize the various factors that are required in the control of the dosage.

(The special report referred to follows:)

PARKINSON'S DISEASE

Parkinson's disease is a progressive neurological disorder affecting the brain centers responsible for control and regulation of movement. Estimates of prevalence range from one case per 1,000 to one per 200 population. Most frequently attacking people in their fifties and sixties, parkinsonism is thought to be increasing in prevalence along with the increase in the average lifespan.

	1968	1969	1970	1971 estimate	1972 estimate
NINDS research support for Parkinson's disease	$2,901,000	$2,673,000	$2,357,000	$2,552,000	$2,474,000

NATIONAL INSTITUTES OF HEALTH

(National Institute of Neurological Diseases and Stroke)

PARKINSON'S DISEASE

The three symptoms most often seen in Parkinson's disease are tremor, rigidity, and a stooping posture. The onset may be insidious, the progression of symptoms almost imperceptible—a trifling general slowness and stiffness of movement and infrequent blinking. The situation changes, however, with the development of trembling in one of the hands or arms and an increase in slowness and rigidity of movement. It is common for these early manifestations to be on one side. Intelligence is usually unaffected.

The full-blown clinical picture of Parkinson's disease is unmistakable. The parkinsonian face is a "mask" and the patient has a hard stare coming from unblinking eyes with little or no play of expression to animate his countenance. He often sits motionless, seldom or never crossing his legs or folding his arms. Willed and automatic movements are reduced in frequency and in range. This reduction in movement is best seen in small-muscle action which affects writing, speaking, eating, chewing, and swallowing.

The tremor of Parkinson's disease tends to decrease or disappear on purposeful movements; it is increased by excitement, anxiety, self-consciousness or such physical elements as fatigue or cold. Usually it disappears during sleep.

Muscular rigidity and resistance to passive movement is usually widespread, but most evident at the larger joints. Slowness of movement accompanies the rigidity. Movements become deliberate, often abbreviated, slow, and stiff. In all the acts of daily living there is a marked delay in execution. Sometimes purposeful activity comes almost to a standstill. The slow, shuffling gait of parkinsonians is highly characteristic. Balance may be difficult and patient may start to stumble forward, backward, or to either side, increasing speed as they go, and be unable to stop.

Muscle weakness may be present, but it is not weakness in the sense of hemiplegia or paraplegia. The muscles usually first and most affected are those related to quiet movements of the smaller muscles throughout the body. Writing deteriorates, becomes shaky, often smaller (micrographia) and trailing off into illegibility. Articulation becomes less distinct, its cadence is lost, the voice drops to a monotone; syllables are slurred and the ends of sentences fade into an unintelligible mutter.

In the characteristic posture of the untreated parkinsonian while standing, the trunk is bent forward giving a general impression of "over-hanging" his center

of gravity; arms are flexed at the elbow and brought together so that the hands come close to each other about the level of the waist. The hands are slightly flexed at the wrists with fingers and thumb extended. Moderate adduction of legs and a little flexion of knees complete the picture.

TREATMENT

Treatment of Parkinson's disease consists of physical therapy to help counteract the muscular rigidity, brain surgery which is now used in only a very minor percentage of cases and is effective mainly against tremor, and drugs. Recent work has indicated that depletion of substances in the brain involved in nerve transmission accompanies parkinsonism, and although the question of how this depletion occurs has not been answered, the knowledge that it does occur has led to a new and highly effective form of replacement therapy. The therapy is based on a gradual buildup to large oral doses of an amino acid, levodihydroxyphenylalanine, abbreviated "L-Dopa."

L-Dopa Therapy

The development of L-Dopa is an excellent illustration of the importance of basic biological research to medical progress. The early history of interest in the substance, dating from its synthesis in 1911, exhibited scientific curiosity with relatively little immediate clinical application. Then in the 1950's, tremendous interest in a group of neurochemical transmitter substances known as catecholamines built up, largely stimulated by the results of studies with the blood pressure lowering drug, reserpine. Contributions to the progress of this period came from a number of countries, but some of the most crucial work was done at the National Institutes of Health by Drs. Bernard Brodie, Sidney Udenfriend, Albert Sjoerdsma, and Julius Axelrod (winner of the 1970 Nobel Prize in Medicine). In the late 1950's, it was shown that reserpine, when given in heavy doses, produces symptoms similar to those of parkinsonism; that one of the amines, dopamine, exists in high concentration in certain parts of the brain; and that resperine depletes these high concentrations. The key finding making these studies (which were primarily aimed at control of blood pressure) relevant to at the University of Vienna found a marked depletion of dopamine in the basal ganglia of parkinson patients at autopsy. This clearly pointed to the possibility of replacement therapy, and brought catecholamine metabolism into the realm of clinical neurological research.

Early efforts to replace dopamine directly were unsuccessful: It was found that it would not cross the blood-brain barrier—a protective biochemical mechanism which screens substances passing from the blood into the cells of the central nervous system. Then suggestions emerged from scientists in several countries (again most prominently from laboratories of the National Heart and Lung Institute at NIH) that dopamine's metabolic precursors—preceding links in the chain of chemical reactions leading to its production—might cross the barrier. The suggestions turned out to be correct, but early trials with Dopa, dopamine's immediate precursor, were inconclusive. As it subsequently became clear, Dopa was not at first given in large enough dosage, or for sufficient periods of time, or by the best route to build up an effective and stable blood level. The first effective method for doing this was worked out by Dr. George C. Cotzias of the AEC's Brookhaven National Laboratories at Upton, Long Island. In 1966 Dr. Cotzias began preliminary trials of Dopa against both natural parkinsonism and the similar symptoms seen in South American manganese miners. He found that by starving patients on small doses and increasing the rate very slowly, he could get them to tolerate effective amounts. His work was confirmed and extended by a number of clinical groups. The largest group was headed by Dr. Melvin Yahr, Director of the NINDS-supported Parkinson's Disease Research Center at Columbia University.

On June 4, 1970, the Food and Drug Administration licensed L-Dopa for general prescription use.

L-Dopa as a Research Tool

Neurological scientists are predicting that L-Dopa's usefulness as a new research tool may turn out to be as important in the long run as its effectiveness against parkinsonism. New interest in all the neurological movement disorders has been generated, and the Institute has initiated, through grants, a number of

new projects aimed at opening up unexplored territory in the chemistry, physiology, and pharmacology of the brain. One of these is at Brookhaven National Laboratory, and is headed by Dr. George Cotzias, L-Dopa's developer. This program has two parts, experiments with animals and clinical studies in humans.

The animal work consists of studies of the gross toxicity of various agents considered for possible use in man; the breeding of strains of mice with high and low Dopa sensitivity; a search for compounds having pharmacologic and metabolic effects similar to L-Dopa; and a study of how trace metals and other biogenic amines affect the action of L-Dopa itself. Dr. Cotzias has found that one genetic strain of mice does not absorb manganese efficiently, and also is highly resistant to the toxicity of Dopa. This relationship is of particular interest because as Dr. Cotzias observed several years ago, the effects of manganese poisoning in humans closely resemble the symptoms of Parkinson's disease.

The investigators are also working with several groups of patients, one with Parkinson's disease and another with such movement disorders as dystonia, Wilson's disease, and Huntington's chorea. Long-term evaluations of L-Dopa in all of these disorders are in progress, and the effects of other drugs which may enhance L-Dopa therapy are being studied. Dr. Cotzias and his group are also searching for a possible role of trace metals in human movement disorders, and plan to attempt visualization of radioactivity labeled L-Dopa in intracerebral structures.

In another new Institute-supported program, headed by Dr. Norman Weiner at the University of Colorado Medical Center, a broad-scale clinical and laboratory investigation of L-Dopa metabolism in man, tied in with a series of studies in both animals and man of the biochemistry, cell biology, and experimental pathology of the extra-pyramidal system in relation to movement disorders is underway. One of the highlights of this program is a double-blind 3-year study of 50 patients with Parkinson's disease randomized for treatment with either L-Dopa or earlier antiparkinson drugs. Catecholamine metabolism in these patients is being analyzed by monitoring levels of some 20 metabolites in sequential samples of urine and spinal fluid. Psychiatric and psychometric analyses are being correlated with the metabolic studies.

Another important part of the Colorado program is a study of the electrical activity of the peripheral nervous system and muscle in parkinsonism. The investigators are using needle electrodes and recording devices to search for histochemical and electrical differences in different types of muscle fibers, with a view toward discovering changes induced by parkinsonism, and also to note differences, if any, induced by long-continued doses of L-Dopa. They have noted abnormal muscle biopsies in 80 percent of enduring cases of parkinsonism, and believe that most of the changes which take place in parkinsonism are in the fast phasic muscles rather than in slow tonic ones.

One of the most serious problems in L-Dopa therapy is that the doses necessary to produce the desired effects are so large that they also frequently produce severe, although reversible, side effects, such as nausea, vomiting, and involuntary movements. The standardized treatment procedure used in early studies and continued by clinical experience entails starting with small doses and increasing them very gradually until side effects begin to appear. An acceptable balance is then attempted between relief from the parkinson symptoms and discomfort from the side effects. The problem stems, at least in part, from the blood-brain barrier, which can be overcome only by saturation of the body with massive doses. Small amounts of L-Dopa are metabolized so quickly into dopamine (which will not cross the barrier) that adequate penetration does not take place. A major experimental approach to this problem, being pursued in Switzerland, Canada, and at several institutions in this country, including the National Institute of Mental Health, is through use of enzyme inhibitors, which slow the process, thus allowing greater penetration, and smaller doses.

In one NINDS-supported project at the University of Chicago, animals are being given several inhibitors together with L-Dopa; a single inhibitor with L-Dopa; and only L-Dopa in a control group. Fluorescence techniques are being used to measure penetration. Also being studied are the effects of inhibitors on animals in which experimental tremor has been induced with reserpine, and the effects of dimethyl sulfoxide when used as a chemical transport carrier of Dopa molecules.

Surgery

Although L-Dopa has materially reduced the indications for surgery in parkinsonism, they have not been entirely eliminated. The compound is most effective against the rigidity and slowness of movement caused by parkinsonism, and the percentage of good results with tremor is much lower. Thalamic surgery, in which a tiny area of the brain where the tremors originate is inactivated by heat, freezing, or other methods, is most effective against the tremor, and less so against the other two principal symptoms. NINDS neurosurgeons reported this year that their follow-up studies have shown that the chance of abolishing tremor with surgery is on the order of 80 to 90 percent.

EPIDEMIOLOGY

The epidemiology, genetics, and natural history of parkinson's disease are allied areas of active research interest. An important new question in this field is whether L-Dopa affects the natural history of parkinson's disease, or is merely symptomatic treatment. NINDS scientists, in cooperation with the National Parkinson Foundation in Miami, are collecting data on patients who had Parkinson's disease between 1962 and 1964 to determine life expectancy and specific cause of death. They plan to match these data with identical data on a series of patients who have recevied L-Dopa, in the hope of throwing light on whether it slows the progression of the disease.

In another study, Institute scientists are reviewing records of members of the Curch of Jesus Christ or Latter Day Saints in Salt Lake City who died with the diagnosis of Parkinson's disease between 1930 and 1940, and checking incidence among their descendants. This group is particularly valuable for such a study because it mains accurate, up-to-date genealogies.

OUTLOOK

The causes and methods of prevention and cure of parkinson's disease are still unknown. However, research offers exciting possibilities toward understanding the pathophysiology of the disease and revealing clues to its etiology and prevention. For the first time an effective treatment for the disease has been found. Gains made thus far, together with expected developments in the near future, have justified a more optimistic attitude among scientists, physicians, and patients, that control of this disabling disease can be achieved.

INSTITUTE WORK ON SPINAL CORD INJURIES

Mr. FLOOD. Both this committee and the Senate committee you will recall have had a strong interest in research on the problems connected with acute spinal cord injuries. This committee and the Senate have evinced special interest in this. What do you have to tell us about that?

Dr. MACNICHOL. In 1971, we funded two grants for spinal cord injury research. At the present time we are negotiating with a number of organizations to set up six studies to find out whether or not it is feasible to set up large-scale spinal cord injury research centers.

Mr. FLOOD. Why should there be any doubt about it?

Dr. MACNICHOL. There is a question. We are not sure in just what direction the research ought to go and what factors ought to be examined first. Before we fund any large grants, we want prospective grantees to spell out what they would do with the money.

To learn more about the problem, our associate director for extramural programs is now in England and Scotland to make a study of their system of acute spinal cord care which we hear is very good.

Mr. FLOOD. What reason could you give for their advanced experimentation and knowledge and research in these areas as contrasted

with ours? You would think ours would be much more advanced, with particular reference to spinal cord injury.

Dr. MacNichol. I think the advantage there may be largely due to the British coordinated health care system where they get the people under treatment rapidly. It is a small country so they can have relatively few good centers to which they can get people quickly and then take care of them during the early critical phases of the injury.

Mr. Flood. Where do they do the best work, England?

Dr. MacNichol. England I understand is very good. I understand they also do well in the Scandanavian countries and Germany, but I don't have as much information.

COLLABORATIVE PERINATAL PROJECT

Mr. Flood. We have talked about your collaborative perinatal project for over 10 long years. How much is budgeted for this in 1971 and 1972?

Dr. MacNichol. We have budgeted $7,660,000 in 1971 and that is to be decreased to $5,560,000 in 1972.

Mr. Flood. How much have you spent on this project since it was initiated?

Dr. MacNichol. About $100 million. This is a very ambitious and very large-scale study.

Mr. Flood. Yes, it is.

Dr. MacNichol. It is the type of study required this time because the children have to be followed practically from the time of conception up until they are 8 years old when a lot of learning disabilities and speech disorders begin to become apparent.

Mr. Flood. Suppose you give us a few of the worthwhile findings now and then place in the record something more to support this expenditure and your belief in the importance of the project. Tell us a few of the things now and then; beef up the record.

Dr. MacNichol. I have a special report on the project.

Mr. Flood. Suppose you highlight it for us now.

Dr. MacNichol. I think probably one of the most important things to come out have been the findings that viruses which were considered relatively harmless, such as herpes virus, do produce a significant number of fetal abnormalities when the pregnant mother becomes infected and passes it on to the unborn child.

Mr. Flood. Infected with what?

Dr. MacNichol. With these ordinarily rather harmless viruses. Herpes viruses. It is similar to the cold sore virus. The recognition that German measles is not just dangerous during the first three months of pregnancy, but that it can cause trouble if it is contracted before conception until any time during the second or third months of pregnancy,

helped top ut a lot of steam behind the rubella immunization program.

(The special report referred to follows:)

THE COLLABORATIVE PERINATAL STUDY—60,000 PREGNANCIES

CONTRIBUTIONS OF THE STUDY

It is estimated that 20 million Americans are afflicted with neurologic abnormalities, three-fourths of which had their origin in injury or disease occurring during the perinatal period (from conception to 28 days after birth). In addition, the United States ranks 13th in the world for deaths of the newborn, many of them due to severe forms of neurologic disorders.

One of the most important contributions made by the study in the prevention of neurological damage has been its role in providing impetus to the campaign to develop a rubella vaccine. Fetal malformation was suspected to be related to infection of the mother with rubella in the first 3 months of pregnancy, but the study showed that rubella threatens the fetus from 2 months prior to conception and during the second 3 months of pregnancy. This extension of the risk of the infection spurred on the campaign to wipe out rubella.

The study has also shown, among other things, that certain viruses in the mother, once thought to be harmless, can lead to neurological damage in the newborn; that several drugs when taken during pregnancy can cause congenital malformations and stillbirth; that the maternal weight gain during pregnancy can have a significant effect on the birthweight of the infant and his development; that a lack of oxygen any time during fetal development plays a major role in causing cerebral palsy; and that diabetes in pregnancy is related to the frequency of congenital malformations in the offspring.

THE SCOPE OF THE STUDY

Groundwork for the collaborative perintal study was begun in 1952 when a planning group met to organize collaborating institutions (see attachment No. 1) with investigators from many disciplines under NINDS as a coordinating center and central laboratory.

The goal of the project was to monitor a group of women during their pregnancy, labor, and delivery and to relate various factors present to the outcome of the pregnancy and the future development of the children, especially concentrating on neurological damage.

In order to carry out this vast task, the planners decided that a study of very large dimension—60,000 pregnancies—was essential for statistical validity. The large number of mother-child pairs was necessary because of the relative infrequency of some of the neurological abnormalities and the complex nature of causal relationships.

After a pretest period of about 18 months, the study was officially begun in January 1959 with the registration of the first pregnant woman. On each of the pregnant women to enter the program, information was gathered about past history, socioeconomic background, obstetric course, and all medication, drugs, and vaccines given to the mother. Blood serum specimens were collected routinely to monitor possible occurrence of viral and other infection during pregnancy and events during labor and delivery were recorded.

Thus, throughout the timespan of the study, the lives of about 100,000 U.S. citizens (the mothers and their children, 45 percent white, 45 percent Negro, and 10 percent Puerto Ricans, American Indians, and Orientals) from many States have been under continuous investigation for over 10 years by hundreds of specialists in 36 professional disciplines working within 39 universities from 25 States. While there is a wide range of social background in the study population, there is a concentration of women in the poorer, high-risk levels of society, as might be expected of women seeking obstetric care in university medical centers.

The cost to the Federal budget during a decade of operation has been approximately $100 per year per person. The total therefore is $100 million. Through fiscal year 1974 approximately $20 million will be needed to successfully com-

plete the planned data collection and to continue comprehensive analysis of the current phase.

After a 7-year period during which women entered the study, the intake was terminated on December 31, 1965, when the goal of 60,000 pregnancies had been enrolled. The last delivery took place in September 1966, and the examination schedule of the children will be completed by September 1974 when the last child born in 1966 has an 8-year speech, language, and hearing examination.

The project children have been intensively studied in hospital nurseries, at 4 months (pediatric exam), 8 months (developmental exam), 12 months (pediatric-neurologic exam), 36 months (language, hearing and speech), 48 months (psychometric), 7 years (neurologic, psychologic, vision screening), and 8 years (language, hearing, and speech including evaluation of reading skills). Measurements of physical growth and medical history of illness and accident have been collected at each interval (see attachment No. 2).

CURRENT STATUS OF THE STUDY

While the 4-year examinations have been completed on all available children, about one-third of the 7-year neurologic and psychologic test batteries, and one-third of the 8-year language, hearing, and speech evaluations remain to be completed. These examinations are particularly important, because it is at these ages, when the children are in school, that the milder degrees of mental retardation can be recognized, and the presence of learning disabilities, particularly dyslexia, can be evaluated.

Data collection is nearing completion. The last children will reach 8 years of age in late 1974. While the data base is not yet complete, analysis of the very large volume of data already in hand is well underway, under the direction of a number of small task force committees of specialists (see attachment No. 3). Two review committees appointed by the Director, NIH, have examined the study and found the data base not only adequate for the task but in many respects unique. The data bank is generally recognized to be unique in the world by those scientists familiar with its breadth and completeness.

DATA ANALYSIS

The huge reservoir of information collected contains statistical data on punch cards and magnetic tapes and includes, in addition, 300,000 blood specimens; and from autopsy material, 1,000 brain specimens, 400 infant specimens and 60,000 microscopic slides. Several hundred scientific articles have been published and a systematic and comprehensive analysis of the data is in process by 12 task forces.

The first major publication is a 500-page monograph called "The Collaborative perinatal Study: The Women and their Pregnancies" which describes the women in the study and the outcome of their pregnancies.

The second major publication, entitled "The Collaborative Perinatal Study: The First Year of Life" describes the infants, their nursery course, and outcome through 1 year. These unique pediatric data have been assembled, the analyses are complete, and the manuscript should be completed within the next 3 months.

While essentially descriptive, these two volumes point out many areas for further analysis, and some areas for public health action and program development.

Some 500 individual scientific papers have been published by staff members of the collaborating institutions and the NINDS staff (see attachment 4), but major publications addressed to the basic goals of the study have had to wait for completion of the data base.

PROMISING LEADS FOR THE FUTURE

The availability of this valuable data and the unique study population has opened up many opportunities for further investigation. An outline of anticipated studies follows:

I. *"Repeat" pregnancies in the study.*—There are about 7,000 women who had two or more pregnancies while participating in the study. These women and their babies offer a rich source of investigation because the woman now serves as her own control. That is, events surrounding the first pragnancy and birth

can be compared with events surrounding the second pregnancy and its outcome and these can be later related to the children's development.

II. *Opportunities for special studies.*—The following are a number of studies based on leads already evident from analyses of core data from the project.

1. The relationship between maternal weight gain during pregnancy and the weight of the baby is to be investigated by a primate nutrition study now under development jointly with the National Institute of Child Health and Human Development (NICHD). This study in monkeys will provide an animal model for studying the effect of nutrition on birth, growth, and development.

2. The relationship of spastic diplegia (weaknes and stiffness of both legs) to short period of development within the uterus or to true prematurity, editorialized in the Journal of Developmental Medicine and Child Neurology (April 1970, vol. 12, No. 2) is a new finding awaiting further exploration by additional studies on available brain specimens as well as by additional studies in neurochemistry.

3. The relationship of maternal factors, such as diabetes and acetonuria (an excess of acetone in the urine which occurs both in diabetes and in digestive disorders) to intelligence is an exciting new lead warranting considerable exploration and expansion.

4. Controlled clinical trials of the relationship between infection in the newborn and mode of delivery are needed to ascertain whether or not Caesarean section would prevent, for example, an infection in the newborn due to a type of virus called herpes.

5. The relationship of maternal factors such as proteinuria (an excess or protein in the urine) to intelligence is an exciting new lead derived from the project. This study, which attempts to correlate blood chemistry with I.Q., awaits further analyses of blood sera collected from the mothers for amino acid determinations.

6. The relationship of estrogen therapy during pregnancy to the development of congenital heart diseases, such as transposition of the heart vessels, in the child is of interest. In cooperation with the National Heart and Lung Institute (NHLI), the unique reservoir of information available in the project on congenital heart diseases has revealed for the first time incidence figures on large samples of blacks and whites, as well as information on the natural history of conkenital heart disease.

7. The relationship between maternal diabetes and congenital heart disease in the offspring is an exiciting finding which points to a risk factor that warrants further exploration to guide preventive action.

8. An exploration of the possibility of identifying a third type of twinning, in addition to the fraternal twin and the identical twin, would be a fruitful area of research.

Scientists outside of the project, recognizing the value of data gathered and the unique study population available, have interest in the following investigations using project data:

(*a*) A study is being designed that will investigate differences among ethnic groups in the study population, with intent to establish an ethnicity index based on blood type and other physical characteristics.

(*b*) A study is now being designed in cooperation with NICHD and five of the collaborating institutions to investigate chromosomal abberations at the final 7- and 8-year examinations.

(*c*) A study is now under development at the Johns Hopkins University and the University of Buffalo to follow-up the study populations through age 12 to investigate learning disabilities.

(*d*) A study is being jointly planned with NICHD to investigate the effect of birth control pills on pregnancy outcome using the 7-year old study population.

(*e*) In cooperation with the Office of Education and the collaborating institutions at Minnesota and Oregon, learning disabilities in the elementary school population are being investigated and correlated with antecedent information available in the project.

(*f*) In cooperation with Tufts Medical School and MIT Computer Facility, studies on the effects of drugs taken during pregnancy on congenital malformations in the offspring, are currently undergoing intensive investigation.

(*g*) A request by an eminent geneticist is currently being considered to collect dental cast impressions on the 7 year olds in the study with a view to

assess the timing of the occurrence of an insult while the child is in the uterus and its correlation with a specific disorder which may affect the child later.

(*h*) The study of the unique population of 615 pairs of twins through age 15 or onset of puberty has been proposed and would be expected to yield important information about maturation.

(*i*) The evaluation of a socio-economic index to be used to predict specific diseases which may affect a child in later life has been proposed. Such an index would relate socio-economic status with subsequent diseases and disorders.

(*j*) NICHD expects to explore the utility of maternal blood samples in checking the possible correlation of maternal-nutritional inadequacy based on the indirect parameters such as weight, height, weight gain in pregnancy, and possibly iron levels with various hormonal measures. They plan to use blood serum samples collected on the mothers in the study population.

(*k*) Harvard and MIT investigators expect to study the utility of cord blood samples to document differences, if any, in levels of various pollutants and possible relationships with differences in child outcome or behavior.

The above examples demonstrate the wealth and potential of this study. Numerous additional leads are anticipated when all the task forces have completed their data analysis.

III. *Followup of Special Groups of Children.*—The followup until adolescence or beyond of special groups of children identified in the study could be of major importance. These groups are unique in the world in the wealth and detail of the prospective information available about them. Four of many possible examples are given below:

1. The twins.—Some 620 pairs were born to study mothers, approximately half to black mothers, providing an invaluable study population.

2. The children with congenital heart disease.—Some 457 such children have already been identified and are being followed in collaboration with the National Heart and Lung Institute. This group offers a unique opportunity to study the causes and evolution of this important condition.

3. The children with minimal cerebral dysfunction (minimal brain dysfunction) and learning disabilities.—The frequency in middle and upper class white patients of these disorders is estimated to be 5 to 10 percent. Incidence may be as high as 30 percent in "inner city" children, both black and white. An indepth study permitting comparison of upper middle class children in the Buffalo sample with "inner city" black and white children in The Johns Hopkins sample would yield valuable information.

4. Children with seizures (epilepsy).—Numerous studies of great importance could be carried out on the children in the study who have developed epilepsy.

[Attachment No. 1]

COLLABORATING INSTITUTIONS

Some 14 medical institutions in different parts of the United States became participants in the Collaborative Perinatal Project; these included:

Boston Lying-In Hospital,
Boston, Mass.
Brown University,
Providence, R.I.
Charity Hospital of Louisiana,
New Orleans, La.
Children's Hospital of Buffalo,
Buffalo, N.Y.
Children's Hospital of Philadelphia,
Philadelphia, Pa.
Children's Medical Center,
Boston, Mass.
Columbia University,
New York, N.Y.
Johns Hopkins University,
Baltimore, Md.
Medical College of Virginia,
Richmond, Va.
New York Medical College,
New York, N.Y.
Pennsylvania Hospital,
Philadelphia, Pa.
University of Minnesota,
Minneapolis, Minn.
University of Oregon,
Portland, Oreg.
University of Tennessee,
Memphis, Tenn.

[Attachment No. 2]

DATA GATHERED ON STUDY POPULATION

To accumulate the needed research information for the study, pregnant women, as they registered for prenatal care in the collaborating hospitals, were selected at random to participate in the program. Information was recorded concerning their past medical history, family medical history, and factors concerning socioeconomics. As the woman progressed through pregnancy, detailed records were kept of her condition at labor and delivery, and independent observers recorded detailed information regarding her progress, noting problems and difficulties. The newborns were closely observed in the first few minutes of life and were given pediatric and neurological examinations in the newborn period. Additional evaluation included a 4-month pediatric examination, an 8-month examination of mental and motor development (Bayley Infant Scale), a 1-year neurological examination, a 3-year speech, language, and hearing evaluation, a 4-year psychological examination (Stanford-Binet, Test, fine and gross motor evaluation, block sort test and behavioral profile), a 7-year neurological evaluation, 7-year psychological evaluation (Wisc, Bender Gestalt, Goodenough-Harris Draw-A-Person, Wrat, etc.), and an 8-year speech, language and hearing test.

Stillbirths and neonatal deaths at autopsy were examined uniformly. Blocks of certain tissues were sent to a central laboratory as were brain tissue specimens.

Serum samples were also collected during pregnancy and at birth to determine antibody response to infectious disease agents, primarily viruses, which infected the women and which might cause deficits in the offspring.

[Attachment No. 3]

TASK FORCES FOR DATA ANALYSIS

Special ad hoc task forces of investigators from the Perinatal Research Branch, the collaborating and other institutions are now systematically pursuing the further analysis of data accumulated by this project in 10 significant major areas of concern. These are:

(1) *Labor and delivery*—This group is analyzing the characteristics of labor and delivery and its complications in relationship to perinatal loss, child development, and neurological and intellectual deficits.

(2) *Infectious diseases*—The main objective here is the investigation of the role infectious agents, particularly viruses occurring in pregnancy and during the perinatal period, play in fetal death and subsequent child development.

(3) *Genetics and congenital malformations*—The focus of this task force is to investigate how genetic factors are related to human development and especially neurological and intellectual deficits. Further, this group is assimilating information regarding cogenital malformation and its distribution in the population.

(4) *Drugs in pregnancy*—This group studies the large number of drugs that are taken by women during pregnancy to explore whether these relate to any observed differences in fetal outcome including congenital malformations and subsequent child development.

(5) *One-Year task force*—The concern of this group is the analysis of prenatal and perinatal factors related to neurological abnormalities identified in 1-year-old children.

(6) *Four- and seven-year task force*—Their objective is the analysis of pre- and perinatal factors related to neurological and intellectual deficits identified from 4 to 7 years of age.

(7) *Three- and eight-year speech, language and hearing task force*—This group is concerned with analysis of pre- and perinatal factors related to speech, language and hearing performance as judged in 3-year-olds, and then again in 8-year-old children.

(8) *Physical growth*—This task force is concerned with the development of physical growth profiles based on physical measurements obtained on collaborative study children from birth on through age 8. Further, the group is looking at physical growth characteristics and many developmental characteristics in children as they differ by socioeconomic background.

(9) *Toxemia*—This task force is concerned with the evaluation of the utility of the clinical signs and symptoms which are part of the toxemia complex and its significance in perinatal mortality and prematurity.

(10) *Pathology task force*—This task force is concerned with the analysis of the brain specimens from children dying during the perinatal period to get insight into the kind and frequency of apparent brain injury identified from postmortem examination.

[Attachment No. 4]

PUBLISHED DATA ANALYSIS

The data analysis has, in general, taken three approaches. One approach is the comparison of outcome characteristics of children of women with specific complications, to outcome characteristics of children from women without these complications using the total population. The second approach is the prospective matched-case approach, in which child characteristics of women with a specific complication, are compared to those of women without this complication, matching on variables such as institution of birth, race, socioeconomic class, and certain other characteristics. Third is the retrospective approach, looking for differences in prenatal characteristics in children with a common deficit matched to a group of children without this deficit.

Obstetrical Factors

Obstetrical factors which have been investigated in relation to neurological abnormalities observed during the first year of life, include maternal organic heart disease (Niswander et al., 1967; Niswander and Berendes, 1968), abruptio placentae (Niswander et al., 1966a), placenta previa (Niswander et al., 1966b), rupture of the marginal sinus (Niswander et al., 1968), prolapse of the umbilical cord (Niswander et al., 1966c, d), other umbilical cord complications (Spellacy et al., 1966), uterine dysfunction and dystocia (Vosburgh et al., 1966). Many of these conditions are associated with an increased perinatal mortality and prematurity rate and a lowering of Apgar scores (a numerical expression of the condition of a newborn) at 1 and 5 minutes. Only small differences were seen in neurological abnormalities at 1 year in these groups as compared to children from the remaining population whose mothers did not have these complications in pregnancy. Where a difference existed, pointing to an increase in neurological abnormalities at 1 year, it disappeared when birth weight was added as a control variable, suggesting that the increase in neurological abnormalities observed at least through 1 year of age is due to an increase in low birth weight children.

Fetal Distress

Clinical fetal distress, defined as depression of the fetal heart below 100 beats per minute during labor, has also been explored as a factor in neurological and mental deficits. The analysis showed the expected strong association with neonatal mortality and depression of 1- and 5-minute Apgar scores consistent by birth weight (Benson et al., 1968). Children with low fetal heart rates during labor exhibited some delay in motor development, and a small increase in certain neurological abnormalities. Adjusting for ethnic and socioeconomic effects, no difference in intelligence as measured at 4 years was seen between these children and the rest of the study population (Berendes, 1968).

Late Prenatal Complications

In addition, comparisons were made between children of women with premature separation of the placenta, placenta previa, marginal sinus rupture, and prolapsed cord, and a group of children from women without these complications matched by institution of birth, race of mother, socioeconomic class, sex of child, and birthweight of child. The observed difference in mean IQ., which was not significant, was 3 points (Beredes, 1968).

Newborn Characteristics

Several neonatal characteristics have been studied. These include birth weight and sex of the child, and Apgar ratings.

The known strong association between neurological disease, low Apgar score and birth weight was confirmed, the lowest birth weight group revealing the highest proportion of neurological abnormalities at 1 year (Drage, et al., 1966). A marked sex difference exists (Singer et al., 1968). Almost invariable, males

show a higher proportion of abnormalities at 1 year, lower performance in mental and motor development at 8 months, or lower intelligence as measured at 4 years of age.

One- and five-minute Apgar scores relate strongly to neonatal mortality (Drage et al., 1964). There is also an increase in neurological morbidity at 1 year for children with low 1- or 5-minute Apgar scores (Drage et al., 1966; Drage and Berendes, 1966). Better differentiation is seen using the 5-minute rather than 1-minute Apgar scores.

Recently, the relationship of Apgar scores to 4-year performance including I.Q. was explored. No consistent differences in intelligence scores were observed by Apgar scores when adjustments are made for ethnic, social, and birthweight effects (Drage et al., 1969).

Cerebral Palsy

A preliminary retrospective analysis was made of a group of children with cerebral palsy matched by institution of birth, race, maternal education, sex, and birthweight to normal children. For these two groups the presence of clinical signs of fetal distress (fetal heart rate depression, meconium staining) and low 1- and 5-minute Apgars were tabulated. Eighteen of 61 children with cerebral palsy and 10 of 61 control children had one or more signs of distress. While the number of cases in specific diagnostic sub-groups was small, the observed difference appears to be due largely to an increase of distress in children with spastic diplegia and possibly complex diplegia (Berendes, 1968).

Maternal Dibaetes

Several prenatal characteristics have been studied in relation to intelligence of 4-year-old children, utilizing the matched case approach. A significant lowering of intelligence was found among the offspring of diabetic women compared to matched controls (Churchill et al., 1969). Further analysis of these data revealed that this relationship only held for children of diabetic women who had experienced episodes of acidosis or acetonuria during pregnancy. This association was consistent whether diabetes was of long duration or only recently diagnosed. This led to the study of the relationship of I.Q. of children of non-diabetic women who had episodes of acetonuria in pregnancy. Such episodes of acetonuria are seen at times in women because of febrile illnesses associated with vomiting, possibly in a marginally nourished individual or in vomiting associated with hyperemesis gravidarum. Lowering of I.Q. was seen in children of women experiencing one or more episodes of acetonuria in pregnancy as compared to controls. These I.Q. differences were consistent by race. The I.Q. differences were greater when acetonuria was observed in the third trimester rather than the first or second trimester (Churchill and Berendes, 1969). This latter observation is to be taken with some reservations since the measurement of acetone excretion in urine was not routine in this program, thus raising the possibility of bias.

Pregnancy Interval

Also of interest are the results of an investigation of the relationship of the pregnancy interval to intelligence in the offspring. This investgation was carried out by comparing children born within a year of the previous child to children born 3 to 5 years apart. Children from the short interval group had significantly lower intelligence at 4 years. Most of the I.Q. difference appeared to be due to the smaller size of the children of the short-interval group (Holley et al., 1969).

Congenital Malformation

Differences in the frequency of certain congenital malformations have been observed between whites and blacks (Chung and Myrianthopoulos, 1968). Anencephaly is several times more frequent in whites, as is cleft lip with or without cleft palate. There is also an increase of syndactyly in whites. Polydactyly is observed many times more often in black babies. Common minor malformations among blacks are preauricular sinus, cleft gum, and supernumerary nipples.

On initial analysis, the congenital malformation rate appears to be higher in black children than white children from the Collaborative Project. Among 19,961 white newborns the malformation rate was 2.7 percent and in 20,899 blacks 5.8 percent. This difference is accounted for almost entirely by the increased frequency of polydactyly, supernumerary nipples and small branchial

clefts in black children. When these malformations are ignored, the malformation rate drops in whites to 2.5 percent and in blacks to 2.3 percent.

Not included in this tabulation was the presence of only one umbilical artery. In a preliminary analysis of a sample of cases, a single umbilical artery was found in .76 percent of all cases (Froehlich and Fujikura, 1966). In whites this malformation was seen in 1.2 percent of the cases and in 4 percent of blacks. Single umbilical artery was seen more frequently in children weighing 2,000 grams than in those weighing more than 2,000 grams. It is relevant to mention the increased frequency of single umbilical artery in children of diabetic mothers (Froehlich and Fujikura, 1966).

Problems ascertaining certain malformations at birth are well recognized. Congenital heart disease, for example, is reported with a frequency of 2.5 per thousand at birth. As the child grows older, the heart malformation may manifest symptoms or additional examinations allow its identification so that with longer followup the incidence of congenital heart disease in our population is 8.2 per thousand (Mitchell, 1971).

Of the prenatal factors examined, only the occurrence of diabetes in pregnancy seems to be related to the frequency of congenital malformations in the offspring. This difference is due primarily to an increase in congenital heart disease (Chung and Myrianthopoulos, 1968).

Comparisons have been made of the frequency of antibody titer changes to several viral antigens for children with congenital malformations of the central nervous system, drawn from stillbirths, neonatal and infant deaths, which had come to autopsy and matched controls. No significant differences were seen in antibody titer changes to 16 viral antigens between the subject and control groups (Elizan et al., 1969). The relatively small number of cases made it impossible to analyze these data by specific malformation.

RUBELLA VACCINATION PROGRAM

Mr. FLOOD. Have you gotten much fallout from the rubella vaccination program?

Dr. MACNICHOL. The vaccine, if given to women when they were about to conceive children, might be dangerous to them. I think Dr. Davis can probably tell you more about this.

Mr. FLOOD. How about the vaccine with reference to children themselves?

Dr. MACNICHOLS. So far as I know, it is not injurious if given to children. In fact, this is the time to give it.

Mr. FLOOD. Up until what age?

Mr. MACNICHOL. I think up until girls reach childbearing age.

Mr. FLOOD. Do they take in age brackets that far up?

Dr. MACNICHOL. I am afraid I have no information on that.

Mr. FLOOD. You might find out about that.

Dr. MACNICHOL. I will be glad to.

Mr. FLOOD. Then if you have any other illustrations besides those two or three you can include those in the record.

Dr. MACNICHOL. All right, sir.

(The information follows:)

To date, more than 19 million doses of rubella vaccine have been given. On the recommendation of experts, the rubella vaccine is being given, in this country, to girls and boys between 1 and 12 years of age since these children are the major source of virus dissemination in the community. Women of child-bearing age are considered for vaccination on an individual basis if the possibility of pregnancy in the following 2 months can be avoided. The immune status of a woman should be determined by performing a rubella hemagglutination-inhibition (HI) test.

BREAKTHROUGHS IN TREATMENT OF STROKES

Mr. FLOOD. You mentioned stroke in passing in your principal statement. Do you want to tell us anything more about stroke now? We will, of course, place the special statement on stroke in the record.

Dr. MACNICHOL. There isn't anything in the way of a major breakthrough at the present time.

Mr. FLOOD. What would you break through?

Dr. MACNICHOL. One would want to find out first of all how to prevent blood vessels in the body anywhere, and particularly in the brain, from getting plugged up. One would want to find out what it is that causes blood vessels to burst; one would want to know if there is anything to stop aneurysms from occurring.

STROKE IN YOUNG PERSONS

Mr. FLOOD. Lately we have discovered that this condition of the blood vessel affects very young people instead of just older people. Why would that be? We had the impression for years that this was connected with age and while that is true there is also a danger in young people. Why? It is not the same reasons, is it?

Dr. MACNICHOL. Most degenerative changes start early and get worse throughout life and it is just a question, I believe, of their being more rapid in some individuals than others and may be accelerated by factors such as the wrong kinds of diets, lack of exercise and various other environmental factors.

Mr. FLOOD. There is more to it than that, isn't there?

Dr. MACNICHOL. There is, of course, the problem of congenital weaknesses in certain spots along cerebral arteries. These inherited defects can become aneurysm sites even in the fairly young. We do not at this point know where they originate.

(The special statement referred to follows:)

STROKE

Stroke (cerebrovascular disease) ranks third among causes of death in the United States, exceeded only by heart disease and cancer. In 1965, 201,000 Americans were reported to have died of stroke, and another 200,000 had stroke listed as a contributory cause on their death certificates. In addition stroke often incapacitates those it does not kill. It is estimated that there are 2 million victims of stroke alive today, one-third of whom were wage earners at the time they were stricken. The economic cost of stroke was estimated in 1962 at more than $1 billion a year—$440 million for direct costs of medical care, and $700 million, or 179 million man-hours, in lost productivity. Today, these figures may be doubled. There are thus immense benefits to be achieved through research in this field—in both dollar and immeasurable human factors.

	1968	1969	1970	1971 estimate	1972 estimate
NINDS research support for stroke (cerebrovascular disease)	$4,987,000	$5,899,000	$5,109,000	$6,004,000	$5,975,000

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE

STROKE

The term "stroke" refers to a sudden loss of brain function resulting from interference with the blood supply to the brain. Strokes range in severity from minor episodes with transient neurological deficit to those causing death within a few minutes. Usually, they are brought on by one of three events: thrombosis—a clot developing within a blood vessel of the brain or a neck artery; 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 hemorrhage—the rupture of a cerebral blood vessel with bleeding into the brain tissue.

All brain cells require oxygen and glucose and they receive their supply entirely from the blood stream. The need for an adequate blood supply to the brain is demonstrated by the fact that although the brain comprises only 2 percent of the total body weight, it normally uses 20 percent of the total oxygen supply of the body. Brain tissue cannot store oxygen, and is completely dependent from minute to minute on an adequate flow of blood. When brain tissue is deprived of oxygen for more than a few minutes, cells begin to die rapidly, and temporary or permanent paralysis of movement, thought, speech, or sensation is the result.

Although the immediate cause of stroke often can be explained simply as obstruction of the blood flow to the brain, the condition presents an extremely complex set of medical, scientific, and technical problems. Scientists representing at least a dozen branches of biology and experimental medicine, as well as physicians skilled in clinical practice, must work closely together to better understand the way the brain cells receive nutrition, the dynamics of blood flow in the brain, the effects of drugs, and many other processes.

THE PROGRAM

Stroke research centers

A team approach to the clinical and fundamental problems of cerebrovascular disease has been a growing trend in recent years. The Institute has sought to encourage this by grant support of multidisciplinary clinical research centers in universities and hospitals. Seventeen of these centers are now active, some staffed by as many as 15 to 20 scientists and physicians, plus technicians and other assistants. The centers vary in their emphasis. Several concentrate on a single broad research approach, as at The Johns Hopkins University, where the epidemiological aspects of stroke are being studied. These include incidence and prevalence, methods for early detection of "high risk" segments of the population, familial aggregation of stroke cases, and similar problems. A center at Boston University concentrates on aphasia—a speech and language disorder which sometimes follows stroke.

Other centers are broader in focus, often working with several related approaches, such as the physical dynamics of cerebral blood flow, metabolism of brain cells, and efforts to control these factors with drugs, inhaled gases, and other means. All centers, except two devoted to epidemiology, have interrelated clinical and basic research programs, and have accommodations for up to 30 research patients. Most also conduct training programs for the younger physicians, scientists, and other staff members.

Project grants

In addition to the targeted efforts of the cerebrovascular clinical and epidemiological research centers, about 60 research projects are being conducted with Institute support. These projects, conducted by much smaller groups, or even single investigators, range from basic laboratory studies in such fields as neurophysiology and biochemistry to clinical investigations of drug effectiveness, the improvement of diagnostic devices and techniques, and development of improved surgical approaches. Also in progress are several large cooperative studies to evaluate effectiveness of various medical and surgical procedures.

Training

Since its establishment in 1950, the National Institute of Nurological Diseases and Stroke has allocated about 25 percent of its budget to training support for teaching and research careers in all the various disciplines within its area of responsibility. The Institute is now funding four stroke training grants at leading universities and hospitals, and is also providing direct stipend support to individuals under a program of special fellowships and research career development awards.

Joint Council Subcommittee on Cerebrovascular Disease

The team approach is also important in the process of stimulating and coordinating the total national effort against cerebrovascular disease (CVD). The Joint Council Subcommittee on Cerebrovascular Disease, composed of members of the National Advisory Councils of both the NINDS and the National Heart and Lung Institute, and aided by consultants in specific areas, has been one of the most important elements in this process. Meeting regularly to review the cerebrovascular research and training activities of the two Institutes and also the Regional Medical Programs Service, another component of the Department of Health, Education, and Welfare, this Committee sponsors meetings, commissions, and supports publications, and maintains close relationships with all agencies, public and private, concerned with CVD.

In 1970, the Joint Council Subcommittee organized several important meetings, including a Fifth Workshop on Stroke Centers, which took place in January 1971, and an Eighth Cerebrovascular Research Conference at Princeton, N.J., to take place in January 1972. The Princeton conferences are large biennial scientific sessions to which leading researchers and physicians from many countries are invited.

Publications

A major publishing project sponsored by the Subcommittee has been a "Cerebrovascular Survey Report," outlining the status of research in the field, and revised every 5 years. The latest revision, published in 1970, contains sections on anatomy of cerebral circulation; neuropathology; atherosclerosis, diagnosis, and behavioral changes occurring in cerebrovascular disease. Other sections deal with the current status of thrombolytic or clot-dissolving agents, epidemiology, several large cooperative studies on clinical therapy, and anticoagulants. This publication has been distributed widely, and is available to physicians, scientists, libraries, and other persons and organizations with a working interest in stroke.

Another important Subcommittee-sponsored publication is the periodical Cerebrovascular Bibliography, now in its 10th year. This bibliography is a computer-produced selection of citations coming from the Medical Literature Analysis and Retrieval System (Medlars) of the National Library of Medicine, and is sent to a limited number of investigators, teachers, and libraries. Medlars is by far the most comprehensive medical literature reference system in the world, and the Cerebrovascular Bibliography is, in turn, the most comprehensive reference within its field.

Several other stroke publications of major importance were produced this year. One was "A Study of New Methods of Measuring Cerebral Circulation," based on a meeting funded and sponsored by the NINDS and the National Heart and Lung Institute in early 1970. At this meeting, which brought physicists and engineers together with medical scientists, particular emphasis was placed on the possibility of applying principles of space age electronics and nuclear physics to the complex problem of detecting and measuring blood flow in all parts of the brain in ways that would be painless and without risk to the patient.

The year 1970 also saw the launching of "Stroke—A Journal of Cerebral Circulation" by the American Heart Association. The first scientific journal devoted exclusively to cerebrovascular disease, this publication will aid greatly in bringing together under one cover important papers dealing with all aspects of the field. Many of the members of its editorial board have served the Institute in various capacities, and of the 57 articles published in volume I (January–December 1970), 35 were contributed by NINDS grantees or intramural scientists.

62-645 O—71—pt. 3——45

In collaboration with the National Heart and Lung Institute, NINDS revised and reprinted "Cerebrovascular Disease and Strokes," a leaflet for stroke patients and their families.

Joint Committee for Stroke Facilities

A lack of uniform guidelines and criteria for the care of stroke patients, including diagnosis, prevention, treatment, rehabilitation, and related specialty training has often been noted. An important step was taken in 1969 to remedy the problem through creation of a Joint Committee for Stroke Facilities, funded by the Regional Medical Programs Service, Department of Health, Education, and Welfare, and sponsored by the American Neurological Association. This Committee has been engaged in organizing working groups of experts in the various areas of the stroke field. Nine study groups are developing guidelines covering epidemiology, clinical prevention, clinical management, special procedures and equipment, nursing, pathology and laboratory procedures, rehabilitation, community health services, and training, education, manpower, and research. Thirty professional organizations participate currently, with liaison representatives from seven Federal agencies, including NINDS. Coordination and editing of the resulting guidelines will be achieved by way of an Advisory Committee and an Executive Committee.

STROKE RESEARCH

Diagnosis

The Institute program of support for cerebrovascular research, amounting in 1970 to approximately $5.1 million, reflects an effort to concentrate funds and manpower on the most promising approaches to the most urgent problems. One of the most urgent problems in cerebrovascular disease is early diagnosis. There are at present a number of methods of detecting and locating circulatory defects in the brain. The following examples illustrate the variety of currently used or patential methods for studying cerebral circulation:

X-ray angiography..—Radio-opaque dyes are injected into the circulation and X-ray pictures of the brain are made. Refinements include cine X-ray, image enhancement by background subtraction, and densitometric measurements of the microcirculation.

Indicator dilution principle.—The amount of an injected or inhaled indicator substance removed from the arterial blood during passage through the brain is measured. Clearance of such indicators as nitrous oxide or antipyrine is monitored in expired air or venous blood.

Isotope arteriography.—Radioactive substances are injected as in angiography, but the distribution of the radioactive material is detected by a gamma camera.

Thermography.—Two narrow strips of skin on the forehead are supplied with blood from the same arterial system that supplies the brain. Heat radiating from this skin can be monitored, and decreased circulation detected by "cold" spots.

Rheoencephalography.—This method measures changes in electrical resistance to high-frequency current that has been introduced into the brain. Electrical resistance of the blood is much lower than that of other tissues; thus gradients can be detected, and some indication of blood flow may be recorded.

Acoustical detection of flow.—Circulatory sounds in the head may be detected as in heart disease. Scientists are also working with ultrasound using the Doppler principle for precise measurements of flow velocity and the pulsation of arterial walls. Doppler pulses which permit velocity measurements from only a very limited region appear to be particularly promising.

Circulatory changes in retinal vessels.—Direct microscopic observation of retinal blood vessels can provide valuable information on intracranial circulation.

However, even the best and most thorough of these methods, angiography, is not entirely satisfactory; for some patients the injection of dye into the arterial circulation can be a traumatic experience. The need for better noninvasive methods, both for screening populations as well as for diagnosing those in whom strokes have already occurred, is one of top priority. At the meeting mentioned above on new methods of measuring cerebral circulation, a number of novel ideas were introduced. One was use of the principle of proton spin resonance for labeling, timing, and measuring blood as it moves through the brain. Protons in the nuclei

of hydrogen atoms in the blood are polarized by placement of the patient's chest in a magnetic field, and a detector over the venous drainage from the head gives an indication of the flow volume and rate. Another idea involves possible use of the Mossbauer effect—emission of a gamma particle by the nucleus of an isotope and subsequent absorption of the particle by another nucleus—to measure very small velocities, in which changes can be detected and used to measure cerebral blood flow.

Also being considered is possible use of a fiber optics device for transillumination of the head with high-intensity light and examination of the circulation with the new light amplification devices used for night vision; ultrasound echoes for production of three-dimensional images of the brain are still another possibility.

Two tentative conclusions reached by the group were that ultrasonic techniques and the application of nuclear magnetic resonance phenomena are at present the most promising new approaches, and that some combination of techniques, rather than a single one, will probably be the ultimate choice.

NINDS grantees are devoting substantial effort to the improvement of diagnosis. For example, scientists at the Duke University Center have recently reported that they have improved gas inhalation techniques for measurement of cerebral blood flow. They have shortened the time required for this procedure from 30 to 40 minutes to 11 minutes, making it far easier to test seriously ill patients whose cooperation might be limited by discomfort or mental deterioration.

Scientists at the University of Oregon Medical School have reported a new cerebral angiographic technique which cuts in half the time necessary to conduct multiple-vessel studies. Using a polyurethane catheter with a fine steel braid built into its wall to provide resilience and a high degree of torsion control, they insert the tip into the femoral artery at the groin, thread it up into the aortic arch (upper chest), and are then able to direct it into any of four cerebral arteries. The femoral approach necessitates only one incision, minimizes patient discomfort, eliminates the need for general anesthesia, and facilitates head positioning because of the elimination of incisions in the carotid arteries in the neck. Overall results with the improved catheter in over 200 patients have been reported as highly satisfactory.

At the University of Miami grantee scientists are attempting to reduce the deleterious effects of radio-opaque materials used in cerebral angiography. Some of the substances used in the past have been potentially neurotoxic if not quickly washed out of the cerebral vessels, and the search continues for an ideal dye. The entry of substances such as sodium diatrizoate into the brain and spinal fluid is being measurd in animals, and the levels correlated with toxicity. Preliminary reports suggest that some anesthetics significantly reduce toxicity in animals.

Thermography, at present a method of definite but limited usefulness, continues to undergo refinement. NINDS supported researchers at the University of Minnesota reported this year that they have developed a technique which increases the detection rate of facial thermography from 58 to 88 percent. One of the problems with thermography in the past has been in detecting whether collateral circulation has compensated for the cooling brought about by a partly blocked carotid (neck) artery. The Minnesota scientists have designed a head clamp which momentarily interrupts blood flow in the arteries which provides for collateral circulation, and have reported their highly favorable results with 80 patients.

Treatment

Steady progress is being made in therapy for cerebrovascular disease. The picture from year to year is one of many small improvements rather than striking changes.

Surgery.—For many years, cerebrovascular surgery has been limited almost entirely to correction of flaws or blockages in the larger arteries. The carotids in the neck are relatively accessible, and the larger intracranial arteries have become more so in recent years. The operating microscope has made it possible for neurosurgeons to operate directly on smaller blood vessels in the brain. Grantees at the University of Southern California have reported removal of clots from very small brain blood vessels, and also the placement of very small blood

vessel grafts in the brain. Grafts are particularly important in the surgery of aneurysms, which often strike persons in the younger age groups.

Drugs.—In a number of centers there has been intense interest in developing better drug therapy for cerebrovascular disease. Anticoagulants in nonhemorrhagic strokes, and blood pressure lowering agents, when indicated, are commonly used, and efforts are underway to improve thrombolytic (clot-dissolving) agents, and also vasodilators—drugs that relax the brain blood vessels and allow them to open to their fullest diameter.

Grantees in New York and in North Carolina have been studying arterial spasm with a view toward drug control of this sometimes life-saving, sometimes life-threatening phenomenon. Arterial spasm is the shrinking of small blood vessels due to contraction of the muscle coat in the vessel wall. It is a common reaction to injury causing bleeding, and is a protective device. However, in stroke, it may make a bad situation worse by reducing blood supply, and preventing development of collateral (alternate pathway) circulation. No satisfactory spasm-controlling drugs have yet been found, but an intensive effort to discover the causes and mechanism of spasm is underway.

Epidemiology and Statistics

One of the greatest needs in the field of cerebrovascular disease has been for reliable data to aid in better treatment and in research and program planning. Thousands of medical journal articles have been published reporting the individual experience of physicians with small numbers of patients, but rarely are there enough patients in any study to produce statistically significant data. It is difficult enough for the practicing physician to get a clear picture of what the majority of other physicians have found to be the best course of action in the majority of patients of a specific type; it is even more difficult for planning committees to focus their efforts when they do not have adequate data.

The Institute is attempting to remedy this situation by providing support for a number of epidemiological projects, the largest at the Johns Hopkins cerebrovascular center mentioned above. Several studies of interest have been reported on this year.

For example, the Johns Hopkins group has been particularly interested in what appears to be regional differences in stroke mortality among geographic areas of the United States. Previous studies have revealed that large differences exist among various areas, Denver, Colo. having the lowest mortality, and the Georgia-South Carolina area having the highest, and that these differences were not due to differing practices among physicians in preparing death certificates, or to different criteria for the clinical diagnosis of stroke. The scientists matched incidence rates in the various areas studied, and found a direct relation, thus ruling out the possibility that medical care practices following stroke are an important factor.

Another study, conducted at Duke University, has given added statistical backing to the view that cerebrovascular disease "runs in families." Three groups of 40 patients each were studied, and it was found that vascular diseases had been the main cause of death for the parents of the majority.

Recent findings from the National Heart and Lung Institute's Heart Disease Epidemiology Study in Framingham, Mass., have indicated that high blood pressure is the most important single factor leading to strokes in general and to atherothrombotic brain infarction (ABI, the most common variety of stroke) in particular.

In this prospective study of 5,209 men and women examined biennially for 14 years, initially asymptomatic hypertension was associated with a risk of ABI about four times that of normotensives: of 86 subjects diagnosed as having suffered an ABI, only 14 were normotensive at the time of their initial examination. No critical level of blood pressure was evident—the risk was simply proportional to the level from the lowest to the highest recorded. Also, there was no evidence to suggest that elevations in the diastolic component of blood pressure contributed more potently to this risk than did the systolic component.

The investigators concluded that "control of hypertension, labile or fixed, systolic or diastolic, at any age, in either sex appears to be central to prevention of atherothrombotic brain infarction."

OUTLOOK

There continue to be many urgent needs in the field of cerebrovascular disease. With increasing numbers of Americans moving into the age groups menaced by stroke, it becomes increasingly important that the Institute's research and training programs continue to gain momentum. The Federal efforts promise to more than repay their supporters in terms of better health.

RESEARCH ON CEREBRAL PALSY

Mr. FLOOD. How about cerebral palsy? You know that this committee has over a period of some years indicated particular concern with cerebral palsy. Do you want to tell us something about that that you didn't tell us last year?

Dr. MACNICHOL. The study of cerebral palsy is a primary objective of the collaborative perinatal project, and in it we are trying to pinpoint those factors that cause it. I will include a report on cerebral palsy.

(The report referred to follows:)

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE

CEREBRAL PALSY

The number of people with cerebral palsy (CP) living in America today is estimated to be about 750,000. The term cerebral palsy refers to a variety of forms of nervous system damage causing crippling, and becoming manifest before birth, at delivery, or early in life. Although these children all suffer some kind of neurological impairment, the affliction can vary greatly in extent and location of symptoms.

	1968	1969	1970	1971 estimate	1972 estimate
NINDS research support for cerebral palsy and related neurological disorders of early life	$11,116,000	$14,375,000	$13,436,000	$14,440,000	$13,356,000

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE

CEREBRAL PALSY

Cerebral palsy is neither contagious nor progressive, but appears in different ways and continues throughout life. A newborn may be diplegic, with both sides of the body equally affected; another may show just a few spastic fingers. Sometimes the impairment does not appear for several years after birth. The life expectancy of those who live past age 5 is 40 years. About 35 percent die before age 5.

Although symptoms vary, two common types of CP are the *spastic*, characterized by tense, contracted muscles, and the *athetoid* type, characterized by involuntary movements of arms and legs. CP is also categorized as monoplegia, diplegia, triplegia, paraplegia or hemiplegia, according to which limbs or regions of the body are affected.

There are many causes of cerebral palsy, although as yet they are mostly unknown. Some nervous system damage is known to be due to events causing stress before, during, or after birth. Some cases result from congential malformations of the nervous system, which may be due to chromosome abnormalities or inborn errors of metabolism. Still other cases are related to injury from maternal infections during pregnancy such as the rubella virus, cytomegalovirus, or toxoplasma gondii. About 10 percent stem from infections of the brain or its

membranes—such as in encephalitis or meningitis—caused by a wide variety of infectious agents including bacteria infecting the victim mostly during the first year of life.

Congenital malformations of the brain and spinal cord are among the leading causes of deaths of infants under 1 year of age. Because the brain is vastly more complex than other organs of the body, and the variety of malformations so extensive, knowledge in this critical area is limited. A large portion of all childhood disabilities involve congenital malformations of the brain and other organ systems.

While many CP victims have normal or above average intelligence, about half are believed to be mentally retarded, and many suffer associated disorders such as conculsive seizures, learning disabilities, or defects of vision, hearing, or speech. Although much is still unknown about how to prevent these conditions, it is important to diagnose CP as early as possible to begin treatment and reduce the extent of the handicap.

PROGRAM DEVELOPMENTS

Research into the causes and prevention of CP has been and must continue to be a top priority among objectives of the National Institute of Neurological Diseases and Stroke. One of the first actions of the newly organized staff of the Institute after it was created in 1950 was to plan a long-range program to study the nature of neurosensory disorders of the newborn. Before this, experiments with guinea pigs and monkeys had demonstrated that severe brain damage could result from prenatal asphyxia, but useful data in man on injuries occuring during pregnancy or around the time of birth was rare.

The Collaborative Perinatal Research Project

The Collaborative Project on Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Infancy and Childhood began in 1959. Before this, such research had generally consisted of tracing the factors causing cerebral palsy or mental retardation years after the victim's birth. Such retrospective research seemed painfully inadequate to the challenge of discovering the causes of these disorders. So NINDS proposed to launch a prospective project for perinatal studies. This project is a notable achievement in the history of perinatal research, because it is a farsighted effort to collect data early in pregnancy from women whose children are being closely checked until the age of 8.

Data have now been gathered on 58,000 pregnancies. Every possible detail of the delivery of the infants has been observed and recorded. Further tests have followed, and each child is being regularly checked until his eighth year.

Investigators are attempting to associate the results of pregnancy with specific maternal characteristics. The mothers have been carefully checked for height, weight, weight gain during pregnancy and menstrual history, and the importance of these factors is being tested. Other studies consider the possible influences of such factors as race, sex, birthweight and gestational age on the development of the child.

This ambitious and unique national research program is being conducted by NINDS in collaboration with 14 major medical centers. The researchers are now engaged in the follow-up of the children from these pregnancies. These follow-up examinations, which will continue until 1974, are to assess mental and motor development, to identify neurological problems, and to evaluate intelligence and other more complex intellectual functions, including concept formation, language performance and learning ability.

With this past year, the NINDS Perinatal Research Branch has shifted its major emphasis from the data collection phase to the scientific analysis of the vast data from the project. With the active participation of the Perinatal Research Committee, 11 task forces have been organized to analyze key portions of the data.

The main purpose of these analyses is to identify diseases and other complications of pregnancy which contribute to brain damage in childhood. The range of such damage extends from severe cases of cerebral palsy and mental retardation to the mildest types of learning disabilities recognized in schoolchildren.

The systematic collection of information from the huge population of the collaborative project is expected to yield insight into the effects on the develop-

ing child of drugs used in pregnancy and during delivery. Researchers also expect to gain important knowledge about diseases of the newborn, the importance of such traumatic events in the perinatal period as infection or anoxia, and additional information concerning adverse events during the first year of life.

These analyses will help explain the effects of socioeconomic, health, and other characteristics of pregnant women on the physical, neurological and intellectual development of children. This should result in eventual identification of children in high-risk groups, and in early identification of children with subtle dysfunctions of the central nervous system.

Such information is crucial for the development of special care programs for those pregnant women in particular danger, and for children subject to unusual risk of brain injury. Early intervention could mean substantial improvement in the lifelong consequences of these events.

An extensive reference bibliography is being compiled on the subject of human teratology, the study of congenital malformations, summarizing the world literature on the subject over the past 200 years. This comprehensive project should also add immeasurably to the information available to many research scientists.

The Laboratory of Perinatal Physiology

Because the gestational physiology of the rhesus monkey is very similar to that of man, scientists at the NINDS Laboratory of Perinatal Physiology have conducted a continuing program of research on that species to complement human studies. By attempting to duplicate in monkeys certain types of nervous system damage believed to cause neurological disorders in man, scientists are learning much about the causes and effects of CP.

In 1968, the former chief of the Laboratory of Perinatal Physiology, Dr. William F. Windle, received the Lasker Medical Research Award largely for his work on CP and mental retardation while he was head of the Institute's laboratory. Dr. Windle and his colleagues correlated patterns of brain damage after asphyiation with symptoms of CP, and their discoveries have made it possible to minimize the effects of brain damage in infants. They were among the first investigators to associate kernicterus with CP.

The past year has seen the transfer of this laboratory from San Juan, P.R., where it was established in 1956, to Bethesda. Control of the island colonies of rhesus monkeys has been transferred to the University of Puerto Rico, which is engaged in primate studies. These changes will make the activities of the laboratory more economical, and at the same time make it possible for the scientists to work more closely with their colleagues throughout NIH at Bethesda.

RESEARCH DEVELOPMENTS

Prematurity

Prematurity is prominently associated with CP, and studies have shown that premature infants with CP usually have the spastic diplegic type. Scientists are studying several possible causes of CP in prematures, which they classify as genetic, traumatic, anoxic, infectious, toxic, and hemorrhagic.

A study of spastic diplegia in babies of low birth weight showed an association between the disorder and low hematocrit levels in the blood of the infants. This sugegsts that some premature babies may develop intracerebral hemorrhage, and the resultant brain damage leaves survivors palsied. Scientists are now striving to determine the specific factors involved, such as the possible role of cranial trauma or of deficiencies of the blood clotting mechanism in prematures, in the attempt to gain a more comprehensive understanding of the causes of this type of CP.

Pregnancy Factors Associated with Fetal Health

Recent analyses of the data from the perinatal project continue to reveal how the physical health of pregnant women and other factors of pregnancy affect the neurological development and general health of the children. A new study indicates that among other factors, the weight of the offsrpring may be influenced by antigenic differences between the mother and her unborn baby. This observation may explain in part the well-known increase in birth weight of second and third pregnancies. Of even greater importance, particularly in undernourished and underweight women, is the observation of weight gain during pregnancy. Data from this project provide valuable support to the hypothesis that expect

attention designed to improve the nutrition of underweight pregnant women substantially reduces low birth weight among the offspring.

Another study of 83 term intrapartum fetal deaths in the perinatal project identified the causes of death in 43 cases. The investigators learned that the most frequent of these causes were prolapsed cord, premature placental detachment, hydrocephalus and uterine rupture. Although the researchers cold not determine definite cases of death in the other 40 cases, they identified these conditions as significant: breech presentation, tightened umbilical cord around the fetal neck, premature rupture of the membranes, prolonged gestation, and a history of prior stillbirth. While these factors do not necessarily indicate critical complications, they can be used clinically to identify the babies who face unusual risk during birth.

Eclampsia in the Collaborative Project

Eclampsia is a form of toxemia occurring in pregnant women, sometimes after delivery, in which the patient experiences convulsions and coma. It is most prevalent among young women and is associated with hypertension, edema, proteinuria, and abnormal maternal weight gain.

Hospital reports from different countries indicate that eclampsia occurs in one out of every 500 to 1,500 pregnancies. Among 55,000 deliveries registered in the perinatal project, eclampsia occurred ine one of every 1,804 pregnancies. Although the percentages of Negroes and whites is about equal in the perinatal project, 75 percent of the eclamptics were Negroes. Remarkably, there were no maternal deaths from eclampsia.

Project scientists consider the results of this study dramatically convincing evidence that eclampsia is not only treatable, but one of the preventable complications of pregnancy. Prevention, they believe, lies in early recognition of symptoms and conscientious obstetrical care.

Neonatal Bacterial Meningitis

Data from the project have been analyzed to identify factors predisposing infants to meningitis and influencing the outcome of this frequently fatal disease. It was found that babies of low birth weight had a significantly higher incidence of meningitis, as well as a higher death rate from the disease. The bacteria responsible for the infections were identified, and the predisposing factors were found to be these: complications during pregnancy and delivery, maternal infections, and fetal membrane inflammation caused by bacterial infection. Among surviving children, brain damage was frequent.

The findings of this study hold important implications for the identification and management of high-risk babies, and may provide the basis for development of new laboratory tests for early diagnosis of bacterial infections of newborns.

Down's Syndrome

Investigators are studying perinatal project data to learn more about the causes of Down's syndrome (mongolism), which results from a congenital defect in which the infant is born with an extra chromosome.

So far the prime maternal factor demonstrated among the 63 mongoloid children in the project is the high frequency of these infants born to older women. Other findings show that at present the outlook for children with Down's syndrome is not promising. In one study, 30 percent of these children had congenital heart disease, and 25 percent died in the first year. Mongoloids were found to have extremely high rates of other complications too, such a pneumonia, which struck half of them.

Biosocial Influences on Human Development

Another study from the perinatal project supports previous analyses relating poor mental and motor development in 8-month-old children of poor socioeconomic background to poor performance at 4 years of age. Such findings are considered important in the search for factors which would allow identification of poor performers early enough in life to provide enriched environmental experiences prior to schooling.

Scientists in many fields consider the objective pursuit of these biosocial factors of human development to be important to the understanding of the conditions necessary for adequate maternal and child care, especially with regard to providing early help to poor performers and with predictable results.

Viral Infections in Utero

A perinatal project study has shown that fetal infection with viruses is more frequent than had been thought, especially among indigent populations. A dozen or more viruses are capable of causing fetal damage, and three viruses are known to produce congenital malformations. These viruses—rubella, cytomegalovirus, and herpes simplex—also produce chronic fetal infections which may persist after birth.

A study of the frequency of viral infections in a population of 30,000 women in the project showed that 5 percent of the pregnancies were complicated by at least one infection. Another study indicates intrauterine infections may account for previously unclassified types of brain damage, particularly among low income groups. Researchers are studying the possible relationships between the presence of certain antibodies in the blood and such factors as race, sex, birth weight, and clinical status of more than 2,500 infants, mostly from lower socioeconomic groups. High immunoglobulin levels in the blood have been found to correlate positively with infection, which in turn is associated with low birth weight.

During the 1964 rubella epidemic, before vaccines were available, an estimated 20,000 to 40,000 children of mothers with rubella were born with defects and there were perhaps 30,000 related stillbirths. Today in the United States, there is a broad national program to eliminate rubella through immunization of children under age 12. This indirect approach is intended to reduce the incidence of rubella in the total population. This will minimize risk of infection of pregnant women without exposing them to the vaccine, which might cause birth defects.

Scientists now want to know how rubella continues to thrive despite apparently adequate antibodies in the blood. They are also seeking to learn how the virus damages cells in the fetus.

There is no vaccine for cytomegalovirus, which may afflict infected fetuses with serious conditions such as microcephaly, hydrocephaly, microphthalmia, encephalitis, cerebral calcification, blindness, seizures, or enlargement of the liver and spleen. However, researchers are currently investigating the possibility of drug therapy for victims of this disease.

Fetal infection with herpes virus may occur during birth or shortly afterward, and may result in fetal disease, congenital malformations or death. Although there is no vaccine or specific treatment, research has provided knowledge important to proper identification and obstetrical management in cases of maternal infection with this virus.

Investigtors are continuing to work toward means of preventing fetal infection and damage from the protozoan Toxoplasma gondii, which is responsible for the disease known as toxoplasmosis. Congenital infection produces effects similar to those caused by cytomegalovirus. A recent study indicates toxoplasmosis may also be a significant cause of spontaneous abortion.

Experimental Models of Nervous System Damage

Scientists at the Laboratory of Perinatal Physiology, now relocated in Bethesda, are continuing their studies on nonhuman primates to learn more about problems of perinatal brain damage, especially in regard to broadening the basic understanding of CP and mental retardation. They are focusing attention on studies of total asphyxia and prolonged partial asphyxia, which result in distinctly different patterns of pathology, to gain new knowledge about brain function, brain metabolism, and conditions associated with perinatal brain injury. They have found that patterns of injury caused by partial prolonged asphyxia in utero in the monkey duplicate exactly certain kinds of damage observed in human infants.

These investigators are studying the ways in which alterations of the physiological condition of the mother may adversely influence the status of the fetus in utero. For instance, they have found that a variety of conditions which interfere with the passage of oxygen between the mother and fetus result in partial asphyxia in the fetus. These conditions include maternal hypotension, maternal hypoxia, and excessive use of certain drugs which hasten the birth process. More dramatic, the investigators have discovered that hormones released under psychological and other kinds of stress can cause physiochemical reactions in the mother which result in less oxygen to the fetus. This means that psychological stress in the mother might actually result in brain damage or in asphyxiation of

the fetus in her womb. However, the implications of these primate studies for the human are not yet certain.

Studies have shown that treatment with alkali can protect the brain against the effects of asphyxia. Other drugs which reduce oxygen consumption by the brain, such as barbiturates, have been found to protect the brain from the effects of total asphyxia. Glucose has also been found beneficial when provided during asphyxia. Further studies are being conducted on the problems of premature detachment of the placenta, blockages of the amniotic fluid and on abnormal blood coagulation. These and other investigations are providing scientists with much precise information on the physiology and the pathological complications of pregnancy.

EPILEPSY

Mr. FLOOD. What is epilepsy?

Dr. MACNICHOL. Epilepsy is a condition of the brain in which large areas of the brain produce an abnormal amount of electrical activity. The cells in the brain appear to discharge synchronously, producing very large alternating electric currents in the brain and the effect of this is to cause muscles to contract in a completely uncontrollable way.

Mr. FLOOD. Is that progressive?

Dr. MACNICHOL. Depending upon the kind of seizure. Some kinds of seizures can start in one place and generalize over the whole body.

Mr. FLOOD. Why are they periodic?

Dr. MACNICHOL. This is one of the interesting questions that we don't know about. One of the things at which research is directed currently is understanding what it is that makes the nerve cells in the brain more sensitive so they all fire off in synchronism and why this will occur for a few seconds or a few minutes and then maybe not occur again for days.

Mr. FLOOD. Do many deaths result from epileptic attacks?

Dr. MACNICHOL. Epilepsy ordinarily isn't a fatal disease. Someone could fall down and hit their head or something like that, but epilepsy by itself is not a fatal disease. Of course, death may occur in status epilepticus. This is a term used to describe a series of rapidly repeating convulsions in which the patient does not recover from the coma produced by one attack before the next attack occurs.

Mr. FLOOD. Do you have anything to tell us about what you have done in the last year?

Dr. MACNICHOL. The principal thing that we have done about it is a contract program in three institutions, the Medical College of Virginia, the Newcastle State Hospital, and the University of Washington, to test new anticonvulsive drugs, and to try to identify and put through clinical testing drugs which look more promising than the ones that we are now using.

Mr. FLOOD. Is this so hopeless that you are not paying much attention to it?

Dr. MACNICHOL. Not at all. This drug testing program is going along very well. Also, we have some experimental studies in animals in which epilepsy is produced artifically and then we try to find out what factors prevent the attacks from occurring.

Mr. FLOOD. That is the prophylactic. Do you have any experiments with reference to the thing itself, basic research?

Dr. MACNICHOL. Yes.

Mr. FLOOD. What sort of research would that be?

Dr. MacNichol. Almost any of our research having to do with the basic properties of nerve cells and how the endings of one nerve cell excite the next nerve cell in the chain. The understanding of how this excitation and inhibition occurs, and the irritability of the nerve cell itself, are studies going on in this area of neurophysiology and neuropharmacology which are very important in trying to get at the basic mechanisms in epilepsy.

(A special statement on the epilepsies follows:)

THE EPILEPSIES

Introduction

Epilepsy is the name for a group of brain disorders that appear as recurring attacks of involuntary physical reactions lasting for a limited time. These may include convulsive body movements, partial or total loss of consciousness, mental confusion or disturbances of functions controlled by the autonomic (involuntary) nervous system. Although original causes of attacks are often not known, it is known that they are triggered by abnormal, uncontrollable, synchronous and excessive electrical discharges of brain cells.

People who have any of the epilepsies often conceal the fact because it can adversely affect their social and economic status and their insurability. It is therefore difficult to learn how many persons are afflicted. Their number in the United States is estimated as more than 2 million.

Conservatively, the epilepsies cost the Nation more than a billion dollars a year. Much of this would be unnecessary if the general public, by better understanding of the disorders, would make available to victims the social, educational, and employment opportunities now denied them largely because of ignorance and fear. Generally, persons with epilepsy have average or better-than-average intelligence and good earning potential. And, a majority of them can live normal lives because their disorders are under control through physician-prescribed anticonvulsant drugs.

	1968	1969	1970	1971 estimate	1972 estimate
NINDS research support for epilepsy....	$3,036,000	$3,260,000	$3,266,000	$3,526,000	$3,358,000

THE EPILEPSIES

Classification

The kind of epilepsy a victim has is characterized in terms of where, how, and for how long symptoms occur, the initiating brain cells, and the type and intensity of their electrical activities through an attack as detected and measured by an electroencephalograph (EEG) machine.

Until the EEG machine was developed, epilepsy classifications depended solely on observation. Now there are two proposed international classifications—one by clinical history, examination and observation, the other way by clinical history and EEG measurements. Still a single, simpler classification is needed to make clinical and research epilepsy information exchange easier and more reliable.

The most universally used and most familiar classifications are grand mal, petit mal, and temporal lobe epilepsies. Grand mal attacks last possibly a minute or more, are more violent than in other types, and are often, but not always, preceded by an "aura," a feeling of an impending attack. The victim may bite his tongue and invariably loses mental and physical control, including control over bodily functions. The post-attack period is relatively long—sometimes several hours—during which the person is confused, drowsy, and often has to sleep. In petit mal, attacks occur more often, sometimes many a day. They last only a short time—one to five (seldom more than 30) seconds and result in brief lapses of consciousness after which there is seldom any memory of the event. Temporal lobe epilepsy attacks originate in the temporal lobes of the brain. The discharging cells influence mental processes as well as muscle movements. A victim exhibits

adversive or torsion movements, dreadful fear, flinging of arms aimlessly, smacking of lips and other incoherent physical and mental behaviors. Action in progress at the onset of an attack may be continued automatically, but not remembered afterwards. Victims may suffer sharp, acute pains in their stomachs and may experience hypertension, perspiration and other disturbances of the inner organs.

Causes

The epilepsies are not contagious. They are not related to mental illness or mental retardation. They have little to do with a person's intelligence, or thoughts and chances of inheriting most of them are small. Still, anyone can become a victim of one or more of them through brain damage.

There is no exact understanding of what causes brain cells to run amok and discharge abnormally to cause epileptic symptoms. There is, however, general agreement among scientists that epilepsy can result from brain injury caused by prenatal and perinatal trauma, head wounds, drugs, congenital malformations, nutritional deficiencies, fever, some infectious diseases, brain tumors and abscesses.

Need for Research

Since little is known about the cause, and because effective treatment is still not available for many, there is need for much continuing research. Twenty percent of those afflicted are not helped by today's drugs or surgery, and another 30 percent need more effective control. The Institute's programs include support of basic brain research, medical and surgical research, clinical testing of new and promising anticonvulsant drugs, better systems for knowledge exchange between scientists, and continuing public education.

PROGRAM

Basic Research

Numerous approaches are being made to improve understanding of the basic mechanisms involved in epilepsy. Most of them work in some way through measuring and localizing normal and abnormal electrical energy-discharge patterns in cell groups and in diverse areas of the brain by use of the EEG machine. In fact, electroencephalography is considered the most useful epilepsy diagnosis and research tool yet developed. Also microelectrodes which can measure electrical activity of single animal and human brain cells are being used. Besides studying brain mechanisms in human victims of the epilepsies, scientists are also developing animal models for study. Various epilepsies are induced in animals by electrical, chemical or sensory stimulation or by metabolic deviations of body chemistry. The aim is to learn what brain cell mechanisms are involved and how they work in changing localized brain lesions (scars) into areas of epilepsy initiation. These approaches are showing the best ways to induce chronic epilepsy in animals so they may be tools for deeper studies. Applying EEG techniques to these animal models enables investigators to test efficacy of new drugs, locate epileptic foci and develop new and better surgical techniques for therapeutic application.

The Institute supports five epilepsy research centers which focus the talents of multidisciplinary basic and clinical scientific teams on the disorder.

At the University of Washington, scientists aim their efforts at the basic mechanisms of the epilepsies. Using experimental animal models, they are collecting anatomic, physiologic, psychologic, and social data and correlating it with human epilepsy forms.

The University of Wisconsin epilepsy investigators concentrate on basic and clinical environmental and behavioral research with human patients. An area of major interest is conditioning patients against sensory occurrences—flashing lights, certain sights, sounds, music, startling events—which trigger symptoms in some types of epilepsy. They are also probing a variety of psychophysiological variables with the possibility that individuals may be able to control mentally some abnormal electrical brain discharges, and thereby some types of convulsive disorders.

At Yale University School of Medicine, research direction is toward learning from animal-model and human-clinical projects what mechanisms and causatives are responsible for initiation, timing, frequency and nature of epilepsy symptoms.

Their goals are better ways for treating and controlling attacks with considerable emphasis on nondrug methods.

University of California scientists study the electrical processes involved in the epilepsies. One major project uses implanted microelectrodes to obtain more precise localization of where in the brain epilepsy attacks originate and uses groups of such implantations to trace the electrical flow of attack activity. Another project uses telemetry packs carried by the patients at home and connected to laboratory computers by radio and phone lines, to collect precise information on when, where and under what circumstances attacks occur. The latter project results from the fact that patients often do not have attacks, or experience fewer attacks, when they are in the hospital and suggests possibilities that determinable and avoidable stresses cause some epilepsies.

The main interest of the epilepsies programs at the University of Utah is how anticonvulsant drugs work on the brain to reduce or control attacks. Their direction is to make deeper explorations of attack mechanisms and more precise location of actions of anticonvulsants possible.

Better understanding of basic brain mechanisms in the epilepsies and improved diagnosis and treatment methods have already resulted from the efforts of scientists at the Institute-supported centers.

Drug Research

So far, the most successful methods for controlling epilepsy attacks have been with anticonvulsant drugs.

Phenobarbital and Dilantin have been used for many years with much success. Dilantin is still considered the most effective drug for treating epilepsy although it causes undesirable side effects in some users and does not achieve adequate control in many others.

Other drugs which have long been used in controlling attacks are primidone and mephenytoin (Mesantoin). Within the past few years others have come into use for particular epilepsies. Diazepam (Valium) has proved effective in interrupting status epilepticus (a series of rapidly recurring attacks) and chloridiazepoxide (Librium) and oxazepam have helped in treating some convulsive disorders when combined with the earlier standard anticonvulsants.

Another problem has been drug-dosage determination to avoid poisoning from too much of a drug or from toxic side effects like ataxia, nausea, headache, drowsiness, skin rash, etc. In 1968 gas-liquid chromatography (GLC), a laboratory method developed in the late 1950's to measure minute quantities of substances in liquids was applied to the problem in relation to Dilantin levels in patients' blood. Now it is being applied to the other anticonvulsants and has become a vital tool in measuring blood levels of epilepsy patients although such blood-level determinations are still not available to the majority of physicians treating epileptic patients. For each drug tested, new techniques are being developed by the researchers as they go. Combining blood-level evaluations with psychological testing, scientists are putting these tools to new uses daily to study both efficacy and toxicity of both established and experimental anticonvulsants.

The Institute supports four epidepsy drug-study projects and is planning others. At the University of Virginia Medical School and the Medical College of Wisconsin, investigators conduct almost identical studies of the effects of ethosuximide (Zarontin) on absence (petit mal) in children. They are using split-screen TV tape recording for observing the patient and the EEG tracing, psychological test batteries and blood-level determinations. Because accurate knowledge of attack frequency is essential to drug testing, patients at the Virginia clinic are first observed for 12-hour periods by telemetered (wirelessly transmitted) EEG information which is recorded on magnetic tape. Similar 12-hour observations are taped after a period of dosage. Tapes, currently reviewed individually by Institute experts and then punched on computer cards to study a drug's effects on frequency and duration of attacks, will soon go directly from patient to computer when necessary facilities are completed. These studies are still in progress.

The New Castle State Hospital, New Castle, Ind., under a research contract with the Institute is in final stages of a double-blind comparison of the value of the experimental drug—albutoin—with that of the standards, Dilantin and primidone. Data are being computer analyzed by the Institute and results of the tests are expected to be published early in 1971.

Another contract has been negotiated with the University of Washington Epilepsy Center for testing sulthiame (Conadil-Ospolot) for treating partial epilepsies. The planned 2-year effort will begin about mid-1971.

A research contract was awarded in June 1970 to the University of Minnesota where a pharmacologist will study gas-chromatography methodology for determining blood levels of the investigational drugs carbamazepine and sulthiame. Metabolism and interaction will also be observed.

Meanwhile, the Ad Hoc Committee on Anticonvulsant Drugs, formed in 1969 from a cross section of medical school, drug industry and Government personnel to extend the work of the Public Health Service Advisory Committee on the Epilepsies and to advise the Institute on drug-study priorities and program progress, held its two scheduled yearly meetings in March and October. It recommended that the Institute next support clinical tests of another experimental drug—carbamazepine—and that experiments in nonhuman primate epileptic models be conducted to learn whether such animal data correlate closely with similar data in humans.

Results of all the currently conducted and planned studies are aimed at making the investigation of anticonvulsants faster and easier.

Surgical Research

Surgery is often performed in intractable epilepsy cases where presently available drugs cannot control attacks, where attacks are frequent and incapacitating, and where they initiate solely or partly in temporal lobe areas. It must also be determined that brain tissue can be safely removed without causing further serious neurological damage or leave a secondary epilepsy-generating scar.

At the Institute's laboratories in Bethesda, Md., advanced surgical techniques for treating such epilepsies in animals and humans have been developed and evaluated and relationships between head injuries and the epilepsies are being studied. Similar techniques are also studied at Institute-supported research institutions.

Brain surgery to treat epilepsy provides excellent opportunities for other valuable brain observations. By surgery, the accuracy of devices and techniques used to locate the damaged areas can be gauged and conversely, better surgery methods develop. Better understanding of which bodily or mental functions are controlled by which specific brain areas can be achieved through more precise locations (by X-ray, stereotactic devices and microelectrodes) of epileptic areas and surgical cuts made to treat them. And from many such cases, carefully plotted and mapped, allowable limits for surgical manipulations are established.

In laboratories associated with brain surgery centers, several physiochemical differences between normal and epileptogenic brain tissues have been found. Notably, it has been shown that acetylcholine—a chemical which transmits nerve impulses—occurs in large amounts in epileptic regions of the brain, suggesting that accumulation of this substance may cause attacks. The fact that injection of the chemical into the head's blood supply or its application to exposed brain areas provokes grand mal epilepsy supports the idea that it is an excitatory transmitter in the central nervous system. Two other substances which are known to affect susceptibility to epilepsy attack are gammaminobutyrate (GABA) and vitamin B6 (pyridoxine).

Investigators continue seeking information about the cause and correction of disturbances of brain fluid-chemical balances toward better understanding of all types of the epilepsies and to reduce the severity of status epilepticus and the possibilities of permanent brain injury which such disturbances may cause.

Perinatal Research

Since 1959, scientists at 14 different medical centers have been collecting neurological data about mothers and their babies during some 58,000 pregnancies and the surviving offspring from birth through age eight. This Collaborative Perinatal Research Project of the Institute has been collecting data prospectively from a population of mothers and babies large enough to be statistically significant in studies aimed at learning the causes of numerous, serious neurological diseases, of which epilepsy is a major one.

At this time data have been compiled an about 25,000 project children who have completed examinations through their eighth year. Because over 50 percent

of epilepsy victims experience their first attacks before age eight, analysis of the already collected data by the end of this year should yield abundant new clues on epilepsy causes. When the project is completed in 1974, and some 45,000 project children have passed the 8-year level, the accumulated information about them will be invaluable to epilepsy research.

RESEARCH PROGRESS

The Public Health Service Advisory Committee on the Epilepsies was originally set up in 1966 with a 10-year mandate to revive and continue stimulating interest in the epilepsies. That it is succeeding is one of the most encouraging research developments of the year. Scientists from many specialties are using their talents for the solution of epilepsy problems. One example illustrates the trend. Reportedly, the Yale Epilepsy Research Center program is having a major impact and influence on the activities not only of the neurological groups, but on the school and medical center in general. It is involving residents, fellows, students, nurses, and others in research and clinical conferences, seminars and other learning experiences. It has become a center for epilepsy research and patient care for a large area and it is hoped that it will help to improve medical and sociopsychological care for epilepsy victims throughout Connecticut.

Basic Research Progress

Last year a Massachusetts neurological scientist proposed the hypothesis that the brain's glial cells are electrical sinks where potassium ions are stored during normal neuron firings, and that damage to glial cells could reduce their potassium storage capacity, forcing an excessive accumulation of potassium ions on neuronal walls and possibly affecting the triggering mechanism of an epileptic discharge. This year, this scientist measured potassium accumulations in sclerotic (scarred) animal glial tissues and, although technical difficulties limited the amount of data obtained, results were sufficiently encouraging to demand further efforts in the same direction.

Two other investigators using different techniques studied the abilities of ions and amino acids to influence activities of chronic epilepsy foci in cat brains. Their findings are compatible with the glial cell measurements in that they agree with the probable roles played by potassium in epilepsy mechanisms.

Two Institute grantees at Stanford added confidence to current diagnostic methods which measure internal brain electrical activity from the outside surface of the brain or skull. Using monkeys in which epilepsy had been induced by application of alumina cream directly to the brain to cause damage which reacts quite like human epilepsy, they measured electrical activity extracellularly and intracellularly (with microelectrodes). Their results showed close association between the intracellular activity and the surface epileptiform waves. This study provides data which affirms the reliability of the tools used in measuring human electrical waves in both normal and epileptic brains.

Experiments at the University of Washington Epilepsy Center found, in cat brain cortex which had been surgically separated from the midbrain, important changes in the amounts of three specific enzymes considered important in epilepsy initiation.

The brain separation technique called undercutting had been studied in detail as a possible way for creating epileptic animal models. Also, lowered levels of one enzyme, "acetylcholinesterase," in cortex tissue had been observed and correlated with treated-animal hyperexcitability. The current work found a large increase in one enzyme and large reduction in two others in undercut cortex tissue, offering possible new leads to why epileptic tissue behaves as it does.

Drug Research Progress

Two significant experiments this past year probed the mechanisms of how anticonvulsants work in epilepsy. In both cases, drug effects were studied in rats in which epilepsy had been induced. In one experiment epilepsy was induced by freezing cortex in two groups of rats. One group had been pretreated with Dilantin and phenobarbital, the other had not. In the latter group, the freezing injury which induced epilepsy-like reaction, caused an increase in the activities of specific enzymes which are relieved to affect epileptic susceptibility. Animals in the group which was drug-treated before freezing injury showed no increase in the enzyme activities.

In the other experiment, rats suffered single electrically induced epilepsy attacks daily for 2, 4 and 6 days. After the second day, potassium content within specific brain cells decreased. At 4 days it was down 27 percent and down 40 percent after 6 days. Administration of diphenylhydantoin corrected the most severe potassium deficiency in 4 days. Both investigations have added to understanding of the anticonvulsant action of the chemistry of epileptic tissue.

A study reported in 1969 pointed to undesirable side effects of diphenlyhydantoin, the long used and generally effective anticonvulsant, and suggested that its inadvertent use in intoxicating proportions could actually destroy certain brain cells called Purkinje cells. In work supported by the Danish Epilepsy Association, a prominent epilepsy researcher probed the subject deeply with monkeys. Two animals were given the drug orally in quantities which kept their drug blood-levels far above those needed to produce symptoms and signs of intoxication for 30 to 43 days. These monkeys and three control monkeys were then sacrificed and their Purkinje cells were counted. All brains had an equal number.

The researcher suggests that earlier findings to the contrary may have been adversely affected by brain-fixation techniques and methods of dosage administration. This would indicate that if the data are applicable to humans the therapeutic dose levels of the drug, carefully maintained through blood-level determinations, are completely safe as far as brain cell destruction is concerned.

For some time there has been controversy over the value of the drug primidone in epilepsy therapy. Because many believed that it was completely metabolized to phenobarbital, they questioned why it should be used at all. Three Institute-supported investigators at the University of Wisconsin found that a percentage of primidone is not changed to phenobarbital and that the amount which remains in its original state is effective in controlling epilepsy attacks.

Additionally, at Wisconsin, another study evaluated previously reported adverse interaction between phenobarbital and Dilantin serum levels in animals receiving both for treating experimental epilepsy. Results with humans showed no significant effect upon Dilantin blood levels of patients by addition of phenobarbital or its accumulation. Conclusions were that, "While an interference effect may occur in experimental animals and in single dose studies in humans, the effect is quite variable and of no real significance in the clinical patients who are taking the two drugs on a continuing basis." The results were in agreement with results recently published by other investigators.

A statistical study made at the Institute should spark interest in some widely held opinions about the thoroughness of drug testing—especially of drugs used to treat epilepsy. More than 800 articles which have been published on the clinical effectiveness of the 13 currently marketed antiepileptic agents were screened. Only 225 articles were suitable for analysis. More than half of those were merely testimonial case reports, not well designed clinical trials. Of the other half, only three papers described double or single blind investigations. The report demonstrated the need for more sophisticated clinical evaluations than have been employed up to now, using team efforts with statistical design and controlled observations.

Progress Through Testing

Scientists working on sensory-evoked (reflex) epilepsy attacks at the University of Wisconsin this past year were able to identify the sound stimuli which caused attacks in a relatively small number of patients who are adversely affected by sounds which are not of sufficient volume or type to be unpleasant or disturbing to most of the populace. They established that such attacks are pathopsychological and not of emotional or functional basis, and that they can be ameliorated by clinical "therapeutic conditioning" wherein the offending sounds are played back (from tapes) often until they become innocuous.

The role of psychological stress as a triggering mechanism in some epileptic attacks was studied at Yale. Patients for the study were chosen on the basis of medically confirmed histories of aggravated epileptic activitity during periods of emotional stress. Results showed that the patients tended to hyperventilate (breathe faster than normal) when anxious, even though it was not always clinically obvious, lowering their carbon dioxide levels by as much as 50 percent. The hypothesis that the lowered CO_2 triggered epileptic activity was confirmed when administration of CO_2 prevented or terminated the abnormal activity although anxiety and overbreathing continued. The study demonstrates the

importance to some epilepsy victims of maintaining normal breathing control in conditions of emotional stress.

In France, a telemetered EEG study was made of 30 petit mal patients (ages 2–20, average 11 years 5 months) while they were engaged in intelligence tests, creative tests, interviews, drawing, school exercises and in periods of inactivity. The frequency of epileptic attacks varied significantly with the various situations in which the subjects were placed. Absences were least frequent during tests of imaginative and creative ability and nondirective interviews. They became five times as frequent during periods of inactivity and during school exercises. Possibly the situation an epilepsy victim finds himself in determines the number of attacks he has, but it is the significance of the situation which is important in triggering the attacks.

IMPROVED COMMUNICATIONS

Scientific Interchange

Epilepsy researchers must keep abreast of all epilepsy research everywhere so that all studies relating to understanding epilepsy mechanisms can be effectively applied to specific programs. To assure that such communications exist and function, the Institute has:

(*a*) Continued monthly publication of *Epilepsy Abstracts*, distributed copies to more than 3,000 subscribers at no cost, and arranged for future printing and distribution by Excerpta Medica at a per-subscription cost of $15 per year.

(*b*) Continued to develop the information base for the computerized Epilepsy Abstracts Retrieval System (EARS) which will eventually provide any abstract which has been published in *Epilepsy Abstracts* since 1947 within seconds to research scientists through teletype consoles.

(*c*) Sponsored, in conjunction with the Task Force on Applied Neuropharmacology of Anticonvulsant Drugs (PHS Advisory Committee on the Epilepsies) and the Ad Hoc Committee on Anticonvulsant Drugs (advisory to the Institute), a workshop, "Pharmacology of Antiepileptic Drugs," in June 1970 at Airlie House, Warrenton, Va. Some 16 investigators and a like number of additional participants discussed their research as it relates to the pharmacology of antiepileptic drugs, evaluated the scattered but growing volume of data which has been inadequately applied to man and determined that this information should be drawn together at a symposium and published for the practicing physicians who treat epileptic patients.

(*d*) Arranged for a symposium on the subject "Pharmacology of Antiepileptic Drugs," to be held at the Camelback Inn, Phoenix, Ariz., Septermer 8–10, 1971.

Education training

Generally, the first physician to see an epilepsy victim is a general practitioner. Unfortunately, many doctors cannot keep up with all the latest knowledge in all diseases. Particularly the unusual types of specific diseases. To overcome this serious problem in health care, the Institute has made a contract with the University of California to develop a "tutorial environment," a programed teaching machine, with which doctors can teach themselves the things they need to know about epilepsy. After a prototype has determined the practicality of the device, these will be made available to many centers where they can be used by interested physicians.

Meanwhile, NINDS training programs at leading medical schools continue to prepare outstanding young scientists for careers in teaching, research and treatment of patients. Trainees pursue balanced teaching and research programs in the basic neurological sciences, clinical neurology, neuropathology and neuropharmacology. Those who are interested in the epilepsies may be assigned to staff men working in these disorders, to learn diagnostic and therapeutic methods, including EEG operation and interpretation. As training progresses, a trainee joins a team which manages epilepsy patients and helps in diagnostic and therapeutic procedures needed and participates in studies of anticonvulsant drugs.

Information—Public

Through its Information Office, the Institute distributed almost 40,000 copies of pamphlets and monographs on the epilepsies in response to requests from

scientists, physicians, paramedical personel and the general public. The materials include *Epilepsy, Hope through Research* for public inquiries, and for scientific use, monographs entitled, *The Clinical Neurophysiology of Epilepsy—A survey of Current Research and Epilepsy—A Review of Clinical and Basic Research.* Interest in the publications was stimulated by newspaper and magazine articles, health columns, and radio announcements.

RESEARCH ON DEAFNESS

Mr. FLOOD. We have the impression that recently there is a nationwide interest—there certainly is around here—in deafness.

Dr. MACNICHOL. The deaf are our largest number of handicapped people.

Mr. FLOOD. Why is it that somebody is deaf from infancy without realizing it until he goes to take an examination to drive an over-the-highway truck and finds that he can't hear in his left ear and never could?

Dr. MACNICHOL. If someone has a good ear, they may not even recognize that their other ear is not working.

Mr. FLOOD. Why? Wouldn't that interest you?

Dr. MACNICHOL. It interests me and surprises me but apparently this is so. I have one ear that is going downhill very rapidly and I notice the progressive change.

Mr. FLOOD. Why would it go down rapidly in one ear?

Dr. MACNICHOL. This is something that occurs to people progressively with age, to some of us more than others. It may be due to injury, very loud sounds, diseases during childhood, middle-ear infection which then doesn't manifest itself until much later in life.

Mr. FLOOD. This is attracting a lot of attention, I suppose because of the jet age and industrial development, but there has been an increased interest in deafness nationwide. Are you people aware of that?

HEARING, SPEECH, AND LANGUAGE

Dr. MACNICHOL. Yes, indeed, we are, and our Institute has a great deal of interest in deafness and hearing research. Again, if you are interested, I have a special report on communicative disorders I would be glad to submit.

(The statement follows:)

HEARING, SPEECH, AND LANGUAGE

To be able to comunicate—to participate in the continuous exchange of information—is a universally inherent need. As the Subcommittee on Human Communication and Its Disorders of the National Advisory Neurological Diseases and Stroke Council wrote: "Communication is a primary ingredient in the biological world, the cohesive force in every human culture and the dominant influence in the personal life of every one of us." Yet for approximately 20 million Americans, this interchange is impeded by a speech, hearing, or language disorder. The subcommittee found approximately 8½ million Americans to have a handicapping hearing impairment with 236,000 of these being totally deaf; 2 million who have either no ability or an impaired ability to comprehend language; and 10 million Americans with speech disorders. One-fifth of these are under 21 years old, and the percentage may go higher as those children affected by maternal rubella infection during the 1964–65 epidemic are screened for possible communication problems.

The Nation is spending more the $500 million annually to provide special education and vocational rehabilitation programs for these Americans, and to seek answers through research.

	1968	1969	1970	1971 estimate	1972 estimate
NINDS research support for hearing, speech, and language	$8,350,000	$8,233,000	$7,267,000	$7,900,000	$7,765,000

National Institutes of Health

National Institute of Neurological Diseases and Stroke

Hearing, Speech, and Language

The Program

Communication disorders have been a major concern to the National Institute of Neurological Diseases and Stroke since its inception 21 years ago. Early in the program, Dr. Grant Rasmussen, who made one of the most significant breakthroughs in audiology was brought to the Institute. He found that, in addition to having certain nerves which relay messages from the ear to the brain (afferent), the body a'so had nerves which carried messages from the brain to the ear (efferent). The discovery of this "feedback" system from the brain to the ear opened a new area of basic research, and has influenced modern audiology research ever since. During the last 11 years, emphasis on communication research has grown exponentially, as laboratory procedures have become increasingly sophisticated and training more precise. The growing financial support for this area reflects the Institute's concern and interests in the field.

Research has centered on both normal and deviant patterns of speech, hearing, and language, to gain more insight into the basic psysiologic processes involved.

Hearing research has focused on defects resulting from malformations of the ear, disorders of the auditory nerve, and of the sound-receiving centers of the brain. Speech research has been concerned with problems of articulation (including studies of cleft palate, and facial malformations coordinated with the National Institute of Dental Research) ; late acquisition of speech or failure to talk at all; laryngeal removal, and recently laryngeal transplants in animals. Language defects being studied include the inability to receive, interpret, retain, and express language which can result from aphasia and central perception disorders.

Many problems remain to be solved, such as the causes of Meniere's disease, sensori-neural deafness, some forms of aphasia (the inability to assign meaning to words), and stuttering. But basic information, gained during the past two decades, has provided a sound basis for some of the significant advances made during the last few years in such areas as laryngectomy, computer diagnosis of laryngeal tumors, audiometric testing, scanning electron microscopy of ear structures, and temporal bone patho'ogy. With the new technological advances have also come new emphases such as the explosion of research on the damaging effects of noise, and larygeal and middle ear transplant research.

Currently, the Institute is supporting 299 communicative disorder research projects in medical centers throughout the country. NINDS has a'so awarded 64 training grants to medical centers. Since communication prob'ems are often so intrinsically bound up with one another, the Institute's five multidisciplinary clinical research centers—at Princeton, Central Institute for the Deaf in St. Louis, the University of Chicago, the Kresge Hearing Research Institute of Ann Arbor, Mich.; and the University of Florida—comprise a major part of the research program. Their integration of every facet of communication research through specialists such as engineers, audiologists, speech therapists, and statisticians, provide the opportunity for a total approach to many complex communication problems.

Additional clinical information comes from the three Institute-supported outpatient clinics—at Stanford, Northwestern, and Pittsburgh—where patients receive thorough care while remaining in their normal environment. Investi-

gators at the Northwestern University clinic are studying sensori-neural deafness, which is one of the most baffling, handicapping, and most common causes of deafness. Often referred to as VIIIth nerve disorder, it cannot be overcome adequately by using hearing aids. It may eventually be overcome by bypassing the ear and directly stimulating the brain to interpret auditory impulses, but much research must be done before this possibility can be evaluated.

Northwestern's investigators, therefore, are continuing to study auditory behavior produced by various types of sensori-neural loss. A recent study has indicated that patients with sensori-neural deficit are more distracted by background noise—and particularly by speech heard in the background—than are persons with normal hearing or those with middle ear (or conductive) hearing loss.

Investigators at the Pittsburgh clinic are interested in cochlear dysfunction, while scientists at Stanford are concentrating on the auditory mechanisms involved in sound transmission.

The Institute's most comprehensive study of communication is being conducted by the collaborative perinatal project. The 14,000 children registered at six participating hospitals (Johns Hopkins University; Boston Children's Hospital; University of Buffalo Hospital; University of Tennessee, Memphis; University of Oregon, Portland), were followed from birth and were tested at age 3 and again at age 8. The studies are enabling early detection and correction of communication problems; affording scientists the opportunity to relate communication disorders to conditions occurring early in life; and they are providing scientists with the opportunity to see which minor communication problem (such as faulty articulation) undergoes a spontaneous recovery.

It was through the collaborative perinatal project that the widespread hearing loss resulting from maternal rubella infection was first documented. These studies showed that a large portion of the 20,000 to 30,000 infants born with congenital rubella during the 1964–65 epidemic had some communication problems.

To aid scientists in keeping up with recent publications in the communication field, the Institute is maintaining its support of the Information Center for Hearing, Speech, and Disorders of Human Communication. Located at the Johns Hopkins University, the network conducts computerized bibliographic searches for researchers, physicians, and laymen. Last year they answered 1,300 requests for a total of 10,000 bibliographies.

In addition to the clinics and centers, the Institute also helps to support four regional temporal bone banks and 40 bone pathology laboratories in this country. The banks and laboratories are providing vital basic information on various aspects of ear disease leading to deafness. In this venture, the Institute is joined by the Deafness Research Foundation, the American Academy of Ophthalmology and Otolaryngology, and the Armed Forces Institute of Pathology. The temporal bone banks are located at the University of Chicago, the Johns Hopkins University in Baltimore, the San Francisco Medical Center of the University of California, and Baylor University in Houston.

Scientists are studying middle and inner ear structures to determine how they were damaged, and which disease processes could have been involved. In cases where detailed auditory and vestibular examinations have preceded death, a precise correlation between symptoms and microscopic pathological changes in the inner ear are being made.

In the publication prepared by the Subcommittee on Human Communication and Its Disorders last year, entitled "Human Communication and Its Disorders—an Overview," the committee recommended 26 research needs to be met, such as refinement of children's hearing tests, linguistic research, and improved hearing aids. Research in many of the suggested areas is currently underway, and this year some significant advances in several areas have been made.

Hearing aids

An experimental model of a permanently implantable hearing aid, which is designed to last a lifetime, has been tested in animals by Institute grantees at the University of Oregon Medical School. The device consists of a tiny crystal, less than one-half inch long and ten-thousandths of an inch in diameter, attached to a small wire probe. It is designed to be implanted in the middle ear, where it would receive electrical impulses causing it to vibrate. Vibration is the essential action in normal ears which causes sound to be converted into nerve impulses.

These impu'ses are then interpreted by the brain, enabling a person to hear. Although the aid wou'd not help patients with nerve damage, it could benefit thousands of people who lose their hearing through inoperable otosc'erosis. Before the device can be perfected, however, scientists must first develop an implantable microphone and an implantable power source. Severa' tests were conducted on animals, and the model was then tested in a volunteer with normal hearing, using a tape recorder rather than the microphone. "Sounds" were reported to be clear and without distortion which is a prob'em found in many currently available aids that amplify sound in the outer ear.

New testing method shows promise

At present, the causes of genetic deafness still are not very we'l understood. The importance of elucidating these causes cannot be underestimated, because it is believed that nearly one-half of all cases of deafness in this country have a genetic origin. Two main problems in genetic deafness research are: The lack of a method for breeding animals specifically for genetic deafness; and, the lack of a direct and re'iable test to measure deafness in test animals. Recent'y, however, a significant advance has been made in both these interre'ated areas through some collaborative research with a National Institute of Dental Research geneticist.

The scientist has adapted a lock-in amp'ifier to measure directly the ability of the animal's ear to convert sound waves into electrical impulses. The amplifier is designed to detect and measure e'ectrical signals of known frequency that are buried in high amp'itude background noise. It is these electrical impulses which are interpreted by the brain, enab'ing the subject to hear. If the wave pattern of the electrical signal from the ear is the same as that of the sound wave, the subject is not deaf. The subject is considered to have impaired hearing when the e'ectrical signal is sma'ler than that of the sound wave.

A histological examination of 28 test animals correlated precisely with the diagnosis arrived at using the amplifier. Since the test results represent different hearing loss patterns, it may now be possible to breed animals specifically for genetic deafness, by pairing animals which are deaf, hearing impaired, and normal. Their offspring can then be studied at a very early age to determine how normals first begin to hear, how hearing degenerates in the hearing impaired, and what genetic mechanisms are involved in total genetic deafness.

To date, an infant born of two deaf parents, was tested by this method and found to be able to hear. This indicated that the test might eventually be a reliable indicator of human as well as animal hearing, and could be especially useful in detecting hearing loss of deafness in infants.

Effects of noise on hearing

Increasing attention is being given to the very real prob'em of noise pollution. Last year, studies established that even steady exposure (2 hours) to rock and roll music seemed to cause hearing loss in some people. Investigators at the Central Institute for the Deaf in St. Louis have been conducting extensive studies on the effects of noise on hearing. They have found that certain exposures to intense sound can produce substantial permanent injury to the inner ear, while at the same time producing little or no immediate'y detectable changes in the audiogram. (Previously, investigators had believed that any permanent shift in the ear's threshold level to noise would be indicated in the audiogram.) These studies indicate, therefore, that exposure to loud noise produces pathological changes resulting in a hearing loss which is delayed or progressive over many years.

They found on histologic examination of animals exposed to noise: regions of substantial sensory receptor loss in all cochleas subjected to low-frequency noise; small hair cell losses in coch'eas exposed to high-frequency noise; and only small numbers of missing hair cells in controls. They concluded that exposure to noise can produce permanent injury to the inner ear even though permanent shifts measured by the animal's behavior are absent or minimal; sound can destroy gradually, bit by bit, the integrity of the inner ear, and eventually, the ability to hear."

An Institute grantee at the University of Minnesota has found that exposure to noise 20 dB above the maximum safe level (considered to be 80 dB) for 1 to 2 minutes will change the ear's threshold level for a few minutes after

cessation of the noise. Full recovery from noise 35–45 dB above maximum safe level takes 10–15 hours; while 50 dB above maximum may take days or weeks for recovery. Chemicals and drugs tested (including the tranquilizer atarax, vitamin B1 and pantothenic acid) afforded no protection. Certain antibiotics have been found to produce destruction similar to that produced by permanent threshold shift caused by noise. In fact a subtoxic dose of the drug Kanamycin was found to make the ear more susceptible to damage from noise.

This same investigator has found that intermittent exposures to high-frequency, high-energy noise—either long bursts or short—often produce a delayed recovery requiring more than 16 hours of rest to restore initial sensitivity. He concludes that in an industrial situation some workers in this level of noise may have a chronic change in their ability to hear (as measured soon after the noise has stopped). Chronic auditory fatigue, he feels, may lead to permanent damage. He advises that men should not be subjected to levels above 100 dB even if periods of quiet pause far exceed periods of noise.

Rapid and permanent damage to cochlear hair cells has been found, by an NINDS-supported scientist at South Louisiana State University, to result from high intensity pulses such as those produced by sonic booms. Animal studies indicate that sonic booms can weaken the cochlea, which could, in turn lead to loss of hearing. Although scientists observed no difference in the ear's outward involuntary (unwilled) movements before and after the boom, histological examinations showed damage to the cochlear hair cells of all test animals. This indicates, according to the researchers, that damage results from exposure to the sonic boom even though it is not behaviorably noticeable.

Inner ear fluid used in diagnosis

Two common diseases affecting the inner ear are Meniere's disease and acoustic nerve tumor. Both produce similar symptoms such as sudden sensori-neural hearing impairment in the affected ear, vertigo (dizziness and rining in the ears) and hydrops (accumulation of fluid in the ear cavity). Their treatment differs significantly, however, and an early diagnosis is imperative because acoustic nerve tumors can be removed successfully only when diagnosed early. Failure to remove the tumor can result in deafness and even death. Grantees at the University of Michigan Medical School and the Massachusetts Eye and Ear Infirmary, have recently found a method for early differentiation of the two disorders. They found that the two diseases produce different biochemical properties in the inner ear fluid, and have developed a method of biochemical diagnosis which has been shown effective in 23 cases studied. They found that fluid of patients with Menier's disease had an electrolyte imbalance (increased potassium and decreased sodium) which is directly opposite to that produced by acoustic tumor (increased sodium and decreased potassium). In addition, fluid of patients with accoustic nerve tumor was found to have an elevated protein level.

This method should be invaluable in helping to save the hearing of patients with acoustic nerve tumors.

Sudden deafness related to systemic disorders

Results of an Institute-supported 5-year study at the University of Michigan Medical Center indicate that sudden deafness can be related to systemic diseases, and is not necessarily a localized problem. They report that 40 patients experiencing onsets of sudden deafness were found to have systemic diseases, including fat embolism and hypercoagulation as well as infection from mycoplasma pneumoniae, adenovirus and parainfluenza virus. According to the investigators, therefore, the ear should be considered, much as the eye has been, a sensitive indicator of vascular and intravascular pathology.

Middle ear transplants

Several transplants of the middle ear (which includes the eardrum and three small middle ear bones) have been performed recently, enabling patients with conductive hearing loss to regain hearing. The latest transplant operation was conducted in March 1970 in Portland, Ore. A middle ear bank is currently being maintained in Palo Alto, Calif., to serve this purpose under a program known as Project Hear Foundation. Only certain cases can be helped with this technique, and it has no value to persons with nerve deafness. But in some cases where the middle ear has been damaged, implantation of the three ossicles and

drum enables transmission of sound to the inner ear and therefore "hearing" once again.

Laryngeal research

It is estimated that some 6,000 persons undergo surgery every year for removal of a diseased larynx or voice box (laryngectomy). If these patients are to learn to communicate verbally instead of tediously writing notes, they must master esophageal speech, or use an electronic larynx, or a prosthetic larynx.

Esophageal speech is accomplished by expelling swallowed air from the food pipe (esophagus). This is difficult to accomplish and the speech usually sounds coarse and explosive. Use of an electronic larynx (a transducer held in one hand and pressed to the neck by the other each time the user wishes to speak) produces mechanical and often distracting speech.

Significant advancement has recently been made by two New York investigators supported by the Department's Social and Rehabilitation Service in perfecting a prosthetic larynx which is insertable (rather than implantable). The insertable device avoids the problem of tissue rejection or infection accompanying implanted devices, partly because it is housed in normal esophageal mucosa and skin flaps. The voice formed by the artificial prosthesis is produced by normal breathing and speaking activity in contrast to that of esophageal and electrolaryngeal speech. The device, which is a physiologic replica of the human larynx, can be inserted and removed by the user without assistance, and requires virtually no training period. The unit consists of a reed and air valve which rests flatly against the neck below collar level.

The artificial larynx is initially intended for experimental use by the estimated 20 to 30 percent of laryngectomy patients who are unable to learn esophageal speech satisfactorily. It is not dependent on any source of power other than the patient's own respiratory system, and enables the wearer to breathe and swallow without any manual manipulation. The investigators plan to conduct further clinical studies concentrating on long-term use, comfort and psychologic acceptability. They predict that mass-produced prosthetic larynges should be available for a broad range of patients before 1972.

Another area of research—larynx transplants—is being carried out in animals. Two main problems have been rejection of the implanted tissue and regeneration of the laryngeal nerves. NINDS-supported scientists at the Washington University School of Medicine, in Missouri, have been studying the problem of nerve regeneration, and have recently found two techniques which greatly aid the regeneration process.

One of these is use of an experimental drug which significantly shortened nerve regeneration time by accelerating protein and RNA synthesis in the nerve cells. This is an important finding because the faster the nerve is regenerated, the better is the chance for restoration of original function. Treated dogs recovered function 32 days faster than untreated dogs, and experienced no toxic effects from the preparation.

The investigators also have improved chances for successful reinnervation by leaving the nerve intact and resuturing only the muscle surrounding the transplanted larynx. With this technique, regenerating nerve fibers have only a short distance to grow to reach their target and therefore have a much better chance of innervating the appropriate one. These techniques should greatly improve larynx transplant procedures.

These scientists have also developed three methods of preventing voice loss in patients having cancer of part of the larynx. The techniques, known as conservation surgery, keep the cordal function of the larynx and essential component parts of the pharynx intact when they have not been affected by the malignancy, preserving the patient's ability to speak. These procedures are far more desirable than removal of the entire larynx when only part of it is cancerous.

Speech, language, and perception acquisition in children studied

Grantees at the Massachusetts Institute of Technology are determining various aspects of language acquisition, syntax, and perception in children, using computer aids and developmental tests. Word discrimination tests (differentiating meaning of words which are spelled the same way but accented on different syllables) have shown that children in grades 6, 7, and 8 as well as adults produce 100-percent correct responses, while kindergartners produce only 49-percent cor-

rect responses. They have found that girls generally acquire proficiency with syllable stress rules at slightly earlier ages than boys, and they are now seeking to determine the relationship between rules of syllable stress and rules of syntax to see which is the prerequisite. Studies of this nature should lead to a better understanding of the process of language perception, and the way words are assigned meaning in sentences.

Collaborative program yields information on communication disorders and development in children

An analysis of hearing, speech, and language development of 4,400 children enrolled in the Institute's collaborative perinatal project has produced the startling fact that only 10.5 percent of those tested were reading orally at their proper grade level. This and other general information on communication development is being gained from results of the study's battery of 12 tests administered to participating children when they were 3 and 8 years of age. The tests included the following: hearing loss, word discrimination, memory for digits and syllables, vocabulary, orientation (sentence comprehension and assessment of common knowledge) understanding a story, silent reading, oral reading, knowledge of grammatical rules, writing to dictation, articulation, and an overall evaluation.

Results from the studies are providing scientists with a better understanding of the extent and nature of early communication problems, and should lead to development of better aids for helping children with communication problems.

USE OF TECHNICAL LANGUAGE IN JUSTIFICATION

Mr. FLOOD. Now, one of the problems we have that we talk about every year that apparently is impossible of solution is the use, with no definition or explanation, of terms that not one lay person out of a thousand could recognize at all, even the members of this subcommittee —and we are not amateurs at this kind of thing.

Suppose you take a look at the last half of page 220. You have "laminar tomography." I am a lawyer and we commit our own sins in this field and I can recite some of those for you. Then you use the term "familial lipidoses", "Refsum's disease," and half a dozen others like that.

Dr. MACNICHOL. You want to know what laminar tomography is? It is an X-ray technique. It is a type of X-ray technique.

Mr. FLOOD. But why didn't you put that in parenthesis when you sent this up here?

Dr. MACNICHOL. I agree. I tried to take them out of the opening statement.

Mr. FLOOD. "Familial lipidoses." Does anybody know what familial lipidoses is?

Mr. MACNICHOL. They are diseases that have to do with fat metabolism. They are inborn areas of metabolism in which fats accumulate in the brain, and familial means that they are hereditary in nature and occur in families.

Mr. FLOOD. I guessed that because earlier this week we discussed something allied to that, so I put two and two together and actually came out with four all by myself.

"Refsum's disease." Who is he?

Dr. MARSTON. Refsum is a Norwegian neurologist who discovered this rather rare and interesting disease in which a certain abnormal

material accumulates in the nervous system and causes progressive neurological disease. It is associated with progressive loss of vision.

Mr. FLOOD. "Hypokalemik periodic paralysis."

Dr. MACNICHOL. That means people have paralysis because they have too little potassium in their blood.

Mr. FLOOD. I would like to suggest in the future you put something like that in parenthesis.

"Dermatomyositis/polymyositis." What is that?

Dr. MACNICHOL. These are muscle diseases.

Mr. FLOOD. "Myasthenia gravis." What is that?

Dr. MACNICHOL. That is a disease of the neuromuscular junction. That is where the nerve impinges on the muscle for controlling it. In myasthenia gravis the message doesn't get across from the nerve to the muscle to tell it to contract. People's eyelids droop and they can't use a lot of their other muscles.

Mr. FLOOD. "Basal ganglia"?

Dr. MACNICHOL. Basal ganglia are a part of the brain involved in Parkinson's disease, for example.

Mr. FLOOD. "Hydrocephalus"?

Dr. MACNICHOL. Water on the brain.

Mr. FLOOD. "Chronic embolization."

Dr. MACNICHOL. The latter is something that plugs up a blood vessel; a clot.

Mr. FLOOD. "Pseudo-hypertrophic muscular dystrophy."

Dr. MACNICHOL. That is a particular kind of muscular disease in which the muscles swell.

Mr. FLOOD. I think we should correct this in the future.

Dr. MARSTON. We will do that, Mr. Chairman. I think the point you make is good. This record serves as a valuable lesson.

LATE APPORTIONMENT OF FISCAL YEAR 1971 FUNDS

Mr. MICHEL. Doctor, do you know when you actually got word of the release of '71 funds?

Dr. MARSTON. As I recall, it was in March.

Mr. MILLER. That sounds about right.

Mr. MICHEL. In other words, March 1971, the year in which we are now. It was 9 months after the fiscal year actually began.

When those funds were released, how much were they, more or less, in terms of what you were operating on under the continuing resolution?

Dr. MACNICHOL. They were $6,310,000 more than the continuing resolution.

Mr. MICHEL. What are we talking about in total dollars and cents?

Dr. MACNICHOL. The appropriation is $105,807,000 and the apportionment was $103,485,000.

Mr. MICHEL. When you were making up this budget for 1972, you had no idea what the final figures were going to be for 1971, is that right?

Dr. MACNICHOL. Yes, sir.

EFFECT OF LATE APPORTIONMENT OF 1971 APPROPRIATIONS ON 1972 BUDGET

Mr. MICHEL. If you were putting together that 1972 budget now that you know the 1971 results, would it be structured any differently than what it is? That may not altogether be a fair question, but what I am saying is that you actually didn't know for sure what you were going to have to spend in 1971 when you were making up the budget for 1972. That is no fault of yours, of course. I am just wondering now if you had known certain information, whether or not there would be any kind of adjustment in the make-up of your 1972 budget?

Mr. MILLER. The congressional increase above the President's budget for 1971 was $8.8 million for this Institute. We held in reserve approximately $3.6 million which we are proposing to release to cover the cost of the pay increases both in this Institute and elsewhere. We can use funds appropriated to this Institute to cover the pay increase costs in the Institute, but that part which is to be transferred to other appropriations to meet the increased pay costs requires congressional approval, which we are seeking in the 1971 Supplemental Appropriation bill.

When we decided now how much of the congressional increase above the 1971 request we were going to spend, we revised the 1972 budget to cover the outlay effect of that increase above the President's budget. So we did revise the 1972 budget to a certain extent, in the light of our spending plans for fiscal year 1971.

However, we did still maintain the specific program cuts in answer to the chairman's first question.

STATUS OF TRAINING IN THE BUDGET

Mr. MICHEL. Are you concerned about the downgrading of training that will be provided for in this budget?

Dr. MACNICHOL. I am concerned about the long-range problems with training and, of course, this will be decided when NIH's study of the effects and impacts of the training programs are completed.

Mr. MICHEL. Have you a target date for completion of those studies?

Dr. MARSTON. They will be available and have an impact on the 1973 budget but not on the 1972 budget.

Again I would make the point here that the dollar level with the exception of the predoctoral fellowships, was maintained at the same level. The apparent decrease is really the proportionate transfer of funds from this Institute's budget to the Manpower Bureau.

Dr. MACNICHOL. That is why I say at this point that I am not concerned about the immediate effects because apparently the training funds will get used for the same purposes; they will be reviewed in the same way as far as the 1972 budget is concerned.

Mr. MICHEL. We have gone over this hurdle several times with the different institutes and I think it is good to have it in the record. It is difficult for us as members here, getting inquiries from people out in the field where the only visible figures convey the general impression that there has been a real diminution of funds or decline here in the

training field. A qpestion is then raised as to whether we know what we are doing here and whether we are familiar with the work of training people in this field.

NEUROLOGICAL RESEARCH CENTERS

I see here in your testimony special mention of the centers that you are at least thinking about. As a matter of fact, in your amended statement did you say there are two centers underway?

Dr. MACNICHOL. Two small research centers that we have funded.

Mr. MICHEL. Does that include the project in Arizona?

Dr. MACNICHOL. Yes. The Barrow Institute in Phoenix is one of them. The one at Northwestern University is the other.

Mr. MILLER. The principal one you have asked about is funded in the Social and Rehabilitation Services appropriation. The principal money comes from there and the project has been funded.

Mr. MICHEL. You said we were going to have six studies or six centers?

Dr. MACNICHOL. Yes, we will have six groups making feasibility studies. Essentially what we are asking them is, if you were going to set up a center, what would you do, what problems do you think are the most important, and what leads do you have that would suggest that you ought to do certain kinds of research in the centers?

Mr. MICHEL. Have those interested in setting up those centers submitted plans to you up to this point? Are you still soliciting them? Where are we?

Dr. MACNICHOL. They have been solicited and are in the process of review.

Mr. MICHEL. Have you received the one, that would be a combination, from Wesley Hospital in Chicago, Chicago Rehabilitation Institute, and Northwestern Medical School? Is that one?

Dr. MACNICHOL. I am sure that is one of them; yes, sir.

Mr. MICHEL. If my memory serves me correctly, we don't really have any competent kind of center in the United States to deal with this problem; do we?

Dr. MACNICHOL. In my opinion, we don't.

TREATMENT OF SPINAL INJURIES IN VETERANS

Mr. MICHEL. With the returning veterans, with very serious problems in addition to the host of accident cases we continue to get from our highway accidents and other fields, it seems to me this is one of those areas in which we ought to move ahead.

I am glad to see there was something in your statement addressed to this particular subject. I think there are some 5,000 or 10,000 of these spinal cord injury cases around the country on a yearly basis. As I recall, about 85 percent of those are able-bodied men in the most productive and active period of their lives.

Dr. MACNICHOL. By the time they get back to this country and get into the VA centers, this is largely a rehabilitation problem. This is where VA and the Social and Rehabilitation Service are essentially

putting their efforts. We are particularly interested in the acute phase, right after they are injured, in order that they become less of a rehabilitative problem.

Mr. MICHEL. I appreciate your clearing up the record, so to speak, on that point. It is a very important distinction to be made.

PROPOSED BUDGET REDUCTIONS

The Eye Institute was taken out of your shop. Is that responsible for the big reduction in the budget, $95 million budgeted for 1972 compared with $128 to $131 million budgeted in 1968–1969?

Dr. MACNICHOL. That is correct, sir. About $23 million were transferred.

Mr. MICHEL. Nevertheless, I must express concern as the chairman did on the number of minuses we see in the justifications for your particular shop.

Dr. MACNICHOL. Again it is a matter of department priorities. It would take a lot of money to move everything at once.

Mr. MICHEL. We appreciate that on this side of the table maybe even more so than you folks do over there. We do not in anyway want to leave the impression for the record that even under those kinds of restraints sometimes we can't move on our own initiative on this side of the table to be sure there is adequate funding for these programs.

That is all, Mr. Chairman.

Mr. FLOOD. Mr. Casey.

Mr. CASEY. The only thing that has gone up in your budget is personnel compensation and benefits which was due to acts of Congress. You drop $3,624,000 on all the rest of your expenses. When we look at the research grant program, there is not a plus in that list on page 215 on the first part of it there.

A couple of them hold their own. The rest of them are all deductions.

MUSCULAR DYSTROPHY

Does your institute work on muscular dystrophy?

Dr. MACNICHOL. Yes, sir.

Mr. CASEY. Are we getting anywhere in that? Do we need more work or less work? It seems we have less requested here.

Dr. MACNICHOL. It is a disease that obviously does need a great deal of work. At the present time Dr. King Engel, who is our Chief of Medical Neurology in the Institute, is a specialist and he and his laboratory staff spend most of their time and effort on this subject and I think they are getting along very well with the identification of the causes of some of these diseases.

(The following special report was submitted for the record:)

MUSCULAR DYSTROPHY AND THE NEUROMUSCULAR DISORDERS

The neuromuscular disorders, characterized generally by weakness, wasting and fatigue of muscles, primarily affect children and young adults. The two

most common disorders in this group, the muscular dystrophies and myasthenia gravis afflict about 200,000 and 30,000 patients respectively. When other less prevalent neuromuscular disorders are included, estimates of victims from these conditions range from 250,000 to as many as 1 million.

NINDS Research Support for Muscular Dystrophy and Other Neuromuscular Disorders

1968: $3,899,000. 1969: $5,139,000. 1970: $5,092,000. 1971: (estimate) $5,476,000. 1972: (estimate) $5,377,000.

MUSCULAR DYSTROPHY AND THE NEUROMUSCULAR DISORDERS

Muscular dystrophy

The muscular dystrophies are a group of inherited disorders characterized by progressive weakening and wasting of the muscles. Usually the voluntary or skeletal muscles, such as the muscles of the shoulder and hip regions, are affected equally on both sides of the body. The three most common types of muscular dystrophy (MD) are: Duchenne muscular dystrophy, which only affects young boys, usually about 2 to 5 years of age; limb-girdle muscular dystrophy, which strikes children and adults of both sexes equally and first affects the use of arms and legs; and facio-scapulohumeral muscular dystrophy which affects teenagers and adults of both sexes and progresses slowly to affect the muscles of the face, shoulder and upper arms.

All three types of MD are inherited, but by different modes. Duchenne muscular dystrophy, the most severe type, is sex-linked and recessively inherited. That is, each pregnancy of a female carrier has a one-in-four chance of producing an affected male child and a one-in-four chance of producing another female carrier. Because it is now possible to determine fetal sex by tapping the mother's amniotic fluid and studying chromosomes in the harvested cells, a pregnant woman who knows she is a carrier can be alerted to her probability of giving birth to a child with muscular dystrophy. If the fetus is male, there is a 50 percent chance that he will be born with muscular dystrophy.

With present knowledge, the most successful method of managing MD is preventive medicine by first detecting female carriers of the Duchenne dystrophy gene and then offering genetic counseling. Although these female carriers usually have no noticeable weakness, it is now possible to detect 50 to 70 percent of them by a combination of the estimation of the enzyme creatine kinase in their serum, quantitative electromyography (a study of muscle electrical reactions), and muscle biopsy.

Research is progressing to reduce the number of unidentified carriers of MD to zero and to simplify the detection methods. The common test for carriers is the serum creatine kinase estimation, but recently scientists at the Medical Neurology Branch of the National Institute of Neurological Diseases and Stroke have found that a histochemical analysis of muscle biopsy from clinically normal carriers of Duchenne MD show atrophy and derangement of scattered grouped muscle fibers after being specially stained.

Other scientists are analyzing by computer electromyograms of patients with MD, known carriers and controls. They have found that MD carriers have a greater proportion of shorter intervals between consecutive potential changes than control subjects, but that these changes are slight when compared with the abnormalities found in the muscles of affected patients. Other promising leads in discovering MD carriers are estimations of total body potassium and rubidium turnover and a search for muscle antibodies specific to this disease.

In initial studies, scientists are attempting to identify elevated levels of creatine phosphokinase (CPK) in cells from amniotic fluid tapped from pregnant women, and thus determine for certain whether the woman is carrying a dystrophic child. Still other scientists are attempting to identify increased levels of CPK in the mother's blood. The further development of one or several of these methods may allow routine screening of suspected carriers of Duchenne MD.

Although there is at present no cure for MD, there is increasing hope that a successful treatment will be developed. Two muscle diseases very much like MD, in fact often misdiagnosed as MD, are now highly treatable. Polymyositis/der-

matomyositis, which often mimics MD, is an inflammatory disorder of the muscle and/or skin characterized, as is MD, by elevated muscle enzymes. Investigators successfully treat this disease with a corticosteroid regimen that effectively controls inflammatory myopathy and maintains a high degree of improvement.

A second muscle disease, hypokalemic periodic paralysis, characterized by attacks of paralysis usually beginning in childhood or adolescence and occurring at daily to yearly intervals, has also been found by investigators to be highly treatable. Patients with this disorder have been dramatically improved by acetazolamide treatment in studies at several institutions including the NIH Clinical Center. This treatment has been maintained for periods as long as 4 years with minimal or no side effects and several patients previously disabled are now without symptoms. Success in managing these two muscle disorders has improved the outlook for eventually finding a treatment for various forms of MD.

The search for effective drug therapy for MD has extended widely, but reports of the benefit of vitamins, amino-acid mixtures, nucleotides and anabolic steroids have all proven to be incorrect. Management of the disorder, therefore, is based on maintaining mobility, building up the less-affected muscles, preventing contractures and treating acute illnesses, such as respiratory distress or cardiac failure, which threaten MD patients.

The development of effective treatment for the muscular dystrophies is impeded by lack of a good, quantitative method of measuring the rate of progression of this group of diseases. Many years often elapse before it becomes apparent that a proposed drug treatment is ineffective in human use. Two groups of NINDS grantees, however, have developed a protocol which should shorten the time required for evaluation of proposed treatments. Two forms of evaluation will be used in these studies: trials of patients carrying out activities of daily living which, therefore, are not likely to be affected by practice, and muscle strength tests. The data will be analyzed by computer.

Although animal models can be helpful in the study of human disease, not all of them are completely relevant to the disease process in humans. A tissue culture technique now appears to have been improved to the point where differences between normal and dystrophic muscle cells of chickens can be shown. The dystrophic cells develop more quickly in culture than do normal cells, but then are found to degenerate more quickly. The application of the technique to diseased muscle should yield important information. According to scientists studying the dystrophic chicken, changes have been found in the structure of one of the contractile proteins of muscle during normal muscle contraction.

NINDS-supported studies have yielded information on oxygen therapy in dystrophic chickens which may represent a contribution toward understanding the progressive degenerating process of MD. In chickens with hereditary MD, these investigators have found that before degeneration occurs in muscle fibers, there is decrease in the enzyme alkaline phosphatase in the capillaries and small arterioles. They have also shown that continuous therapy at oxygen levels of 70 percent is successful in delaying the onset of muscular dystrophic symptoms in these chickens. Dystrophic symptoms were delayed for approximately seven weeks, after which continuous oxygen therapy did not prevent a progressive increase in the onset of dystrophy. Oxygen therapy was unable to affect the expression of this trait in chickens which showed it prior to treatment.

Indicators of the nature of the underlying disease process in MD are just beginning to appear. Studies of this sort have been hampered somewhat because it is difficult to obtain large quantities of dystrophic muscle for the study of chemical and tissue changes.

A new tissue culture technique developed by an NIH grantee which contains living neuromuscular junctions—the motor nerve fiber and the muscle fiber it activates—is expected to answer many questions about the basic defect in MD, myasthenia gravis, and other neuromuscular disorders. This investigator will soon obtain dystrophic mice and culture spinal-cord sections and muscle from the animals to attempt to locate where on the neuromuscular junction the defect occurs.

The most striking biochemical derangement in patients with Duchenne MD is the very high level of the enzyme creatine phosphokinase in the blood serum. This, however, is believed to be the muscles' response to injury, rather than the real underlying defect involved. Several biochemical studies have recently shown that

there is an abnormal protein synthesis in MD, but scientists have concluded that the increased protein synthesis is not directly related to the severity of tissue changes. The changes could be secondary to the overall disturbances in cell metabolism rather than a reflection of a fundamental hereditary defect.

Histochemical characterizations of muscle, and the recognition of its two principal types of fiber in the Medical Neurology Branch, has provided much impetus to the investigation of muscular dystrophy and other muscle diseases. Investigators here have found that there are two muscle fiber types in human muscles, each of which have distinct chemistry and metabolism and therefore could be expected to react in different ways to a metabolic defect. Recognizing this difference, scientists now have a means of looking at and categorizing a number of muscle disorders. Their analytical approach places major emphasis upon determining whether there is selective or nonselective involvement of muscle fiber types in human diseases. They have found, for example, that in Duchenne MD, both fiber types are affected.

MD has traditionally been accepted to be a primary disease of the muscle itself, but the answer to the cause of MD might be found in an entirely different approach. A new hypothesis on the pathogenesis of one form of MD from the Medical Neurology Branch suggests that the muscle damage in patients with the Duchenne type of progressive muscular dystrophy is produced by abnormalities of the small blood vessels within the muscles, rather than by a primary defect in the muscle fiber itself. These findings are based on evidence obtained from histochemical and electron microscope studies of muscle biopsies from patients with Duchenne MD and carriers of Duchenne MD, and from an experimental model of the disease produced in rabbits by experimental embolization (blockage) of the small arterial vessels within their muscles. They suggest that additional work should be devoted to confirming the role of small blood vessel abnormality in this disease and that consideration should be given to possible therapeutic agents which might enhance the blood supply to the muscle fibers in Duchenne MD.

Myasthenia Gravis

Myasthenia gravis is a neuromuscular disease characterized by weakness and abnormal fatigue of the voluntary muscles. A relatively common disease, it accounts for about 30,000 patients in this country—most of them between the ages of 10–40. Although it may affect any voluntary muscle in the body, myasthenia gravis most frequently affects those of the eyes, face, lips, tongue, throat and neck.

Research into the cause of myasthenia gravis is important if optimum treatment is to be developed. The exact cause of myasthenia gravis is unknown, but the trouble exists somewhere along the motor unit which consists of the lower motor neuron, which is a branching nerve fiber, and the muscle fibers it innervates. Many studies on the etiology of myasthenia gravis have centered on the junction between the axon of the nerve and muscle fibers where nerve impulses liberate an excitatory chemical—acetylcholine—which stimulates the muscle to contract.

Abnormalities in the thymus—an organ situated over the heart which normally atrophies with maturity—are often found associated with myasthenia gravis. Exact relationships between this mass of tissue and neuromuscular function is still largely unknown.

A number of research studies are concerned with the possibility that myasthenia gravis is an autoimmune disorder. In support of this, immunofluorescent techniques have confirmed that one-third of all patients with myasthenia gravis have circulating antibodies directed specifically against skeletal muscle and thymus. Although these antibodies are present in virtually all myasthenia gravis patients with thymoma (tumor of the thymus gland), and in some patients who do not have myasthenia gravis but do have thymoma, it is believed that these antibodies themselves do not cause the symptoms of the disease. Their presence, however, suggests an immunological disorder.

Support for the hypothesis of an autoimmune pathogenesis of myasthenia gravis was obtained in Edinburgh recently. Scientists there report success in producing thymus lesions, disturbances in neuromuscular transmission, and serum autoantibodies in experimental animals. Results obtained from their animal experiments suggest that the neuromuscular transmission block may be caused by

a substance released from a thymus gland that has become chemically abnormal. This substance, however, has not yet been identified. Spontaneous development in a rodent of a syndrome characterized by thumus lesions and serum auto-antibody phenomena corresponding with symptoms of human myasthenia gravis may provide an opportunity for scientists to elucidate the relationships between pathology and serum autoantibodies.

An NINDS grantee reports experimental evidence in guinea pigs supporting the hypothesis that myasthenia gravis is a disorder in which the body causes inflammation of its own thymus gland and overproduction of a proposed thymic "hormone." This "hormone" in turn is proposed to interfere with the transmission of nerve messages to muscle, thus causing muscle weakness.

Investigators at the NINDS Medical Neurology Branch have developed a new working hypothesis to study myasthenia gravis. They propose that a secondary defect in myasthenia gravis is located at the neuromuscular junction, but that it is due to a primary abnormality of the total motor neuron, possibly an abberation in the metabolism in the cell body of this neuron located in the spinal cord. This theory does not rule out the role the thymus may play in the disease, according to these scientists, for it is possible that a circulating factor from the thymus and other tissues may exert a detrimental influence on the motor neuron.

Drug treatment, primarily with anticholinesterase-type of agents, has aided many patients with myasthenia gravis, some to the point that they are able to lead relatively normal lives. Drug regimens now available, however, are not always optimum, so new drug therrapy is constantly being sought. Treatment with the adrenocorticotrophic hormone (ACTH), as reported recently, has resulted in marked improvement in some difficult cases of myasthenia gravis. ACTH treatment, however, still has some disadvantages—the patient's condition tends to worsen before it improves, patients must be carefully observed for untoward side effects during treatment, and the drug must be injected.

Other patients are being helped by surgical removal of the thymus. Data on almost 300 thymectomies showed that this therapy is most effective in women who have had the disease for less than 5 years and who do not have a thymoma.

NINDS Intramural scientists report remarkable and sustained improvement of 4 myasthenia gravis patients using a high single-does alternate-day oral prednisone program for treatment of myasthenia gravis. Although experience to date is limited and more extensive trials are being set up, these investigators believe that this may become the treatment of choice in myasthenia gravis. The alternate-day as opposed to the daily prednisone program results in greater benefit and fewer or absent side effects.

Other promising drugs are undergoing testing at an NINDUS grant-supported institution. One is a veratrine-type of drug, germine mono-acetate which appears to be superior to other drugs of that type because it does not tend to cause high blood pressure and slowing of the heart beat. In skeletal muscle this agent has been found to evoke muscle contraction of greater strength, but of slower duration than with other veratrum alkaloids. Clinical trials limited to 1–2 weeks have demonstrated that improvement in muscle strength has been between minimal and dramatic and varies widely from patient to patient, but no adverse side effects have been observed.

Other Neuromuscular Disorders

The term "neuromuscular disorders" refers to a large and important group of diseases due to a disturbance in function at some point in the motor pathway from the spinal cord to and including the muscle. A partial list of these neuromuscular disorders, from which an estimated 250,000 people suffer, includes familial periodic paralysis, Friedreich's ataxia, Charcot-Marie-Tooth disease, amyothrophic lateral sclerosis, myotonic dystrophy, periodic paralysis, polymyositis/dermatomyositis, and myasthenia gravis.

Scientists from several laboratories at NIH have recently confirmed an interesting metabolic finding associated with one of these neuromuscular diseases, myotonic dystrophy, an inherited progressive disorder of skeletal muscle characterized by muscle wasting and spasm. They have found that in 7 of 12 patients with myotonic dystrophy, insulin response to oral glucose markedly exceeded the normal range. This exaggerated insulin response occurred in young patients with very mild disease as well as in older patients with more severe muscle involvement. This is a unique form of hyperinsulinism, according to the

scientists, because although the patients have an intolerance to oral and intravenous glucose, they have nearly normal sensitivity to injected insulin.

Patients with amyothrophic lateral sclerosis (ALS), a motor neuron disease characterized by degeneration of motor cells in the spinal cord and brain, have also been found to have an intolerance to oral glucose. The most probable explanation for this, according to NINDS investigators, is loss of muscle bulk rather than a specific metabolic defect.

It has been thought for a long time that myotonic dystrophy, a hereditary progressive muscle weakness with wasting, early frontal baldness, cataracts, and abnormal metabolism, is primarily a problem of the muscle fiber. NINDS scientists, however, are assembling evidence to indicate that this disease is rather a problem of the distal nerve—more specifically of the terminal axonal branch of the nerve. This hypothesis, which is part of a larger program in the Medical Neurology Branch to differentiate between primary disorders of nerves—the neuropathies and primary disorders of the muscles—the myopathies, may redirect some of the research to discover the precise cause of myotonic dystrophy.

A two-year investigation of the metabolic basis of myotonic dystrophy partially funded by NIH, has shown abnormalities in skin fibroblasts taken from these patients and grown in culture. Myotonic dystrophy, which is inherited in an autosomal dominant pattern, affects skeletal, cardiac, and smooth muscle, the central nervous system, the reproductive system, the lends of the eye, the skull, and scalp hair, but no single metabolic aberration has been found to explain the many physiological and anatomical abnormalities associated with this disease. Because of these widespread manifestations and because of inheritance patterns in this disease, fibroblast cultures from patients would be expected to express the inherited disorder in some way. When skin biopsies from four unrelated patients with myotonic dystrophy were grown in culture and compared with control cultures from normal persons and patients with other neuromuscular disorders, the myotonic dystrophy cultures were found to contain an excess of acid mucopolysaccharide. Although results do not necessarily implicate this acid in the pathogenesis of myotonic dystrophy, it is evident that the cultured skin fibroblasts express the disorder and provide a marker to guide further analysis in the cell culture system.

In the NINDS Medical Neurology Branch, a number of neuromuscular disorders have been successfully treated, testifying to the fact that more and more of these disorders will yield to therapy. Thyrotoxic perodic paralysis, in which patients suffer paralytic attacks, is probably due to a latent defect which becomes evident only in the presence of excessive thyroid hormone. Following treatment with specific antithyroid drugs, attacks were eliminated in the patient and there was striking improvement in his baseline muscular strength. The patient also stopped experiencing sensitivity attacks induced by glucose and insulin.

Genetic studies of neuromuscular disease from the basis of gentic counseling which is at present the main preventative measure against such disorders. Scientists at the Academy of Medicine in Warsaw, in cooperation with the NINDS Medical Neurology Branch, have discovered a genetic specific protein defect in patients with progressive musclar dystrophy. Abnormal beta-1-globulin was found in the blood streams of patients with progressive muscular dystrophy and their carrier mothers. Control patients with other types of muscular dystrophy did not reveal the presence of this abnormal globulin.

Other genetic studies conducted in the NINDS Epidemiology Branch, of 65 families, including more than 400 persons, have shown dystonia musculorum deformans, a disease involving severe, progressive muscle spasms, to have autosomal dominant and recessive modes of inheritance. This study, which will be of great importance to physicians engaged in genetic counseling of patients and their families, will continue and observation will be made in additional 200 patients. Previously, this disorder was thought to be passed on solely as an autosomal dominant form, primarily in Jewish families.

Intracellular recording and stimulation techniques in the NINDS Laboratory of Neural Control, are allowing scientists to study in detail the motor unit, the smallest functional unit in movement. Recently it has become possible for these scientists to "mark" the muscle fibers belonging to a single motor unit. They can place an electrode into a motor nerve in the spinal cord and hence

control the electrochemical input. Knowing exactly what potential has been put into the neuron, they can now measure the mechanical output in the muscle, as indicated by movement or tension, and correlate this with input. Results from studies on cats using these techniques have already shown at least two distinct types of muscle fibers—fatigue-susceptible, fast contracting fibers; and fast fibers which are fatigue-resistant. Attempts will be made to match the physiological types to histochemical differences already documented in the Medical Neurology Branch and applied to disease diagnosis.

PRIORITY OF NINDS IN THE NIH BUDGET

Mr. CASEY. You stated earlier you are just a victim of priorities, is that right?

Dr. MACNICHOL. That is my impression, sir.

Mr. CASEY. You are the last one at the table, like in a large family if a kid plays a little too late he doesn't get the food he wanted, or maybe he doesn't get the end piece of the cake, is that right?

Dr. MACNICHOL. That is right.

Dr. MARSTON. The development of the 1972 budget and the availability of the 1971 budget were close together. We had some increases and decreases prior to the upward adjustments that Congress made in the 1971 budget. We gave an awful lot of thought to how one would best distribute the dollars that were available to us during the development of this budget, and Dr. MacNichol and his staff were very much involved during the development of the budget, in how one could best distribute the funds that were available to this institute to the most important programs. So I think we would want to stand on the fact that we, within the limits of the do lars we have, have put a great deal of effort and expertise which went into making up these figures and the distribution.

With this budget the program levels will not be maintained in 1972 at the levels they were in 1971.

Mr. MILLER. Could I also make this mild point: We are covering the costs of all the work that we now have underway, that is, all the continuation costs. We are covering it in this budget. It is a question of not starting as much new work. We are starting a lot of new work, but not as much.

I want the record clear that we are not making serious inroads into our ongoing effort in the field of neurological diseases.

COLLABORATIVE R AND D CONTRACTS

Mr. CASEY. What is collaborative research and development?

Dr. MACNICHOL. Primarily it has to do with contract operations. The institute and other organizations get together on a contractual basis and the institute and these other organizations then work together.

Mr. CASEY. By organizations do you mean a medical center or school?

Dr. MACNICHOL. Yes, both medical schools and medical centers.

Mr. CASEY. Private organizations?

Dr. MACNICHOL. Yes.

Mr. CASEY. Nonprofit organizations?

Dr. MACNICHOL. Yes, and even profitmaking organizations.

The difference in how we use the collaborative and contract mechanism as compared with the grant mechanism is that the grant is usually initiated by the person who is going to get the grant. They have work they want to do; they come to us with a proposal. In our collaborative research programs, we have a piece of work we want to get done and we try to hire somebody to do it, using the contract method. That, I think, is the main difference.

CUT IN THE PERINATAL RESEARCH PROGRAM

Mr. CASEY. I notice you are dropping there to the extent of $2,060,000; is that right?

Dr. MACNICHOL. This was a cut strictly directed at the perinatal research program. The Secretary's office made a study of it and felt that the program could take this amount of cut and still accomplish its main objective.

Mr. MARSTON. Again I would want to say that that particular cut involved a number of considerations, including the fact that we are now at the data analysis phase of the program. We felt, in view of the budget development, that we could stretch out the time of analysis of the data rather than making choices in other areas of the budget. There is no implication that we are not going to make use of the $100 million investment that we have already put into that program. We will just get these results over a longer period of time than if we had stayed at a higher level of spending.

CENTERS FOR SPINAL CORD INJURY

Mrs. REID. In regard to the spinal cord injury studies do you have a target date for these studies?

Dr. MACNICHOL. Yes. Because of the lateness in the appropriation this year, or the actual apportionment, we were not able early in the year to invite people to submit grant applications because we didn't feel justified in asking them to do all that work until we knew that there really would be the money available.

Then it has taken them quite a while to respond. We are now reviewing the applications, but we will not be able to actually award these grants until sometime after the beginning of the next fiscal year.

Mrs. REID. My point is that sometimes studies can go on ad infinitum.

Dr. MACNICHOL. This is a one-shot deal. They spend a year telling us what they want to do. We look it over and at that point we say, "OK, we are going to try to fund the center," or "No, we don't think that this work looks feasible to do."

Mrs. REID. What would be the actual cost of the studies?

Dr. MACNICHOL. For the feasibility studies, we have reserved $300,000, six of them at $50,000 each.

If they come up with the kind of proposals we hope they will come up with, we will pick two or three and then try to fund them in fiscal year 1973. We estimate that each operational center would cost about $1 million.

TIME FRAME FOR DEVELOPMENT OF THE CENTERS

Mr. MICHEL. Now, if the funds are available the first of the fiscal year, that is, July 1, 1971, and the study goes on for a year, you will have already then made up your budget for 1973, and we have gone through the hearing stage for 1973 before the study is completed. So, under this kind of time frame, we couldn't have any kind of request by fiscal year 1973 to really get moving, so we are still in the study stage in the next fiscal year, are we not, unless there be a request for a supplemental or something of that nature?

Mr. WIPF. The awards are to be for about 15 to 18 months which should carry us into 1973.

Mr. MICHEL. We are really 2 years away from moving on the establishment of the centers for spinal cord injury. Is there any way to speed that up?

Dr. MACNICHOL. I don't think there is and do it wisely.

Mr. MICHEL. This is an area where you can study and study and study and we have all agreed that here is one area where we have done almost nothing. I am just wondering whether or not we really have to take that long a time to study the thing before we get off dead center and move?

Dr. MACNICHOL. I think it depends entirely on how our grantees respond. If they can complete their studies faster than we anticipate, we will be able to move more rapidly.

Mr. MICHEL. Just so it is a matter of record, we want to push this as fast as we can.

Dr. MACNICHOL. The other matter is that our Advisory Council has recommended this course of action, after considerable thought and debate.

STROKE RESEARCH CENTERS

Mrs. REID. Doctor, you said there were 17 institutes which supported clinical stroke centers. Would you list those for the record?

Dr. MACNICHOL. Yes, I will be glad to.

(The information follows:)

STROKE RESEARCH CENTERS

1. Cornell University, New York, N.Y.
2. University of Minnesota Medical School, Minneapolis, Minn.
3. University of Miami, Miami, Fla.
4. Boston University, Boston, Mass.
5. The Johns Hopkins University, Baltimore, Md.
6. Duke University, Durham, N.C.
7. Philadelphia, General Hospital, Philadelphia, Pa.
8. Bowman Gray School of Medicine, Winston-Salem, N.C.
9. Mayo Foundation, Rochester, Minn.
10. University of Maryland, Baltimore, Md.
11. Indiana University, Bloomington, Ind.
12. University of California, Berkeley, Calif.
13. University of Tennessee, Memphis, Tenn.
14. Washington University, St. Louis, Mo.
15. University of California, San Francisco, Calif.
16. University of Alabama, Birmingham, Ala.
17. Baylor College of Medicine, Houston, Tex.
18. Presbyterian-St. Luke's Hospital, Chicago, Ill.

SCREENING TESTS FOR INFECTIONS OF THE NEWBORN

Mrs. REID. In last year's hearings you gave a report about the development of a screening test which can be used to alert doctors to infections of the newborn. Can you tell us how this system is developing? Is it now in general use?

Dr. MACNICHOL. I think you are referring to the test of Dr. Sever's colleagues for viral infections of the newborn.

Mrs. REID. I asked you about this last year.

Dr. MACNICHOL. I am afraid I will have to supply that for the record if I may.

Mrs. REID. Would you do that, please?

Dr. MACNICHOL. I will be glad to.

(The information follows:)

A new, inexpensive and easy to perform screening test, developed by scientists in the perinatal research program, is alerting doctors to the presence of infection in the newborn. The test, which requires only one milliliter of blood (the equivalent of a finger prick) from the baby, is based on the finding that immunoglobulin M, one of three kinds of antibodies the body produces against infection, does not cross the placental barrier between mother and fetus. Therefore, an elevated IgM level in the newborn's blood serum indicates that the infant has responded to an invading infection which was either passed on to him by his mother or acquired in the newborn period.

CURATIVE AND OTHER EFFECTS OF LEVODOPA

Mrs. REID. From your statement on page 2 you indicate that you do not have the answers to the questions about the effect of L-Dopa therapy in the treatment of Parkinson's disease, whether it arrests the progress of the disease or merely controls it.

Dr. MACNICHOL. I think this will take several years to answer. We really don't know. Every time I see the people who have been treating the patients with L-Dopa for a long time I ask them, if they are getting worse. None of them has said that they could make that statement. It may take several more years to find out whether or not the disease is arrested by the treatment.

Mr. CONTE. What are the severe side effects of L-Dopa?

Dr. MACNICHOL. Nausea and vomiting up to an extent that they just simply can't take the drug any more and they can't eat properly. That is one of them. The other is transient changes in blood pressure which may be up or down in a rather unpredictable fashion. Over a long period of time they develop involuntary movements, either grimacing or lipsmacking, or moving their arms in some curious way.

These are the principal things. There are other suggestions of impaired judgment and things like that, but these may be the result more of people being able to do things they haven't done for many, many years and overdoing them rather than any direct effect on the nervous system.

Mr. CONTE. How many people are taking this right now?

Dr. MACNICHOL. I haven't any idea. Since the drug has been released, I think it would be almost impossible to get the statistics now.

Dr. MARSTON. One encouraging point about L-Dopa is that, while we don't know whether taking it slows down the progress of the dis-

ease, it has been effective in the case of severely ill patients with Parkinson's disease. Unlike some drugs, there is no evidence of loss of effectiveness on patients who have been on the drug for some years. We are very interested in knowing whether the disease process itself is slowed down—whether in the future, early treatment might help individuals with minimal disease. But on the bright side, it is not something that helps for a year and then loses its effectiveness. Nor is its ability to control the symptoms limited to those mild or moderate cases.

NUMBERS OF PERSONS TAKING LEVODOPA

Mr. CONTE. Don't you keep any statistics on this? I asked how many are taking the drug and you don't know. It seems it would be very important to have this kind of statistic, to find out whether the drug is working or not and where it has been beneficial.

Dr. MACNICHOL. In studies that are under our control, these questions are being looked at very carefully. There are a number of grantees of ours who are making studies of this kind on the drug, however, we won't know the answers for the whole population of the United States, but we will know about it for the limited population being studied under our grants.

Mr. BERLINER. Ordinarily when a drug is released under a new drug application by the Food and Drug Administration there are no further requirements for keeping track of the individuals. In this particular case, however, the conditions of the release were rather unusual because they released the drug before they had some of the information they ordinarily require in the case of new drugs—because of the severity of the illness which is being treated and the pressures to release the drug to people who are greatly improved by it. Consequently, in this case the manufacturers are required to keep records of the use of the drug for some time. I don't believe that phase has ended. This information will be available through the manufacturers and the FDA in this particular case. Ordinarily that is not the way it is.

MULTIPLE SCLEROSIS

Mrs. REID. In the foreseeable future can we look forward to something to combat diseases such as multiple sclerosis, parkinsonism, and other degenerative diseases?

Dr. MACNICHOL. If they turn out to be virsus diseases, and there is some evidence they may be. If so, there is a good chance. First of all, we have to isolate the infectious agent or agents and find out how best to immunize the body against them. Some of this is set forth in the multiple sclerosis report which I will include.

Mrs. REID. You don't feel we are on the verge of a breakthrough?

Dr. MACNICHOL. I feel we are on the verge of it, but I don't know when or how it will come. Dr. Davis may have something on this. The fundamental virus work of NIAID is something that we also build on.

(The report referred to follows:)

NATIONAL INSTITUTES OF HEALTH—NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE

MULTIPLE SCLEROSIS

Multiple sclerosis is the commonest disease of the nervous system affecting men and women in the prime of life in northern Europe and North America. This disease afflicts approximately 250,000 in the United States. Perhaps another quarter of a million Americans suffer from closely related disorders.

Although there is no specific treatment, rehabilitation including counseling, physiotherapy, and proper bracing, can be helpful symptomatically. Many drugs, including cortisone, are used to increase comfort and counteract complications.

NINDS research support for sclerosing disorders

1968	$3,043,000
1969	3,163,000
1970	2,892,000
1971 (estimate)	3,129,000
1972 (estimate)	3,016,000

The problem

Early warning signs of multiple sclerosis include tingling sensations and numbness, slurred speech, visual disorders, or poor coordination on walking. Muscle cramps, weakness, and paralysis develop as the disorder progresses.

Neurological symptoms of the disease are apparently caused by the patchy destruction of the material known as myelin, a system of membranes wrapped in a spiral around the central component of the nerve fiber, the axon. This fatty substance can be compared to the insulation around a telephone wire. When the myelin sheath surrounding a nerve fiber breaks down, the conduction of impulses along the new exposed fiber is disrupted. Eventually scar tissue forms (sclerosis) in the demyelinated areas, producing the hard plaques for which the disease is named.

It is most important to realize that the disease is not necessarily progressive. Many patients have remissions that last for years, and some may have one attack or a series of minor episodes that are not completely disabling.

Although its clinical history, its symptoms and signs have long been well known, the cause of multiple sclerosis remains to be solved.

The Search for a Cause

Investigators seeking cause and cure find multiple sclerosis a most baffling disease. Etiologic hypotheses have ranged from diets too rich in fats to the level of subsoil water, from infection with spirochetes to poisoning by toxic substances, and from dietary deficiencies to endocrine disturbances.

Of the major research approaches to multiple sclerosis, epidemiology of the disease was the first to be extensively investigated. Multiple sclerosis is most prevalent in the world's temperate zones; it is less prevalent in warm regions. Consequently, investigators have long sought the etiology of multiple sclerosis in some factor related to geography.

Although the cause of multiple sclerosis is not known, a virus is suspected and if this is true the come and go aspects of the disease could be the result of changes in immunity. Mounting evidence indicates that viruses in certain animals can be "latent"—causing slowly developing degenerative diseases, whose symptoms appear as much as 20 years after the virus enters the body. Efforts to transmit multiple sclerosis to animals have not been successful, thus making this line of research more difficult.

Another important area of research is seeking to understand the exact chemistry of the myelin sheath, in order to explain how and why it is damaged during multiple sclerosis.

Another approach involves the so-called autoimmune mechanism. Scientists have found that in certain instances, individuals become allergic to tissues of their own bodies. Why this is so is unknown. Viruses are suspected as possible triggering agents in the autoimmune process.

Most present investigators now think multiple sclerosis is most likely a disturbance of the mechanisms of immunity or else a manifestation of "slow viruses" or possibly a combination of these.

PROGRAM DEVELOPMENTS

Extramural Program

The National Institute of Neurological Diseases and Stroke is now supporting 67 research grants on the sclerosis disorders at an annual cost of about two and a half million dollars. An additional $4 million was spent in 1970 to provide 62 neurology training grants, which are preparing neurological scientists for research on the program of multiple sclerosis and other sclerosing disorders of the nervous system.

Since the etiology of multiple sclerosis is unknown, researchers are basing their attack on a wide area of basic research. Extensive studies are being conducted in neuropathology and biochemistry. These include studies on chemistry and metabolism of brain lipids, immunoglobulins in multiple sclerosis, tissue culture of nervous tissue, chemical nature of myelin, cytologic studies in diseases of nervous system and proteins in chronic disease. Few studies are being conducted on drugs and other methods of therapy because there are so few promising leads in this area.

Reed Neurological Center

The Reed Neurological Research Center at UCLA is a facility designed for clinical and basic research on disease of the nervous system. Emphasis at the Reed Center is on little understood neurological diseases for which present treatment methods offer little hope. The Center was constructed from funds provided by Dr. Clarence C. Reed, a California physician, and from matching construction funds from NIH.

The Center has received a three-year program project grant from NINDS to conduct extensive studies of multiple sclerosis as well as other neurological diseases. The Center is unique in its conception of a new "team approach" in attacking multiple sclerosis. Through the use of volunteer outpatients and hospital patients, scientists at the Center hope to reduce the time lag between advances in the basic sciences and clinical studies. A broad program of basic research is also being conducted. Work now underway concerning multiple sclerosis includes studies on protein and lipid chemistry, tissue culture, immunology, pathology, electronmicroscopy, neurophysiology, clinical investigations, and therapeutic trials.

Slow Virus Laboratory

Because no neurologic disease in a nonhuman species is considered completely analogous to multiple sclerosis, proof of infectious etiology may hinge on its transmission to animals. Other chronic neurologic diseases, such as kuru and Jakob-Creutzfeldt disease, were ascribed to infectious origin only after transmissibility to other species was shown.

The NINDS team that succeeded in transmitting kuru to chimpanzees is now inoculating many species with material from brain biopsies and material obtained at early autopsies of multiple sclerosis patients. The inoculated monkeys, chimpanzees, and small animals will be held for eight to ten years at the Institute's slow virus lab. During that time, serum and spinal fluid will be checked regularly for antibody development and for known viruses.

A massive tracking operation, coordinated by an NINDS scientist, is now being undertaken by a number of teams to isolate transmissible agents. In this collaborative study, a large number of known viruses are being screened in animal tests. Before an animal is inoculated with brain material from a multiple sclerosis patient, its serum and spinal fluid are analyzed for antibodies. After inoculation, the animal is checked again. If there were antibodies that were not there before, the researchers would have a viral clue. Animals not inoculated with human brain material, but only with test virus, serve as controls for the normal pattern of antibody formation and persistence.

Institute scientists are placing particular emphasis on the study of patients with Jakob-Creutzfeldt disease, progressive multifocal leukoencephalopathy, multiple sclerosis and Parkinson's disease. They are employing the brain tissue culture techniques which have been so successful to date in the elucidation of the disease, subacute sclerosing panencephalitis (SSPE) due to a form of measles virus.

The results thus far obtained in these long-term studies have firmly established a new group of infectious agents: the subacute spongiform virus encephalopathies that include kuru, and Jakob-Creutzfeldt disease of man and scrapie and mink encephalopathy of animals.

Epidemiological Program

The Institute scientists are conducting or planning several epidemiological studies. Studies are underway in Boston investigating immigrants from Ireland and Italy to establish whether the country of origin or the country of residence determines the rate of the disorder. Italy is an area of low multiple sclerosis incidence while Ireland and Boston have high rates. A similar study is underway among the Japanese on the West Coast. Results of these investigations may elucidate whether multiple sclerosis is caused by a disease of childhood or by an unusual pathogenesis in northern climate.

Preliminary planning is also underway toward a survey of the population of the Shetland and Orkney Islands. The prevalence of multiple sclerosis on these islands is at least 200 per 100,000, which is three times higher than the rates in any other known population. Institute scientists believe that a thorough epidemiological survey of these island groups might reveal conditions which could predispose the population to the extraordinary high rate of multiple sclerosis.

RESEARCH PROGRESS

Multiple Sclerosis an Environmental Disease

The answer to the riddle of multiple sclerosis may lie in the discovery of environmental factors responsible for the disease. In fact, much of the rather skimpy body of hard fact so far known about multiple sclerosis has been gathered through the intensive study of populations, particularly of populations that have migrated from one environment to another.

It is known, for instance, that populations migrating from high incidence areas of multiple sclerosis to low incidence areas, retain the high rate of the country of origin. This suggests that events early in youth (possibly infectious) cause multiple sclerosis. A new study provides corollary data about migration from low risk areas to high risk areas and about multiple sclerosis rates among first generation migrants.

In the latest study, incidence data on multiple sclerosis were compiled among American, Japanese and Chinese migrants to California and the State of Washington. It was found that death rates with multiple sclerosis were higher among native-born whites in Washington than in California.

Death rates among migrants from high risk areas were also higher in Washington than in California. However, rates among migrants from low risk areas did not differ between California and Washington and in fact were similar to the rates in their area of birth. The finding of high rates from multiple sclerosis among native-born Washingtonians and intermediate death rates from multiple sclerosis among native-born Californians supports the previous finding of others that the cause of multiple sclerosis is related to latitude.

In a second study, an epidemiological survey was made of 600,000 government workers and their dependents in Mexico City. In this population only nine patients with multiple sclerosis were discovered, or an incidence rate of only 1.5 per 100,000. This rate is among the lowest reported anywhere in the world.

The multiple sclerosis rates in Mexico are very similar to those in Japan, another very low rate area. Mexico and Japan have a high rate of enteric diseases. Both countries are technologically advanced but are backward relative to the United States and many other advanced countries in environmental sanitation. This lends some support to the hypothesis that environmental sanitation is inversely related to the frequency of multiple sclerosis in a situation similar to poliomyelitis. Apparently, the incidence of multiple sclerosis is higher in those parts of the world that have improved hygiene. It has been speculated that a virus may be transmitted through the gastrointestinal tract, carried there because of unsanitary situations. An immunity might thus be established.

Antibody Level in Multiple Sclerosis Serum Studied

A number of investigators have noted that measles virus antibody levels are more frequently and more consistently elevated among multiple sclerosis patients than other viruses tested. In a more recent study, it was found that serum titers of multiple sclerosis patients were higher than those of carefully matched unrelated controls for measles, influenza C, herpes virus hominis, parainfluenza

type 3, mumps and varicella. However, serum titers among multiple sclerosis patients were not higher for any of these agents than those of their siblings of the same sex born within three years of the patient, suggesting a familial effect on these responses. The observed pattern indicates that viruses and immune responses somehow play some indeterminate role in the causation of multiple sclerosis.

However, these differences may be misleading because of the difficulty of accurately matching controls for multiple sclerosis patients. The incidence of multiple sclerosis is known to be higher in more northern latitudes, among higher socioeconomic groups, and among urban dwellers, and there is evidence that the above factors are particularly important during the first 20 years of life. These and other variables may exert an independent effect on measles antibody levels which would result in misleading correlations or lack of correlations.

Autoimmune Studies

In a number of diseases affecting the central nervous system (CNS) in man, it is suspected that tissue destruction may be due to a delayed hypersensitivity-type autoimmune reaction directed against normal CNS tissue, similar to that occurring in experimental encephalomyelitis (EAE). These disorders include acute disseminated encephalomyelitis, rabies, multiple sclerosis, and Schilder's disease. This view is based largely on the fact that the pathologic changes in each of these conditions bear a certain resemblance to those found in EAE. In acute disseminated encephalomyelitis, the autoimmune hypothesis has received additional support from the observation that a high proportion of circulating lymphocytes in this condition exhibit lymphoblastic transformation upon exposure to myelin basic protein.

A suggestion of how a virus might turn on the autoimmune mechanism comes from investigators at Albert Einstein College of Medicine in New York. Within the coat of the canine distemper virus, they believe there are protein structures that are in some ways similar to the basic protein of the CNS. Since basic protein is antigenic, this raises the possibility that antibodies attacking some viruses may not be able to distinguish the invaders from the structurally similar components within the body.

Other researchers believe that a combined effect of two or more viruses may be involved. This possibility is being checked at Wistar Institute in Philadelphia. In these studies, combinations of viruses are injected into animals to see whether disease will occur.

Therapy

No therapy has been found that provides significant benefit in the treatment of multiple sclerosis. However, last year a report on the results of a 5-year collaborative study on adrenocorticotrophic hormone (ACTH) showed this drug to be slightly beneficial during the first few weeks of treatment. However, there is no evidence that the drug is effective for long-term treatment of multiple sclerosis.

Mrs. REID. Thank you, Mr. Chairman.

EFFECT ON NINDS OF A 6-PERCENT CUT

Mr. PATTEN. Doctor, I may be called upon to cast a vote for a 6-percent reduction in the overall United States budget as we did in previous years. This is in the committee as a whole.

If we vote a 6-percent reduction in how much you can spend, instead of $95 million that you ask for, you will get less than $90 million. Your budget, as a whole, will be subject to a 6-percent overall cut if we adopt this and the Congress adopts it as we did last year. Does this change any of the answers you give?

I notice on page 208, in 1968 your neurological disease institute had the Senate vote $135 million. This year you requested $95 million. The difference is forty-some-million.

If you take a further 6-percent cut, you will have another $5 or $6 million less. Can you live with a 6-percent across the board cut in your department?

Dr. MacNichol. Well, we feel that our budget has been pared just about to the bone as it stands. As it is now, there are highly approved new projects that we can't undertake in it. In the proposed budget there will be even more highly approved projects that will not be funded.

Mr. Patten. We represent the taxpayer. The biggest issue at home as far as I can see, with the people I meet, is their complaint about high taxes. A fellow could therefore be a hero voting for a 6-percent overall cut.

Mr. Chairman, have I stated this accurately; we might be asked to vote for a 6-percent cut in controllable programs as last year?

Mr. Flood. This has been talked about.

Mr. Miller. Well, when the Congress decides what the ceiling will be, it will be a ceiling for the Government as a whole and the Office of Budget and Management will not necessarily apply it across the board. The Department will get a figure for its ceiling. We will have to have an expenditure plan that meets that figure; it may not affect this Institute at all and, on the other hand, it might.

Mr. Patten. I never met a department head that felt he could take the cut, whether you mention Post Office or any of the other many departments.

In your almost $2 billion budget, Doctor, you have to lose over $100 million. I don't know what other department will be good to you. Anything they allow you to take they have to make up some other place. Is that right?

Dr. Marston. Yes.

BALANCING HEALTH NEEDS AND SCARCE RESOURCES

Mr. Patten. In the light of the conversations we have had here today, I would love to be a hero with my taxpayers and vote for that 6-percent cut, but I started out this year with the thought that this Congress would be known as a health Congress; that would be our satellite. We would have a $50 billion insurance plan and everything else. We would make a real drive to give the American people good medical treatment and carry on research. But now that we are here, considering your particular department, I think your request is $40 million less than what the Senate voted in 1968. You actually received $128 million. I don't know if I can tell my people I am voting for a real drive for health and all the wonderful programs you have mentioned—you have mentioned 30 or 40 here, all of which we need—and also vote for an across-the-board cut.

FUNDS FOR ORAL CANCER

I have a comment on your page 129, referring to oral cancer. Under oral cancer, for instance, you say "Studies of this type will be continued although at a lower level of activity than in previous years."

I take it then that relatively this doesn't have the priority some other things do. It might just happen that my group has been hit a little bit worse than your national average. I was amazed at the low figures for oral cancer that were stated here this morning by the dental group. It seems there have been 12 or 15 fellows I know cut in the last 2 years for oral cancer. There has been a high incidence in my personal experience. Certainly the figures don't bear out that the average

American would have that many people close to him. They said 6,000 deaths and about 15,000 cases. Maybe oral cancer isn't anywhere near as high as I thought it was.

I know in my group many have been cut in the last 2 or 3 years and it has shaken me up, but here we are decreasing the work.

Dr. MARSTON. I might make a couple of brief comments on it. As I said earlier, this justification was put together before the $100 million additional money for cancer and my guess is we will not decrease the activity in oral cancer.

In another part of the budget as far as the neurological and stroke disease institute is concerned—that is the Eye Institute, we are asking for $32 million. That was included in the 1968 figures as a part of the neurological disease institute at that time.

Mr. PATTEN. Doctor, this is a terrific program.

Dr. MACNICHOL. Thank you.

Mr. PATTEN. It would give us great satisfaction for you to make progress in any one of these areas.

Members of this committe are wondering if we are going to have a reputation of being a health Congress if we do almost as much as we did last year or a little bit less. I am left with the opinion that on the whole the budget is a little bit less. If we follow this budget I am going to stop telling my people this is going to be the health Congress and that we are doing business as usual in an effort to balance the budget and do a lot of other things.

BRITISH COMPETENCE IN SPINAL INJURY TREATMENT

Mrs. REID. When we were discussing spinal cord injuries, you said on page 5 that the management of spinal cord injuries is further advanced in European countries. What is the reason for the lag, because of a lack of scientists?

Dr. MACNICHOL. My impression is it is largely through lack of organization. That is why I have sent our Associate Director for Extramural Research over to England to study the problem; he is there now.

I think they have a tremendous advantage.

Mr. FLOOD. Lack of organization?

Dr. MACNICHOL. As far as this particular thing is concerned. First of all, having centers that are available to the whole country. Of course, England is a small country and it is easier to do this. Getting people there promptly and then having things all set up in this center to do the best possible job.

Mr. BERLINER. We should say organization of the health care system and not organization of research because these are health care facilities.

HYPERTENSION AND STROKE INCIDENCE

Mrs. REID. One other question: Has the number of cases involving strokes been decreased due to the study made by the Veterans' Administration which confirmed that blood pressure being controlled decreases strokes?

Dr. MACNICHOL. This came out clearly in the studies. However, the routine use of antihypertensive drugs has not been carried out nationwide and probably won't be at least until the Heart Institute study,

has had a chance to run for a while. We can then see if this holds true for a larger population.

There are a lot of problems associated with this kind of thing. The people are mostly well, so they often don't take their medicine. One of the big problems in a study like this is to make sure they take their pills. Hospitalized veterans are under more pressure to take the medication than people treated as outpatients.

Mr. FLOOD. Mr. Conte.

NINDS BUDGET CUTS

Mr. CONTE. How do you justify a $9.3 million cut from last year's appropriation on top of the 6 percent inflation figure?

Dr. MACNICHOL. It is a matter of the Department's priorities and once these are established we try to put our money where it will do the most good.

TRAINING PROGRAM

Mr. CONTE. How does this cut affect the training program?

Dr. MACNICHOL. Our training programs are a little bit less than they were last year.

Mr. CONTE. Can you tell us how much less?

Dr. MACNICHOL. It is essentially the same. If you take the amount that has been transferred to the Bureau of Health Manpower Training and consider that that really is a part of the budget, since it will do the same job in training as it would have done had we administered it.

Mr. CONTE. Page 205 of the justifications indicates that the Institute has made every effort to continue as many training grant programs as possible with available resources.

Tell me exactly how many you are actually continuing.

Dr. MACNICHOL. Actually in 1971 we had 208 training programs and we will lose ten, cutting it down to 198, with essentially the same money. This is a result of inflation and increased cost.

INCIDENCE OF NEUROLOGICAL DISEASES

Mr. CONTE. What percent of the U.S. population is affected by diseases that are covered by your Institute?

Dr. MACNICHOL. I think that would be a very hard question to answer.

Mr. CONTE. Maybe you can work something out.

Dr. MACNICHOL. We will try to make an estimate of it. More than 20 million is a rough estimate and it depends on whether you include deafness. Also, the degree of deafness you consider a serious disease is important because there are at least 25 million fairly deaf people in the country. It is a hard figure to get, but we will supply what we can for the record.

(The information follows:)

Current estimates indicate that 20 percent of the Nation's population have a neurological or sensory disorder.

ANTISTROKE BENEFITS OF HYPERTENSION TREATMENT

Mr. CONTE. According to VA studies by now how much can the chances of having a stroke be decreased by providing drug therapy to hypertensive patients?

Dr. MACNICHOL. I can't answer that offhand, but I would be glad to submit that for the record.

Dr. MARSTON. By chance I went to a presentation at the VA this past Sunday night. I think that any answer you get is going to be incomplete because they actually stopped the study because the benefits were so much greater for the patients who were on the drugs that were lowering the blood pressure that they really were not justified in denying them to control patients just to find out, over a period of years, what the benefits would be. The differences between the control group and the other group was so great that one was not justified in really trying to arrive at an answer to your question. I think 4 years was——

Mr. FLOOD. As a matter of fact, they did stop the program.

Dr. MARSTON. They stopped the program after 4 years because the benefit was so clear from treatment. We probably will never really know what difference it would make over a 15-year treatment period.

POSTSTROKE BLOOD CIRCULATION STUDIES

Mr. CONTE. What research projects are you pursuing in attempting to come up with a method for quickly restoring blood circulation in stroke victims?

Dr. MACNICHOL. There are a number of studies being made. I think the most important one are experimental surgery. Either repairing places where the arteries have become narrow or getting clots out where they can be reached outside the head.

Mr. CONTE. How about in the head?

Dr. MACNICHOL. In the head, aneurysms that burst are a very serious problem. As you know, an aneurysm is a little balloon that rises in a fork where the artery branches. There is a new method which has been developed in which a probe is put into the aneurysm which is magnetic and a magnetic fluid is injected. The iron settles around the magnet and forms a basis for a clot which then fills the aneurysm. It is eventually covered with tissue and the needle can be withdrawn and in this way it is a kind of a blow-out patch that keeps aneurysms from bleeding any further. This has been tested and has proven quite successful.

Mr. CONTE. If there are any further treatments I think we ought to have them for the record.

(The information follows:)

There are other treatment efforts in progress, such as trials with vasodilating drugs; however, these are generally experimental and somewhat controversial, and are not of great clincal importance at this time.

GAS INHALATION STROKE DIAGNOSIS

Mr. CONTE. At page 4—how are you able to shorten the gas inhalation technique for diagnosing stroke patients from 30 minutes to 11?

Dr. MACNICHOL. I am sorry, I don't remember the details of that. I can insert it in the record if you like.

Mr. CONTE. You have it in your statement.

(The information follows:)

The time required for measuring regional cerebral blood flow has been shortened by scientists at Duke University through better selection of sites for extracting samples, and also through simplification of the mathematical computation process. They have reported obtaining reliable readings in approximately one-third to one-fourth the time formerly required. Gas inhalation is one of several current methods for measurement of cerebral blood flow. The technique involves measurement of the quantity of an inhaled inert gas taken up by the brain tissue from the arterial blood, minus the quantity leaving the tissue via the venous blood in a given time. Since the initial concentration is zero, the uptake of the gas per unit of brain tissue can be determined from the difference in concentration in arterial and venous samples.

COLLABORATION WITH DOT ON HEAD INJURY

Mr. CONTE. You mention research on injuries caused by auto accidents and the needed information for improving safety devices.

I just came from upstairs where we are hearing a highway safety agency and they are asking for millions and millions of dollars in this particular area. How closely have you worked together?

Dr. MACNICHOL. Very closely. Actually Dr. Ayub Ommaya, an intramural scientist in Bethesda who has been working most actively on head injury problems, has a part of his program funded through interdepartmental agreement and fund transfers with the Department of Transportation. They are helping us out financially on this particular study and he and Dr. Hirsch of DOT have worked very closely together on this problem for several years.

Mr. CONTE. Are you providing DOT with the expertise on what a blow to the head from a windshield or visor would do?

Dr. MACNICHOL. That is not the kind of thing we do.

We are interested in an injury caused under controlled conditions. Under known and controlled conditions of impact, we find out what damage this does and how the damage is done, then it is up to DOT or the automobile industry to develop ways of preventing this kind of damage, but we don't get into the actual design-engineering of vehicles.

Mr. CONTE. I didn't think you did, but I thought maybe you would advise them that if you didn't have a plastic bag in an automobile to capture you from the impact, that you could hit the dashboard with your head and cause certain damages and you compare this with a car that was equipped with a plastic bag.

Dr. MACNICHOL. What we do is to tell them if you give the animal a certain kind of acceleration in a certain direction, it will do so much damage and then it is up to them to interpret this in terms of a given accident situation.

COLLABORATIVE PERINATAL STUDY

Mr. CONTE. When will the massive study of pregnant women and their offspring described in your statement on page 7 be completed?

Dr. MACNICHOL. The data intake will be finished I believe in 1974; that is, all of the children will have completed their seventh and eighth-year examinations. We have started sometime ago to analyze the data as they have become available and that anlaysis will probably continue for several years at least.

NEW PRACTICES TO CUT DEFECTIVE BIRTHS

Mr. CONTE. Also on page 7, will you describe some of the new obstetrical practices that have been introduced to decrease the number of defective children born each year as a result of data collected from this project.

Dr. MACNICHOL. I think the main thing that has come out of this is the whole problem of the permissible weight gain of a pregnant woman. The correlations that come out very clearly in this study are that if a woman starts out not very heavy and gains relatively little weight, the chances of her child being small at birth are very considerable. Prematurity is more likely under this condition.

Mr. CONTE. With a heavy woman?

Dr. MACNICHOL. Prematurity is also more likely under these conditions as compared with the woman having a moderate weight gain, a weight gain of say 25 to 30 pounds.

Mr. CONTE. You can almost judge the size of the child by the size of the mother.

Dr. MACNICHOL. By the weight gain of the mother. If the mother is heavier, she doesn't need as large a weight gain. But obstetrical practice in this country has been to restrict the weight gain very much more than this study has indicated.

CONTINUED FUNDING OF THE PERINATAL STUDY

Mr. CONTE. How much more money are you going to spend on this program? Are you just about cleaned up?

Dr. MACNICHOL. I would think over a period of several years the completion of the data intake and the completion of the data analysis would be at least another $20 million.

TREATMENT OF HOGDKIN'S DISEASE

Mr. CONTE. I didn't see anything and maybe I missed it—what are you doing on Hodgkin's disease? Anything?

Dr. MACNICHOL. That is a cancer of the lymph node and not in our area of responsibility.

Dr. MARSTON. It is an area in which there has been considerable progress both in terms of treatment with radiation and——

Mr. CONTE. I thought there was treatment by radiation.

Dr. MARSTON. It is one of the areas that has seen some of the most excitement in recent years. We would be glad to supply you with additional data on it.

Mr. CONTE. I would appreciate it.

Mr. PATTEN. The prognosis of that disease is pretty poor isn't it?

Dr. MARSTON. You know we have to be cautious when we talk about serious, life threatening diseases, whether they be strokes or myocardial infarctions or cancer. The prognosis in Hodgkin's disease has a wide range, but in recent years has been improving about as dramatically as any of the cancers.

It is to the point now that people make very optimistic statements about the ability to prolong life for many years in Hodgkin's disease.

I don't want to overdramatize this, but I guess it was a year- and-a -half ago we had a scientific meeting at the National Institutes of Health, the title of which was "Hodgkin's Disease: Is It a Curable Disease?" It is not to the point of saying that it can be cured in all cases. When I was in medical school, it certainly was a very depressing prognosis. Now when one makes the diagnosis, one does reassure the patient that there are things that can be done.

Mr. PATTEN. If we vote the extra $100 million for cancer, some work can be done in this area?

Dr. MARSTON. Yes, sir.

Mr. CONTE. Thank you.

Mr. FLOOD. Thank you, Doctor.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Amounts Available for Obligation

	1971	1972
Appropriation	$105,807,000	$96,521,000
Real transfer to:		
"Departmental management"	-17,000	---
"National Cancer Institute" (proposed transfer for increased pay costs)	-1,879,000	---
"Division of Biologics Standards" (proposed transfer for increased pay costs)	-308,000	---
"National Institute of Child Health and Human Development" (proposed transfer for increased pay costs)	-62,000	---
"John E. Fogarty International Center for Advanced Study in the Health Sciences" (proposed transfer for increased pay costs)	-30,000	---
"St. Elizabeths Hospital" (proposed transfer for increased pay costs)	-26,000	---
Comparative transfer to:		
"Office of the Director"	-67,000	---
"Office of the Director"	-1,088,000	---
"Health manpower"	-2,844,000	---
"Departmental management"	-4,000	---
Total, obligations	99,482,000	96,521,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
211	Research.....	--	$58,802,000	--	$57,492,000	--	-$1,310,000
	General research support grants...	--	(5,027,000)	--	(4,481,000)	--	(-540,000)
	Scientific evaluation and planning	--	(130,000)	--	(130,000)	--	---
	Categorical clinical research centers.....	--	(3,154,000)	--	(3,154,000)	--	---
	Specialized research centers...	--	(840,000)	--	(840,000)	--	---
216	Fellowships.....	--	2,782,000	--	2,595,000	--	-187,000
218	Training.....	--	11,456,000	--	11,456,000	--	---
	Direct Operations:						
220	Laboratory and clinical research	252	10,319,000	252	10,572,000	--	+253,000
222	Collaborative research and development.....	165	9,752,000	165	7,831,000	--	-1,921,000
225	Biometry, epidemiology and field studies.....	84	3,482,000	84	3,476,000	--	-6,000
227	Review and aproval of grants	77	2,318,000	77	2,492,000	--	+174,000
227	Program direction	30	571,000	30	607,000	--	+36,000
Total obligations.....		608	99,482,000	608	96,521,000	--	-2,961,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	608	608	--
Full-time equivalent of all other positions	52	52	--
Average number of all employees	633	633	--
Personnel compensation:			
Permanent positions	$ 7,942,000	$ 8,404,000	+$462,000
Positions other than permanent	311,000	426,000	+115,000
Other personnel compensation	213,000	253,000	+40,000
Subtotal, personnel compensation	8,466,000	9,083,000	+617,000
Personnel benefits	731,000	777,000	+46,000
Travel and transportation of persons	418,000	399,000	-19,000
Transportation of things	130,000	124,000	-6,000
Rent, communications and utilities	354,000	338,000	-16,000
Printing and reproduction	171,000	163,000	-8,000
Other services:			
Project contracts	7,667,000	5,567,000	-2,100,000
Payment to NIH Management Fund	5,235,000	5,394,000	+159,000
Other	1,595,000	1,514,000	-81,000
Supplies and materials	1,315,000	1,275,000	-40,000
Equipment	362,000	346,000	-16,000
Grants, subsidies and contributions	73,040,000	71,543,000	-1,497,000
Deduct quarters and subsistence charges	-2,000	-2,000	---
Total obligations by object	99,482,000	96,521,000	-2,961,000

Summary of Changes

1971 estimated obligations	$99,482,000
1972 estimated obligations	96,521,000
Net change	-2,961,000

	Base Pos.	Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase costs	--	---	--	+452,000
2. Federal Telecommunications System rate increase	--	---	--	+26,000
3. Within Grade Pay costs	--	---	--	+193,000
4. One additional Day of Pay in 1972	--	---	--	+39,000
5. Non-competing Research Grants	--	33,192,000	--	+1,451,000
B. Payment to "National Institutes of Health Management Fund" for centrally furnished services	--	5,088,000	--	+212,000
Total, increases			--	+2,373,000
Decreases:				
A. Program:				
1. Research Grants	--	58,802,000	--	-2,761,000
2. Fellowships	--	2,782,000	--	-187,000
3. Laboratory and Clinical Research	252	6,538,000	--	-83,000
4. Collaborative Research and Development	165	9,244,000	--	-2,100,000
5. Biometry, Epidemiology, and Field Studies	84	3,234,000	--	-100,000
6. Review and Approval	77	1,395,000	--	-50,000
B. Payment to "National Institutes of Health Management Fund" for centrally furnished services	--	5,088,000	--	-53,000
Total, decreases			--	-5,334,000
Total, net change			--	-2,961,000

Explanation of Changes

Built-in increases--These increases will provide $452,000 for annualization cost of the 1971 pay raise effective January 10, 1971; $39,000 for an additional day of pay in 1972; $193,000 for within grade pay increases in 1972; and $26,000 for the increased cost of using the Federal Telecommunications System. The $1,451,000 in non-competing research grants will fund in 1972 those project grants which were funded in 1971 and are being continued in 1972 as a commitment made prior to 1972.

Program decreases--All of the program decreases result from the need to provide funds for special scientific initiative programs.

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1971 House Report	
1. The Committee expressed hope that followup studies of Parkinson patients treated with levodopa and the search for other similar drugs would continue (page 23 of the House Report).	1. The Institute continues intensive research efforts with levodopa in an effort to find the cause of Parkinsonism, to reduce the side effects of the drug, to find a less expensive form of the drug, and to determine the effect of levodopa on diseases similar to Parkinson's disease.
2. The Committee expressed a desire to see as many as possible of the established training grant programs continued until the completion of the training grant study early in Fiscal Year 1972. (page 24 of the House Report)	2. The Institute is making every effort to continue as many programs as possible with the resources available to it.
1971 Senate Report	
1. The Committee expressed a strong desire to see an expanded effort in stroke research, particularly the stroke clinical research center program. (page 41 of the Senate Report)	1. In 1971, the Institute increased the number of project grants investigating stroke, but will not increase the number of stroke centers.
2. The Committee felt that six additional pilot centers on spinal cord injury were necessary in an effort to focus research expertise on the problem of acute spinal cord injury. (page 41 of the Senate Report)	2. The Institute plans to fund the additional spinal cord centers in 1971 and anticipates selecting two of these as full-scale, operational categorical clinical research centers in 1972.
3. The Committee expressed interest in the research on finding a substitute for lost sight and hearing by direct stimulation of the brain. (page 42 of the Senate Report)	3. Efforts will continue in 1972 through contracts to determine the best ways to stimulate the brain and to study the effects of materials implanted in the brain.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation Requested
Public Health Service Act Section 301--Research and Investigations in general.....	Indefinite	$96,521,000
Title IV, Part D--National Institute of Neurological Diseases and Blindness.....	Indefinite	96,521,000

PUBLIC HEALTH SERVICE ACT

The legislative authority which provides for the award of grants for research, research training, and fellowships is included in section 301 of 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 co-operation 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."

Public Law 90-489
90th Congress, H.R. 12843
August 16, 1968

"Sec. 453. The name of the institute for neurological diseases and blindness is hereby changed to the "Institute for Neurological Diseases."

Public Law 90-639
90th Congress, H.R. 14096
October 4, 1968

"Sec. 7. The name of the National Institute of Neurological Diseases and Blindness is hereby changed to the National Institute of Neurological Diseases and Stroke."

Explanation of Transfers

	1971 Estimate	Purpose
Reat transfer to:		
Departmental management.....	$ -17,000	To establish the Facilities Engineering and Construction Agency.
National Cancer Institute...	-1,879,000	Proposed transfer for increased pay costs.
Division of Biologics Standards.....	-308,000	Proposed transfer for increased pay costs.
National Institute of Child Health and Human Development.....	-62,000	Proposed transfer for increased pay costs.
John E. Fogarty International Center for Advanced Study in Health Sciences.....	-30,000	Proposed transfer for increased pay costs.
St. Elizabeths Hospital.....	-26,000	Proposed transfer for increased pay costs.
Comparative transfer to:		
Office of the Director.....	-67,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director.
Office of the Director.....	-1,088,000	To provide an equitable distribution of the Management Fund in 1972.
Health manpower.....	-2,844,000	Transfer of institutional support funds to health manpower.
Departmental management.....	-4,000	Transfer mental retardation functions to Office of the Secretary.

National Institute of Neurological Diseases and Stroke

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$ 54,100,000	$ 57,624,000	$ 80,000,000	$ 70,812,000
1963	71,206,000	77,506,000	86,506,000	83,506,000
1964	88,407,000	87,675,000	88,407,000	87,675,000
1965	88,608,000	87,889,000	88,089,000	88,089,000
1966	96,403,000	96,403,000	102,153,000	101,153,000
1967	106,418,000	111,296,000	116,296,000	116,296,000
1968	128,633,000	128,633,000	135,633,000	128,633,000
1969	131,195,000	126,674,000	132,674,000	128,934,500*
1970	103,485,000	101,256,000	112,700,000	107,365,000
1971	93,813,000	100,807,000	115,807,000	105,807,000
1972	95,496,000			

*$21,519,000 transferred to National Eye Institute

Justification

National Institute of Neurological Diseases and Stroke

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	608	$ 9,197,000	608	$ 9,860,000	--	$ +663,000
Other expenses.....	--	90,285,000	--	86,661,000	--	-3,624,000
Total	608	99,482,000	608	96,521,000	--	-2,961,000

General Statement

This Institute is concerned with a variety of diseases which afflict the brain and sense organs. Disorders such as cerebral palsy, epilepsy, multiple sclerosis, muscular dystrophy, parkinsonism, and deafness result in long-term disability while cerebrovascular disease (stroke) is the third largest cause of death in this country and a major cause of serious disability. Progress against these inadequately understood diseases would relieve mankind of some of its heaviest disease burdens.

These neurological and sensory disorders fall into 13 major program areas, each subject of a specifically focused research effort. The research effort in these areas is carried out through extramural project research grants, center or program project research grants, intramural research projects, collaborative and field research projects and contract research projects. The program areas are as follows.

The neurological disorders of early life include all those diseases of the nervous system which occur in early life whether they are acute or chronic.

The neurological disorders of adult life are those diseases of the nervous system which manifest themselves late in life, but are chronic and debilitating.

The cerebrovascular disorders include all those disorders of the central nervous system related to blood circulation including stroke, CV functions, blood-brain barrier and angiography.

Epilepsy and related paroxysmal disorders are those conditions in which recurrent seizures require constant medication or treatment, and in some cases surgery. It also includes migraine and headache.

Sclerosing disorders in general include such diseases as multiple sclerosis, amyotrophic lateral sclerosis, allergic encephalitis, and others which are chronic and incapacitating but for which there is no certain cause or treatment.

Muscular disorders are those diseases which involve both nerves and muscles and their interactions. These may occur at different periods of life, but are chronic and, incapacitating, and often fatal.

Infectious diseases are all those diseases caused by known infectious agents whether bacterial, viral, rickettsial, fungal, or other.

Trauma and injury to the nervous system include all those physical agents which can accidentally cause injury to the nervous system.

Tumors of the nervous system include all the neoplastic growths which occur within the confines of the nervous system and include the metastatic tumors of the nervous system which originate elsewhere in the body.

Neuroendocrine Studies. This category includes also studies on the autonomic nervous system, including control of body temperature, micturition and respiration.

Neural Aspects of Learning and Behavior. Studies of the brain tissues and complex nervous system in regard to sensory and motor behavior, such as perception, memory, learning, and locomotion.

Nervous System Studies related to normal functions. This includes the subcategories of anatomy, physiology and pharmacology in their applicability to normal functions. (For example, a study of the molecular structure of biological systems, or the metabolism of nervous and related structures.)

Sensory disorders include three areas, disorders of hearing and equilibrium, speech and other higher CNS functions, and disorders of other senses.

The Institute maintains an overview of all the program areas through special task forces, Advisory Council Subcommittees, and its scientific information network now centered in two of the Nation's strongest university libraries and research laboratories. These facilities have been developed to advise the Institute staff of research needs and current progress.

From the outset, the use of focused and directed research efforts has been a major part of the Institute's program. The program for the identification and testing of new anticonvulsant drugs is a good example of this kind of activity. The longest study of this type is the Collaborative Perinatal Project, which is now in its thirteenth year. Other cooperative and collaborative studies are in progress and a major segment of direct research is devoted to the direction and coordination of these investigations, frequently using the contract mechanism.

Faced from the outset with a critical shortage of highly specialized scientists required for neurological and sensory research, the Institute has devoted approximately 20 percent of its grant funds to the training of personnel, although this has receded to about 15% for 1972. Former trainees form an important segment of developing programs, such as the newly established stroke centers. The expanding number and size of medical schools are increasing the manpower demands from our training programs.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Research Projects.....	$49,651,000	$48,887,000	$ -764,000
Special Programs.....	9,151,000	8,605,000	-546,000
Total Research Grants....	58,802,000	57,492,000	-1,310,000

Introduction

The research grant programs of the National Institute of Neurological Diseases and Stroke include research projects, research program projects, outpatient clinical research projects, clinical research centers, and, in the cerebrovascular and head and spinal cord injury areas, specialized research center grants. The primary objectives of these grant programs 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 neuromuscular apparatus, the ear, and human communication. Some of these diseases are among the major causes of death in the United States (stroke, head injury, and spinal cord trauma) and of permanent disability (paralysis, epilepsy, deafness, loss of speech). They include diseases of the young (cerebral palsy, epilepsy, deafness, aphasia), of adults (head injury, paraplegia, multiple sclerosis, deafness) and of the aged (stroke, brain tumor, parkinsonism, otosclerosis and other forms of degenerative deafness, pre-senile and senile dementias).

Program Plans for 1971 and 1972

In 1971, approximately 1,267 regular research projects totalling about $49,651,000 will be awarded by the Institute. It will be possible to continue many of the ongoing projects and to initiate a limited number of new projects of special quality and importance. The program will continue emphasis in the fields of stroke, parkinsonism, epilepsy, brain and spinal cord injury, deafness, and loss of speech. New programs at pilot levels will be directed towards special efforts in the neurological and sensory disorders as outlined in the following areas of research emphasis.

Research Project Grants

The importance to the mission of NINDS of some 1,166 regular research projects cannot be overemphasized since they constitute the major part of the extramural research program. They represent the ideas and approaches of the individual, independent scientists in laboratories and clinics throughout the nation. Some studies are largely clinical; others are effective and essential combinations of clinical and basic research. Many are fundamental studies on the important basic mechanisms by which cells, genes, protein molecules, and other fundamental biological entities reproduce and function in the nervous system. This information is vital to finding new approaches to the cause, treatment and prevention of diseases of the nervous system and human communication. Building upon this broad base of independent research, the Institute is establishing special projects and programs directed toward specific categorical objectives. In this way the most effective attack on each of the Institute's disease problems is being developed and maintained.

Disorders of Human Communication
(Hearing, Language, and Speech)

Other than prevention, the prime public health needs with respect to communicative disorders is their early identification and management. If action is taken soon enough, such disorders are correctable by medical and surgical remedial measures followed by proper training and education. Therefore, it is especially important that they be diagnosed as early as possible before they become so firmly established that corrective measures will have limited effectiveness.

Clinical research centers and outpatient clinical research programs have been established to provide for comprehensive research programs on the development of improved methods of diagnosis and treatment of these communicative disorders. The centers are multidisciplinary and include experts in many aspects of human communication. Major developments in the detection, diagnosis, therapy, and natural history of communicative disorders are being perfected in them.

The development of improved instrumentation and sensory aids will be encouraged. In no other area is the participation of the engineer and the physicist more important for the design of mechanical and electronic aids. Every effort will be made in FY 1972 to maintain the present level of research in these crucial areas.

Epilepsy

Epilepsy is recognized as a major national health problem. It is generally estimated that there are at least one and a half to two million epileptics in the United States. However, because of the social stigma and unfavored economic and insurance position of epileptics, no reliable data are available about the true prevalence of this disorder. The economic burden in direct and indirect costs is probably well over one billion dollars a year. Despite a good deal of special attention over the past several years, progress has not been rapid in the areas of drug therapy, surgical treatment, electroencephalography, or basic research. This is true even though reasonably good experimental animal models are now available for laboratory studies.

Epilepsy has many manifestations and expert opinion differs on its cause or causes. Some believe that all forms of epilepsy arise from a single disease entity. Others feel that certain common mechanisms of neuronal discharge may occur in all cases, but that the specific etiologic chemical, anatomical, or functional defect may vary widely. At the present time most seizures can be controlled, but not cured.

The Institute's program is built on a broad base of individual research project grants to scientists representing many disciplines in many laboratories. Studies on the structure, chemistry, and function of the normal brain are also essential to provide the firm base on which the abnormal brain can be examined. Basic studies on normal and epileptic brain tissue can be expected to provide significant advances in such areas as neuroanatomy, neuropharmacoloby, neurochemistry, neurophysiology, and central nervous system circuitry that may underlie the basic mechanisms of the epileptic discharge. This requires sophisticated electronic and microchemical instrumentation. Such investigations will lead to the development of more effective anti-convulsant compounds and a better understanding of the disease process. As a corresponding program, the Institute has supported an important contract effort on drug therapy. This is explained in the collaborative budget activity.

Parkinsonism

It is now clear that levodopa (levodihydroxyphenylalanine) will revolutionize the treatment of Parkinson's disease. Clinical trials of this amino acid have demonstrated considerable relief of disabling symptoms, including rigidity, akinesia, and tremor. This is gratifying news to the over 1,000,000 people in the United States who are afflicted with this crippling disorder for which there was no effective form of therapy.

This breakthrough does not mean that the research effort on parkinsonism can be reduced. On the contrary, research must be accelerated because levodopa provides us with a tool to explore the cause of the disorder, and hopefully, its prevention. For the first time, hope is available that the riddle of this cruel disorder and other related diseases such as Huntington's chorea and Dystonia Musculorum Deformans may be solved.

In regard to the clinical use of levodopa, research is underway to improve the drug and to follow up the new approaches to parkinsonism. The drug must be taken in large amounts, is very expensive, and the side effects frequently are very unpleasant if not dangerous. The immediate problem being worked upon is altering the drug chemically or synthesizing a similar compound which will be at least as effective in treating parkinsonism but will be less expensive, more palatable and without side effects. Most important of all, perhaps, the discovery of the effectiveness of levodopa may make it possible to elucidate the fundamental defect in parkinsonism and to devise an even more satisfactory program of prevention and therapy.

Acute Head and Spinal Cord Injury
(Accident and Injury)

The incidence of spinal cord injury as a result of both civilian and military activities is increasing. These injuries, often resulting in paraplegia, have disasterous consequences for the victim, his family, and the community. Although on-going, but financially limited research programs are already in existence, an intensified national effort is essential.

More information is necessary especially concerning the immediate damage in the injured spinal cord. Preliminary data suggest that if the acute injury is promptly and properly treated, permanent damage may be prevented. Therefore, the development of methods of treatment of the acute injury is of great importance. Greater efforts are needed to develop instrumentation to utilize still viable muscles even though long tracts of the spinal cord have been damaged. Again, this is an area where the multidisciplinary approach of neurological scientists, biophysicists, and engineers is essential.

As a result of modern machines of peace and war, both the frequency and severity of head injuries also are increasing. The Institute continues to intensify its attack on the medical aspects of this problem through the establishment of clinical research centers in order to provide a firm base for the important combination of clinical material, laboratory facilities, and experienced researchers. Much fundamental research is underway on the basic mechanisms of reaction to head injury. These studies increase the importance of providing clinical research centers to relate the findings in the laboratory to the problems of the patient.

Presently supported groups continue to direct their efforts to such problems as brain swelling after injury, the physiological and metabolic consequences of head injury, the physical forces involved in brain damage, the structure and function of the blood-brain barrier, and the evaluation of new diagnostic and therapeutic procedures in the management of head injury.

Despite the great need, however, this research area has not moved ahead rapidly. Institutions with superb clinical material may not have the other requisites for a clinical research center. Consequently, eight specialized research center grants have been awarded to develop head injury clinical research centers. Additional institutions must be supported in their plans to develop centers and it is hoped that some of the groups presently under development will show sufficient progress in the near future to warrant support as a full scale head injury clinical research center. Also, in 1971 six grants amounting to $300,000 will be awarded for feasibility studies on the development of spinal cord injury clinical research centers to evaluate whether there is sufficient knowledge and scientific opportunity for further research in this field to justify an expanded effort. If these studies prove successful, it is planned to establish two fully operational spinal cord injury centers in 1972 estimated to cost $150,000 each.

Stroke

Stroke continues to be one of the three leading causes of death and disability, frequently occurring during the victims' most productive years. Survivors often suffer life-long physical disability and/or mental incapacity.

Studies are desperately needed to insure more effective treatment of stroke by devising means to anticipate and prevent complete obstruction of cerebral vessels, and to supplement or replace vessels diseased beyond repair. Fundamental research on the cerebral blood vessels of laboratory animals and on regional and cerebral blood flow continue to provide the information which is essential prior to undertaking similar studies in man.

The main thrust of the Institute's attack on the stroke problem continues to be through the stroke clinical research centers, seventeen of which are presently supported. Through the specialized research center programs, several of the present centers were first supported through a developmental phase. Some institutions did not have all of the essential resources required to justify a full scale center, but did have the potential for such development if given assistance.

Continued support of basic laboratory research also is essential to complement the clinical research center program as it provides the laboratory experimental base from which techniques applicable for human research are developed.

Support must be continued for the carefully designed national cooperative studies of the surgical and medical treatment of aneurysms and of the efficacy of drugs for the prevention of stroke due to hypertension. These are long term studies initiated several years ago and will be continued over the planned period. There is increasing evidence that anti-hypertensive therapy is effective in preventing stroke in moderate hypertension as well as in severe hypertension. Research on this subject will be developed as rapidly as possible. The area of patient care will also be of considerable interest. During 1971 increased research emphasis will be directed towards more effective methods of care of the acute stroke patient.

Other Program Areas

The areas of primary emphasis mentioned above represent only a few of the more than 200 diseases known to afflict the brain and sense organs. Other areas of special importance are: sclerosing disorders of the nervous system, muscular and neuromuscular disorders, infections and viral diseases, tumors of the nervous nervous system, and studies related to the normal function of the nervous system.

Research Grants Program Analysis

Fields	1971 Estimate	1972 Estimate	Increase or Decrease
I. Neurological Disorders.....	($37,735,000)	($37,240,000)	($-495,000)
A. Neurological Disorders of Early Life.....	6,000,000	5,900,000	-100,000
B. Chronic Neurological Disorders of Aging.....	2,220,000	2,180,000	-40,000
C. Cerebrovascular Disorders	5,755,000	5,755,000	---
D. Epilepsy and Related Paroxysmal Disorders...	2,430,000	2,390,000	-40,000
E. Sclerosing Disorders.....	2,590,000	2,540,000	-50,000
F. Muscular & Neuromuscular Disorders.....	4,970,000	4,890,000	-80,000
G. Infectious Diseases.....	320,000	315,000	-5,000
H. Trauma and Injury.....	3,150,000	3,150,000	---
J. Tumors of Nervous System.	690,000	680,000	-10,000
M. Neuroendocrine Studies...	2,850,000	2,800,000	-50,000
N. Neural Aspects of Learning and Behavior.....	1,210,000	1,190,000	-20,000
P. Nervous System Studies related to Normal Function	5,550,000	5,450,000	-100,000
II. Sensory Disorders.....	(11,470,000)	(11,283,000)	(-187,000)
A. Disorders of Hearing and Equilibrium.....	6,400,000	6,290,000	-110,000
B. Disorders of Speech & Other Higher CNS Functions...	1,430,000	1,413,000	-17,000
C. Disorders of Other Senses	3,640,000	3,580,000	-60,000
III. Multi-Categorical.....	4,440,000	4,358,000	-82,000
Subtotal.....	53,645,000	52,881,000	-764,000
IV. Scientific Evaluation.....	130,000	130,000	---
V. General Research Support Grants.....	5,027,000	4,481,000	-546,000
VI. Total Research Grants.....	58,802,000	57,492,000	-1,310,000

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Non-competing.....	871	$33,192,000	861	$34,643,000	-10	$+1,451,000
2. Competing renewals	256	10,873,000	228	10,458,000	-28	-415,000
3. Supplementals.....	(110)	1,175,000	(110)	1,175,000	-	---
4. New.....	140	4,411,000	77	2,611,000	-63	-1,800,000
5. Subtotal Regular Program.....	1,267	49,651,000	1,166	48,887,000	-101	-764,000
6. General Research Support.....		5,027,000		4,481,000		-546,000
7. Scientific Evaluation		130,000		130,000		---
8. Categorical Clinical Research Centers		3,154,000		3,154,000		---
9. Specialized Research Centers.....		840,000		840,000		---
10. Total	1,267	58,802,000	1,166	57,492,000	-101	-1,310,000

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Total Fellowships.....	$2,782,000	$2,595,000	$-187,000

Introduction

The research fellowship program of the Institute is designed to encourage physicians and laboratory scientists to acquire the specialized research training and experience essential for careers as teacher-investigators in the neurological and human communication sciences. This includes specific areas such as stroke, acute head and spinal cord injury, epilepsy, hearing impairment, and speech and language disorders. The research fellowship program includes Postdoctoral Fellowships and Research Career Development Awards.

Postdoctoral Fellowships

The Postdoctoral Fellowship Program of the Institute provides financial support for scientists who have recently completed doctoral (Ph.D. or M.D.) preparation and who desire additional research training in highly specialized health and health related research areas. These individuals frequently become authorities in their research areas. During 1972 emphasis will be given to training in fields relevant to laboratory and clinical research on problems of cerebral vascular disease, epilepsy, parkinsonism, speech and language impairments, deafness, and vestibular disease.

More than a decade of experience indicates that the Postdoctoral Fellowship Program of the Institute has proven highly effective in meeting its objectives. A significant number of research scientists whose projects are currently being supported by NIH Research Grants received their professional preparation under this program.

Research Career Development Award Program

Research Career Development Awards provide stipend support during a five year period for the most brilliant young scientists who have completed all or nearly all of their formal research training and who desire and require additional research experience prior to assuming positions of scientific leadership. RCDA's enable scientists to become established as independent investigators in selected areas of research. The awards are especially important for clinician-researchers who are able for the first time during their training to develop the experience essential for an academic and research career for which they have a long prior period of clinical preparation. Many more such individuals are needed who can combine extensive knowledge in one or more of the basic sciences with first hand clinical experience in the neurological and communicative impairments.

Program Plans for 1972

Funds requested for 1972 will provide for 123 fellowship awards, compared to 135 in 1971, a decrease of 12.

62-645 O - 71 - pt. 3 - 49

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting.....	73	$2,020,000	73	$2,020,000	--	--
2. Competing renewals..	44	575,000	33	400,000	-11	$-175,000
3. Supplemental.....	(39)	32,000	(39)	32,000	--	--
4. New.....	18	155,000	17	143,000	-1	-12,000
5. Total fellowships...	135	2,782,000	123	2,595,000	-12	-187,000

Fellowships (by type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Postdoctoral.....	45	$ 366,000	42	$ 339,000	-3	$ -27,000
2. Research career:						
a. Career.....	12	356,000	12	356,000	--	--
b. Development....	78	2,060,000	69	1,900,000	-9	-160,000
3. Total fellowships...	135	2,782,000	123	2,595,000	-12	-187,000

Training Programs

	1971 Estimate	1972 Estimate	Increase or Decrease
Total training grants.....	$11,456,000	$11,456,000	--

Introduction

The Extramural Training Grant and Traineeship Programs of the Institute have as their primary objective assisting training institutions in the recruitment and training of academicians, teachers, clinical and basic scientists, and community health leaders for careers in the fields of neurological and communicative disorders and stipend support of selected trainees during the period of training. The Institute has the responsibility for providing the resources necessary for training the individuals who will become future teachers responsible for training physicians and scientists who will develop the advances needed for understanding, preventing, and successfully treating diseases and disorders of the nervous system and the problems of human communication. From these training programs emerge our leading academicians, teachers, and medical scientists.

Graduate Training Grants

These grants are awarded on a competitive basis to institutions and organizations providing training in the disciplinary areas related to neurological or communicative disorders. The primary objective of these grants is the training of teacher-investigators, scientist-physicians, and community health and public health personnel in the specialty, discipline, or field for which the grant is made.

Teacher-Investigator Special Traineeships

The Teacher-Investigator Program, now in its second year, offers the most competitive and prestigious training and development award made by the Institute to an individual. The award provides support for the clearly superior individual who has a high potential for an outstanding academic career. This support bridges the gap between a postdoctoral period of study and a secure academic appointment. The T-I award provides a continuing five-year period of support for the development of future academicians. Awards are primarily for those who are identified as having potential as opposed to those who have already demonstrated superior achievement.

Special Traineeships

Special Traineeships are awards to individuals who have completed at least three years of postdoctoral training or research experience. The program provides the financial support required by scientists, particularly clinical scientists, who are interested in becoming highly qualified in the diversity of essential research skills in areas such as neuroanatomy, neurophysiology, neuropathology, neurochemistry, neuropharmacology, audiology, otolaryngology, speech pathology and biophysics. Such skills are critical to advances in solving neurological and communicative disease problems or, more important, preventing such problems. Scientists must continually update their skills as knowledge advances in their specialized areas and in related areas and they must acquire competence in the utilization of new techniques and instrumentation.

Program Plans for 1971 and 1972

The Institute will continue to train teachers and researchers in areas involving the nervous system and human communications, as it has in the past. The demand for such personnel continues to increase as a result of the establishment of new medical schools and the increasing requirements for highly skilled personnel. Funds requested for 1972 will provide for 351 awards compared to 365 in 1971, a decrease of 10 Graduate Training programs and 4 traineeships.

Distribution of Training Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting.....	162	$ 7,118,000	149	$ 6,784,000	-13	$-334,000
2. Competing renewals.....	135	3,134,000	143	3,650,000	+8	+516,000
3. Supplementals.....	(56)	328,000	(35)	244,000	(-21)	-84,000
4. New.....	68	741,000	59	643,000	-9	-98,000
5. Scientific evaluation..	(3)	135,000	(3)	135,000	--	---
6. Total training grants..	365	11,456,000	351	11,456,000	-14	---

Training Grants (by type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Graduate.....	208	$ 9,536,000	198	$ 9,536,000	-10	---
2. Traineeships.....	157	1,785,000	153	1,785,000	-4	---
3. Scientific evaluation and planning.....	(3)	135,000	(3)	135,000	--	---
4. Total training grants..	365	11,456,000	351	11,456,000	-14	---

Laboratory and Clinical Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	252	$ 4,103,000	252	$ 4,353,000	--	+250,000
Other expenses.....	--	6,216,000	--	6,219,000	--	+3,000
Total.....	252	10,319,000	252	10,572,000	--	+253,000

Introduction

The intramural research activities of the Institute are directed toward a broad program of investigation concerning the basic characteristics of the nervous system and its diseases. Supporting this program effort are three branches and eight laboratories with a personnel staffing at the end of 1970 totaling 225.

Program Plans for 1971 and 1972

In 1971 and 1972 the Institute's basic and clinical research in neurological disorders will encompass both ongoing and new projects. During this period it is estimated that 160 research projects will be conducted. The following are among the most important:

A careful theoretical study of a new approach to laminar tomography and design of improved apparatus was conducted in collaboration with Case Western Reserve University. The principles of design and its optimization were tested in a bench model. A fully operative instrument which will promise a significant advance in the diagnosis of cerebral tumors and cerebrovascular lesions is under construction.

Emphasis will be maintained on research in neurochemical disorders, particularly in familial lipidoses. These poorly understood, devastating, and untreatable neurological disorders of genetic origin have recently begun to yield to biochemical investigation so that much progress in this area is expected over the next few years.

Emphasis will also be given to clinical research in neuromuscular disorders since new methods of treating disorders such as Refsum's disease, hypokalemic periodic paralysis, dermatomyositis/polymyositis, and myasthenia gravis have been found. A new system of classifying neuromuscular diseases continues to provide clues to differential diagnosis--a skill which will become increasingly important as treatment regimens for more of these disorders become available. New surgical approaches to diseases of the basal ganglia and hydrocephalus are being developed.

Basic studies using animal models provide many opportunities to make important advances in our fundamental knowledge of disease mechanisms as well as normal physiological processes. Chronic embolization of the blood stream of rabbits has produced muscle pathology essentially identical to progressive pseudo-hypertrophic muscular dystrophy. Evidence suggests that this type of MD, traditionally thought to be a primary disease of the muscle itself, is rather a disorder of the small blood vessels.

After extensive observation of head injury and whiplash in lower primates, a theoretical model of head injury has been developed which provides for a scaling relationship to man. It is believed that extrapolation to man is possible and further study of the pathogenesis of head injury is planned.

Major efforts will continue in basic studies. For example, studies are being conducted to understand how trophic factors in nerves influence the structure of the muscles to which they connect; to learn the nature of the blood brain barrier, the parameters controlling vascular permeability in the brain, and the aging of neurons and glia; and to elucidate the neurophysiological mechanisms involved in sensory systems, motor action and integration within the central nervous system.

Collaborative Research and Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	165	$2,180,000	165	$2,319,000	--	$ +139,000
Other expenses.....	--	7,572,000	--	5,512,000	--	-2,060,000
Total.....	165	9,752,000	165	7,831,000	--	-1,921,000

Introduction

This activity includes (a) the Special Projects Branch (Head and Spinal Cord Injury, Epilepsy, and Cerebral Death), (b) the Perinatal Research Branch, and (c) the Sensory Prosthesis program.

Program Plans for 1971 and 1972

The planned collaborative programs for 1971 and 1972 will emphasize the following research.

Head Injury

The two major contractors on the head injury model construction program have completed testing of the material properties of the human and animal head. Two smaller studies are underway of the mechanical properties of the head-neck junction and the dynamic material properties of cerebral blood vessels. One of the principal contractors is currently engaged in an in-depth review of all data collected and analysis of that data for the presentation of a definitive final report on the material properties of the tissues of the head.

The field survey of 875 head-injured veterans of the Korean Campaign and 121 noninjured controls has been completed. Interview data on employment patterns, post-traumatic symptoms and post-traumatic epilepsy, obtained by field workers of the American Red Cross Service to Military Families, have been analyzed by the National Research Council Follow-up Agency. The National Research Council has prepared a final report. When editing and review of this final report are completed, it will be published as either an NINDS or National Academy of Science publication.

A classified bibliography of head injury and related topics is prepared and issued quarterly to interested neuroscientists.

Epilepsy

A program to further the development of new anticonvulsant drugs has been a major thrust of the Institute's epilepsy program. Staff efforts in programming and coordinating projects has been augmented by an NINDS Ad Hoc Committee on Anticonvulsant Drugs. During 1970 and in 1971, priorities have been established for the investigation of promising new drugs. Projects are underway for the clinical testing of two experimental new drugs and for a systematic clinical trial of ethosuximide, an established drug utilized in the treatment of petit mal epilepsy which is to be used as a standard against which new drugs will be compared.

In an effort to improve communication from basic and clinical investigators studying the many facets of the problem of epilepsy, a multi-phase program has been implemented. Publication of Epilepsy Abstracts, a monthly abstract journal, has been continued. Retrospective Epilepsy Abstracts--1947-1968 has been published and distributed to recipients of Epilepsy Abstracts. Preparation of an annotated bibliography of epilepsy from 1900-1950 has begun. Basic Mechanisms of the Epilepsies, the proceedings of an Institute-sponsored symposium, were published in January 1970. Efforts to automate the epilepsy data base, made possible through the Epilepsy Abstracts effort, have proved successful. The major priority for 1972 will be continued investigation of promising anticonvulsant compounds. Technical communication projects beyond the new developmental stage which have proven their value will become self-supporting or transferred to other support.

Cerebral Death Research

In FY 1971 the Institute, recognizing the problems of defining cerebral death, prepared to launch a study which will hopefully provide sufficient data to allow individual institutions to develop operational criteria for cerebral death. This effort is important in that an increasing number of deeply comatose patients' lives are pointlessly being maintained by extraordinary measures, an expensive process in terms of money and manpower. The ability to define carefully the occurrence of cerebral death in a comatose patient will be of great assistance to the attending physician, the institution providing care, and the patient's family. In addition, these criteria will be most important in determining whether or not it is justifiable to remove organs for transplantation.

Sensory Prosthesis Research

The ultimate aim is to develop devices using suitable sensors, data processors, and stimulating electrode arrays implanted against the brain of a blind or deaf person to permit the subject to abstract meaningful information from his environment. Five contracts for preliminary studies were awarded in 1970 and an additional three in 1971 totalling $400,000. Efforts will continue in 1972 to determine the best way to stimulate the brain in humans and experimental animals to determine if this can be done safely and to study the effects of the implanted materials on the brain and of the body fluids upon implanted electronic devices. This information is of utmost importance in the design of sensory prosthesis for the blind or the deaf. FY 1972 efforts will continue at the same level for this program.

Collaborative Perinatal Project

The program is a comprehensive prospective investigation of events and complications of pregnancy which arise before and around the time of birth and which are suspected to contribute to neurological disorders such as cerebral palsy, intellectual deficits, learning and reading disorders, epilepsy, and congenital malformations in children. Observations on some 60,000 pregnancies were made during the years 1959 through 1965 at 14 collaborating major medical centers distributed through the United States. Currently the major emphasis is on the follow-up of children from these pregnancies to age 8. The seven-year follow-up examination includes a neurological, psychological and visual screening examination, and an evaluation of the socio-economic environment in which these children grow up. At eight years, there is a detailed assessment of speech, language, and hearing function. These evaluations at age 7 and 8 are designed to identify specific neurological problems including those subtle deficits of the central nervous system, such as learning disabilities and minimal brain dysfunction, the etiology of which is for the most part unknown.

As indicated by the summary table for this entire budget activity, there is a net decrease in the 1972 funding level of $1,921,000. This consists of a plus $145,000 for mandatory increases (1971 pay act, within grade pay increases, federal telecommunications cost), $34,000 to the "National Institutes of Health Management Fund", and a decrease of $2,100,000 from the collaborative perinatal project.

To enable this project to reach its basic goals, at the decreased level of funds available in 1972, several adjustments and deletions to segments of the program will be made.

Initially a downward adjustment of 25% will be applied to data collection from the twelve collaborating institutions which constitute the "core" of the program.

Analysis of the data collected by these institutions will be limited to the central objectives of the program. This is the association of pre- and perinatal problems with neurological and intellectual deficits of children. The number of task forces planning and guiding this analysis will also be decreased.

The excellent quality control program of the study which provides for investigators of one institution to review the findings of investigators at others will be decreased to half of the present rate.

The sample maintenance concerned with the retention rate of children for examinations at age 7 and 8 will be reduced, but every effort will be made to maintain essential elements in the data collected and still continue the same quantity and quality of effort. The exploration of infections as possible causes of fetal abnormalities will be restricted to those 10 or 15 agents which are highly suspect of causing these adverse effects.

Biometry, Epidemiology, and Field Studies

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	84	$1,337,000	84	$1,412,000	--	+75,000
Other expenses.....	--	2,145,000	--	2,064,000	--	-81,000
Total.....	84	3,482,000	84	3,476,000	--	-6,000

Introduction

The organizational structure of this activity includes the Epidemiology Branch, the branch conducting studies of slow viruses and their relation to neurological disorders, the Office of Biometry, and the Neurological Information Network.

Program Plans for 1971 and 1972

Program Plans presently focus on a continuation of activity already begun. The Epidemiology Branch will place emphasis on continuing studies which show promise of producing understanding of the pathogeneses of such unremitting and inevitably fatal diseases as amyotrophic lateral sclerosis and parkinsonism-dementia. Investigations into climatic conditions, genetic composition of the population, and immunologic abnormalities as factors in the incidence of diseases such as multiple sclerosis, torsion dystonia, amyotrophic lateral sclerosis, parkinsonism and stroke will continue as major activities. The program on chronic disorders of the central nervous system has already shown that certain nervous system diseases may have a virus infection as their etiology and the search will continue to see if this same factor is involved in similar neurological diseases. As an aid to this search, attempts will be made to find more animal models that could have utility in studying human nervous system diseases and the character of the infectious agent. The Neurological Information Network has developed an effective system for the prompt exchange of information in the medical and scientific communities, and these efforts will continue and the Office of Biometry will continue its mathematical and statistical assistance to the Institute's staff and to the Collaborative Perinatal Project in particular.

Following is a detailed description for each program area.

Epidemiology

Epidemiologic studies will be carried out on a broad range of neurological disorders. Studies of patients with amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia (PD) on Guam, where the incidence of these diseases is high, have demonstrated that the unusual pathological changes that occur in the brains of these patients also occur in Guamanians who do not show clinical evidence of these diseases. Such findings favor an environmental factor being the cause. Biochemical studies have suggested that the ALS and PD seen on Guam may be responsive to treatment with drugs of the dopamine series. Therapeutic trials of levodopa are underway and, on initial review, appear promising.

Studies of multiple sclerosis (MS) have indicated that the disease occurs more frequently in cold climates. Migration studies recently completed reveal that those born in warmer low-risk areas are protected against MS even after migration to higher risk areas; while the incidence of the disease in those born in high-risk areas is slightly diminished after migration to a lower risk area.

Central Nervous System Studies

Research will continue in the highly successful study of slow, latent, and temperate virus infections of the central nervous system. The disease kuru, the first chronic degenerative neurological disorder to be experimentally transmitted from man to animal was for a time the only such disease known to be capable of acting in this way; furthermore the only animal model that had been used successfully was the chimpanzee. In subsequent continued studies, spongiform encephalopathy also known as Creutzfeldt-Jakob disease, and pre-senile dementia, a related disease occurring in the United States, have been successfully transmitted to the chimpanzee, and both diseases have now been transmitted to other primates--the squirrel monkey, the Capucin monkey, and the spider monkey. Some progress has been made in the characterization of the viruses responsible using the primate laboratory animals, and attempts to grow these viruses in tissue cultures. Several viral agents have now been isolated in tissue cultures from human central nervous system and muscle tissues of victims of chronic encephalopathies, amyotrophic lateral sclerosis, and polymyositis. A virus agent from the brain of sheep with Montana sheep disease has been isolated and shown to be related or identical to Visna, a virus caused demyelinating degenerating disease of the brain of sheep in Iceland. These discoveries have stimulated further more specific tissue culture and virus studies.

Neurological Information Network

Within this budget activity, the Institute supports the national Neurological Information Network. This network in 1970 and 1971 facilitated the prompt exhange of information within the medical and scientific community through information centers in universities having outstanding library facilities. These are the Information Center for Hearing, Speech, and Disorders of Human Communication at Johns Hopkins University and the Brain Information Service at the University of California at Los Angeles.

Review and Approval of Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	77	$1,168,000	77	$1,238,000	--	+70,000
Other expenses.....	--	1,150,000	--	1,254,000		+104,000
Total.....	77	2,318,000	77	2,492,000	--	+174,000

Introduction

The Extramural Programs administers the Institute's grant and award programs in support of medical research and training in the neurological and communicative disorders. Research grants, program project grants, research center grants, training grants, fellowships, and traineeships, are programmed, examined, processed and administered by the professional, administrative, and clerical staff of the Institute's Extramural Program. Advice on technical merit and program significance are provided by organized and ad hoc bodies of non-governmental authorities in the health and science fields, including the National Advisory Neurological Diseases and Stroke Council, training review committees, clinical center-program project review committees and study sections of the Division of Research Grants, National Institutes of Health.

Program Plans for 1971 and 1972

Management's expanding need for access to multiplex data and its comprehensive analysis to provide a firm base for program planning, evaluating and reporting, demands a fully automated information system capable of being adjusted to changing requirements. Such a system is being established and will permit a more refined assessment of institute support patterns and needs in research and research training in neurological and communicative disorders.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	30	$409,000	30	$437,000	--	$+28,000
Other expenses.....	--	162,000	--	170,000		+8,000
Total.....	30	571,000	30	607,000		+36,000

This activity supports professional and administrative direction of the Institute's activities. The Office of the Director provides for the centralized supervision, coordination and review of these programs, as well as for the direction of the administrative functions of finance, personnel, supply, travel, space utilization and management analysis.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Program Purpose and Accomplishments

Activity: Research Grants

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$58,802,000	Indefinite	--	$57,492,000

Purpose: This program supports the development and implementation of broad programs and projects of research on disorders of the brain, special senses, and human communication.

Explanation: The method most frequently used is the research project grant to support the independent investigator. Also, program projects or clinical research center grants are awarded when complex clinical problems, such as research on stroke or on head and spinal cord injury, require the support of a multidisciplinary team within a single institution.

Accomplishments in 1971: In 1971, 1,256 grants will be awarded. Of these, 871 will be continuations and 385 will be competing awards.

Objectives for 1972: The estimate for 1972 provides for 1,166 awards, a decrease of 90 from 1971. Greater emphasis will be placed on research into stroke, spinal cord injury and speech and hearing.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Program Purpose and Accomplishments

Activity: Fellowships

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$2,782,000	Indefinite	--	$2,595,000

Purpose: The research fellowship programs are designed to encourage physicians and laboratory scientists to acquire the specialized research training and experience essential to prepare them for careers as teacher-investigators in the field of neurological disorders, including stroke, acute head and spinal cord injury, epilepsy, and disorders of hearing, speech, and human communication.

Explanation: The program provides the financial support scientists must have in order to become highly qualified in the diversity of essential research skills, such as neuroanatomy, neurophysiology, neuropathology, neurochemistry, neuropharmacology, audiology, otolaryngology, speech pathology, neuro-otology, biophysics, all of which are critical to advances in solving the neurological and communicative disease problems. More than a decade of experience indicates that the fellowship programs have proven highly effective in meeting these objectives.

Accomplishments in 1971: In 1971 it is estimated that 135 fellowships will be made, including 45 postdoctoral awards, 12 research career awards and 78 research career development awards.

Objectives for 1972: The 1972 estimate would provide for 123 fellowship awards, 12 less than 1971.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Program Purpose and Accomplishments

Activity: Training Grants

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$11,456,000	Indefinite	--	$11,456,000

Purpose: The training grants program, graduate training grants and traineeships assist, as their primary objectives, training institutions in the recruitment and training of academicians, teachers, clinical and basic scientists, and community health leaders for careers in the field of neurological and communicative disorders, and to provide stipend support to selected trainees.

Explanation: Graduate training grants are awarded on a competitive basis to institutions and organizations providing training in disciplinary areas related to neurological, sensory, or communicative disorders. Traineeships provide individual stipend support to basic or clinical scientists who desire highly specialized training in these same disciplines.

Accomplishments in 1971: In 1971 an estimated 365 awards will be made including 208 graduate training grants and 157 traineeships.

Objectives for 1972: The estimate for 1972 provides for 351 awards, a decrease of 10 graduate training grants and 4 traineeships.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Program Purpose and Accomplishments

Activity: Laboratory and Clinical Research

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
252	$10,319,000	Indefinite	252	$10,572,000

Purpose: The intramural research activities of the Institute are directed toward a broad program to investigate the basic characteristics of the nervous system and its diseases.

Explanation: Supporting this program effort are four branches and eight laboratories. The following are in the Clinical Research area: Medical Neurology, Surgical Neurology, Electroencephalography, and Neuro-otology. Under the Laboratory Research area are: Neuropathology and Neuroanatomy, Biophysics, Neurochemistry, Neurophysiology, Molecular Biology, Experimental Neurology, Neural Control, and Perinatal Physiology.

Accomplishments in 1971: Several promising new therapies were developed for treatment of epilepsy, and understanding the burst of abnormal electrical activity of brain cells during the epileptic seizure. In the Laboratory Research area, advancement in knowledge has been obtained of the structure of the nervous system and interpreting basic abnormal changes, the blood-brain barrier and its functions, and the chemical organization of the brain and nerves.

Objectives for 1972: The Institute's basic and clinical research in neurological and communicative disorders will comprise both ongoing and new projects. These projects will include research in the field of cerebral trauma, particularly head injury. Emphasis will also be given to the experimental production of head injury in primates and in formulating mathematical models of whiplash injury. Also included are research in the field of muscular disorders.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Program Purpose and Accomplishments

Activity: Collaborative Research and Development

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
165	$9,752,000	Indefinite	165	$7,831,000

Purpose: This activity supports many of the most important categorical research programs conducted by investigators in collaboration with other Federal institutions and non-Federal institutions largely through contracts.

Explanation: This activity includes the Special Projects Branch (Head Injury, Spinal Cord, Epilepsy, and Cerebral Death), the Perinatal Research Branch, and Special Programs of the Institute such as sensory prosthesis research. This research tends to be more specifically goal-oriented in nature than that supported through grants.

Accomplishments in 1971: Research emphasis was on Head Injury, Epilepsy, and the Perinatal Research Projects. The study of 875 head-injured veterans of the Korean Campaign and 121 non-injured controls was completed and resultant interview analysis has shown the effects from employment patterns, posttraumatic symptoms and posttraumatic epilepsy. Research contracts were awarded for continued studies of the anticonvulsant properties of ethosuximide (Zarontin) for treatment of epilepsy. The major emphasis in the perinatal project is on the follow up of children to age 8. Also, the program for experimental research directed toward a useful substitute for vision and hearing was continued.

Objectives for 1972: The research emphasis will continue to be on Head Injury, Epilepsy, and the Perinatal Research Projects. Also, programs will continue to be directed towards evaluating the feasibility of development of a sight substitute for blind people.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Program Purpose and Accomplishments

Activity: Biometry, Epidemiology, and Field Studies

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
84	$3,482,000	Indefinite	84	$3,476,000

Purpose: This activity provides for the conduct and support of epidemiological and biometrics research, and clinical trial studies to seek knowledge of the causes of neurological and sensory health problems.

Explanation: The Office of Biometry furnishes the Institute's staff with computer and biometrical formulas and concepts in the Institute's extramural, collaborative, and clinical programs. In the Epidemiology Branch, studies of the incidence and prevalence of a wide range of neurological disorders are underway. This activity also supports the Institute's significant studies relating to the causes of neurological and sensory disorders from infection to slow viruses.

Accomplishments in 1971: Epidemiology studies were carried out on a broad range of neurological disorders including parkinsonism, multiple sclerosis, and therapeutic trials of levodopa. The central nervous system studies continued the highly successful research of slow, latent, and temperate virus infections of the central nervous system. Among the research accomplishments has been the ability to transmit certain diseases to other primates as well as the chimpanzee.

Objectives for 1972: Program plans presently focus on a continuation of activity already begun. The Office of Biometry will continue its mathematical and statistical assistance to the Institute's staff. The Epidemiology Branch will place emphasis on continuing studies which show promise of producing understanding of the pathogeneses of such unremitting and inevitably fatal diseases as amyotrophic lateral sclerosis and parkinsonism-dementia. The program on chronic disorders of the central nervous system has already shown that certain nervous system diseases may have a virus infection as their etiology and the search will continue to see if this same factor is involved in similar neurological diseases.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Program Purpose and Accomplishments

Activity: Review and Approval

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
77	$2,318,000	Indefinite	77	$2,492,000

Purpose: This activity supports the administration of the Institute's grants and award programs in support of medical research and training in the neurological and communicative disorders. The activity also includes the Office of Program Analysis which maintains an overview of all the program areas of the Institute.

Explanation: Research grants, program project grants, research center grants, training grants, fellowships, and traineeships, are programmed, examined, processed and administered by this activity.

Accomplishments in 1971: The development of the Extramural Program Data Analysis and Report Section has provided a base for data storage and retrieval and program analyses. Advice on technical merit and program significance was provided by organized and ad hoc bodies of non-governmental authorities in the health and science fields.

Objectives for 1972: Maintain the same level of administrative support as furnished in 1971 with emphasis on the refinement of the extramural reporting system.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Program Purpose and Accomplishments

Activity: Program Direction

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
30	$571,000	Indefinite	30	$607,000

Purpose: This activity supports the professional and administrative direction of the Institute's activities.

Explanation: The Office of the Director provides for the centralized supervision, coordination, and review of all the Institute's programs, as well as for the direction of the administrative functions of finance, personnel, supply, travel, space utilization, and management analysis.

Accomplishments in 1971: Maintained a high level of efficiency in providing services as outlined in paragraph above.

Objectives for 1972: To continue to provide administrative services and make improvement where required.

62-645 O - 71 - pt. 3 - 50

THURSDAY, MAY 6, 1971.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. DORLAND J. DAVIS, DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. JOHN R. SEAL, SCIENTIFIC DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
WALTER H. MAGRUDER, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
GERALD F. MEYER, CHIEF, HEALTH BRANCH, DIVISION OF BUDGET

National Institute of Allergy and Infectious Diseases

Object Classification (in thousands of dollars)

Identification code 09-30-0885-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	7,883	8,274	8,496
11.3	Positions other than permanent	174	136	136
11.5	Other personnel compensation	145	150	150
	Total personnel compensation	8,202	8,560	8,782
12.1	Personnel benefits: Civilian employees	824	860	884
21.0	Travel and transportation of persons	322	350	350
22.0	Transportation of things	83	85	85
23.0	Rent, communications, and utilities	242	270	278
24.0	Printing and reproduction	53	60	60
25.0	Other services	16,312	18,680	17,472
26.0	Supplies and materials	2,159	2,300	2,300
31.0	Equipment	350	400	400
41.0	Grants, subsidies, and contributions	68,520	70,378	67,833
42.0	Insurance claims and indemnities	1	----------	----------
	Subtotal	77,068	101,943	98,431
95.0	Quarters and subsistence charges	−13	−13	−13
99.0	Total obligations	97,055	101,930	98,431

Personnel Summary

Total number of permanent positions	687	687	687
Full-time equivalent of other positions	23	18	18
Average number of all employees	698	705	705
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,431

Program and Financing (in thousands of dollars)

Identification code 09-30-0885-0-1-651		1970 actual	1971 est.	1972 est.
	Program by activities:			
	1. Grants:			
	(a) Research	57,463	57,657	56,999
	(b) Fellowships	3,908	3,749	3,504
	(c) Training	11,413	8,972	7,330
	Total grants	72,784	70,378	67,833
	2. Direct operations:			
	(a) Laboratory and clinical research	16,236	17,842	16,732
	(b) Collaborative research and development	12,898	11,830	11,857
	(c) Review and approval	1,533	1,534	1,622
	(d) Program direction	326	346	387
	Total direct operations	30,993	31,552	30,598
	Total program costs, funded [1]	103,777	101,930	98,431
	Change in selected resources [2]	−6,722	----------	----------
10	Total obligations	97,055	101,930	98,431

Program and Financing (in thousands of dollars)—**Continued**

Identification code 09-30-0885-0-1-651		1970 actual	1971 est.	1972 est.
	Financing:			
25	Unobligated balance lapsing	235	1,132	
	Budget authority	**97,290**	**103,062**	**98,431**
	Budget authority:			
40	Appropriation	103,694	102,249	98,431
40	Portion withdrawn (Public Law 91-204, sec. 410)	−2,936		
41	Transferred to other accounts	−3,469	−31	
43	Appropriation (adjusted)	97,290	102,218	98,431
46.10	Proposed transfer for wage-board increases		64	
46.20	Proposed transfer for civilian pay act increases		666	
46.30	Proposed transfer for military pay act increases		114	
	Relation of obligations to outlays:			
71	Obligations incurred, net	97,055	101,930	98,431
72	Obligated balance, start of year	57,587	60,205	65,048
74	Obligated balance, end of year	−60,205	−65,048	−64,051
77	Adjustments in expired accounts	−1,420		
90	Outlays, excluding pay increase supplemental	93,017	96,260	99,411
91.10	Outlays from wage-board supplementals		58	6
91.20	Outlays from civilian pay act supplementals		655	11
91.30	Outlays from military pay act supplementals		114	

[1] Includes capital outlay as follows: 1970, $633 thousand; 1971, $400 thousand; 1972, $400 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $35,810 thousand; 1970, $29,348 thousand; 1971, $29,348 thousand; 1972, $29,348 thousand.

NOTES

Includes $738 thousand in 1971 and $738 thousand in 1972 for activities previously financed from: Research resources, 1970, $738 thousand.

Excludes $802 thousand in 1972 for activities transferred to: National Heart and Lung Institute, 1971, $802 thousand.

Excludes $1,769 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	*1971*
National Institute of Arthritis and Metabolic Diseases	1,023	1,023
Office of the Director	349	643
National Institute of Child Health and Human Development	10	
Research resources	91	
Health manpower	109	103

Excludes $506 thousand in 1971 and $506 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970
Office of the Director	6
Fogarty International Center	500

Excludes $1,642 thousand for activities transferred to: Health manpower, 1970-$1,642 thousand, $1971, 1,642.

INTRODUCTION OF DR. DAVIS AND ASSOCIATES

Mr. FLOOD. We continue with the National Institutes of Health. We now have the National Institute of Allergy and Infectious Diseases.

The presentation will be made by Dr. Dorland J. Davis, the Director. We have a biographical sketch of you, Doctor.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH OF DORLAND J. DAVIS, M.D.

Position: Director, National Institute of Allergy and Infectious Diseases.
Birthplace and date: Chicago, Ill., July 2, 1911.
Education:
B.S., University of Illinois, 1933.
M.D., Johns Hopkins University, 1937.
Dr. P. H. (epidemiology), Johns Hopkins University, 1940.
Certified by the American Board of Preventive Medicine and Public Health, 1949.
Experience:
Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1964 to present.
Associate Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1956–1964.
Chief, Laboratory of Infectious Diseases, National Microbiological Institute (now National Institute of Allergy and Infectious Diseases) NIH, 1954–56.
Commissioned officer on duty at National Institutes of Health (1943–44 on duty in North Africa for the State Department) advanced through grades to Assistant Surgeon General, 1968 to present.
Association Memberships:
Fellow, American Academy of Microbiology.
Fellow, American College of Preventive Medicine.
American Association of Immunologists.
American Epidemiological Society.
American Society of Tropical Medicine and Hygiene.
World Health Organization Panel on Virus Diseases.
Board of Directors, Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc.
Member National Research Council, Division of Medical Sciences (executive committee).
Special awards, citations, or publications:
Edward Rhodes Stitt Award, Association of Military Surgeons of the United States, 1955.
Meritorious Service Medal, Commissioned Corps, USPHS, 1967.
Publication of 47 papers on infectious diseases.

Mr. FLOOD. Do you have anybody here we don't know that you would like us to meet?

Dr. DAVIS. On my left is Mr. Magruder, the Executive Officer, and beyond him Dr. Seal, the Scientific Director of the Institute. I believe you have the biographical sketches of each of these.

Mr. FLOOD. We would like those in the record.

(The biographical sketches follow:)

BIOGRAPHICAL SKETCH OF JOHN R. SEAL, M.D.

Position.—Scientific Director, National Institute of Allergy and Infectious Diseases.

Birthplace and Date.—Charleston, W. Va., March 10, 1912.

Education.—M.D., University of Virginia School of Medicine, 1937.

Experience.—Scientific Director, NIAID, Bethesda, Md., 1969–present; Director, Intramural Research, NIAID, NIH, Bethesda, Md., 1965–69; U.S. Navy—1942–65; assistant resident physician and instructor in medicine and cardiology, New York Hospital and Cornell School of Medicine, 1940–42; instructor

in pathology, University of Virginia School of Medicine, 1938–40; intern, internal medicine, Strong Memorial Hospital, Rochester, N.Y., 1937–38.

Association memberships.—Member, NIH Committee on International Centers for Medical Research and Training, 1961–65; Department of Defense Liaison Member (alternate for Deputy Assistant Secretary Defense H. & M.) National Advisory Health Council, NIH, 1961–65; Member, Committee on Naval Medical Research, Division of Medical Sciences, National Research Council, National Academy of Sciences, 1966–69 (Chairman, July 1969–).

Societies.—American College of Physicians; Association of Military Surgeons of the United States; American Society of Tropical Medicine and Hygiene; Infectious Diseases Society; American Epidemiology Society.

Special awards, citations.—Alpha Omega Alpha, Honoray Medical Society, 1937; Fellow, American College of Physicians, 1952; Stitt Award, Association of Military Surgeons, 1954; Secretary of the Navy Commendation Medal, 1965; Founders Medal, Association of Military Surgeons, 1968; DHEW Superior Service Award, 1969.

BIOGRAPHICAL SKETCH OF WALTER HASWELL MAGRUDER

Position.—Executive Officer, NIAID.

Birthplace and date.—Washington, D.C., April 13, 1915.

Education.—1932: Graduated from Richard Montgomery High School, Rockville, Md.; 1935–39: Attended law school, Washington College of Law, Washington, D.C.

Experience.—May 1966 to present: National Institute of Allergy and Infectious Diseases, NIH, Executive Officer; October 1955–May 1966: National Cancer Institute, NIH, Administrative Officer; September 1952–October 1955: National Institutes of Health, Budget Examiner; April 1948–September 1952: Atomic Energy Commission, Administrative Officer, Program Analyst; April 1946–April 1948: War Assets Administration, Accountant, Collections Officer.

Association memberships.—None.

Special awards, citations, or publications.—None.

GENERAL STATEMENT

Mr. FLOOD. I see you have a prepared statement, Doctor. How do you wish to proceed?

Dr. DAVIS. I would be glad to read it.

Mr. FLOOD. Suppose you do that.

Dr. DAVIS. Mr. Chairman and members of the committee, in recent years, the general public has become increasingly aware of the effect of the environment on human health. We at the NIAID have been deply concerned about this relationship—earlier with the problem of sanitation in substandard living areas and the control of vectors of infectious diseases, and, more recently, with factors that can trigger allergic conditions in many Americans.

We estimate that approximately 31 million Americans—about 15 percent of the population—have one or more allergies, such as hay fever, food sensitivities, drug reactions and life-threatening asthma; and this figure does not include countless Americans who react to poison ivy, poison oak, poison sumac, and insect bites.

For 15 years, this Institute has emphasized research in basic immunology to seek answers to allergic disorders. We believe we are now at a stage to take advantage of new knowledge in immunology, pharmacology, and other fields of science and apply it to the solution of allergic disease problems. Several recent achievements have led to this belief.

For example, an NIAID-supported scientist now at Johns Hopkins University discovered an antibody in the blood, called *Immunoglobulin E*. This antibody reacts with a specific antigen leading to a chain of biochemical events that produce the symptoms of hay fever and many other allergic reactions. We have learned new facts about how body chemicals—histamine and "slow reacting substance"—are produced and cause physiological changes that result in hay fever, or asthma.

Another advance in research concerns "allergoids." Just as tetanus toxin was "tamed" when treated with formaldehyde to produce a toxoid for vaccination, Institute-supported investigators in Baltimore have tamed the pollen substance causing hay fever and called it allergoid. Allergoids have been tested as potential desensitization agents in guinea pigs and in normal human volunteers. They are now being given to a small group of hay fever patients. Although another year will be required to evaluate the results of this first clinical study, scientists involved believe that, within 5 years, allergoids may be used routinely to treat allergy patients.

ASTHMA AND OTHER RESPIRATORY DISEASES

Use of an experimental drug, known as disodium cromoglycate, has helped open up a new approach to treatment of severe asthma.

Mr. FLOOD. From where I come, in the coal fields, all asthma is severe. What do you mean by severe asthma vis-a-vis just plain asthma?

Dr. DAVIS. Asthma is really intermittent. Asthma is defined as almost any kind of wheezing.

Mr. FLOOD. Is it progressive?

Dr. DAVIS. Much asthma is.

Mr. FLOOD. And you include emphysema in that?

Dr. DAVIS. No, emphysema is a different disease.

Mr. FLOOD. How?

Dr. DAVIS. Asthma we think of as based on an immunologic reaction, that is, sensitivity to something in the environment.

Mr. FLOOD. Coal dust?

Dr. DAVIS. The coal dust produces a different kind of disease.

Mr. FLOOD. Black lung?

Dr. DAVIS. That is a different kind of disease. That is pneumoconiosis. That is a pathologic reaction.

Mr. FLOOD. We call it miner's asthma. It's probably a wrong term.

Dr. DAVIS. Yes.

Mr. FLOOD. You differentiate between asthma, severe asthma, anthracosilicosis and emphysema, four different things.

Dr. DAVIS. That is right.

Mr. FLOOD. They are all caused by a foreign substance?

Dr. DAVIS. They are all reactions to a foreign substance. But in the kind of reaction that one has in asthma, the kind that we see so frequently in children, the body reacts in a different way by developing antibodies against it.

Mr. FLOOD. Is it inherited, any kind of it?

Dr. DAVIS. The disease seems to run in families. Perhaps it's susceptibility to asthma.

Mr. FLOOD. Mendel's law again, or just one after the other?

Dr. DAVIS. I don't know of any studies that have worked the genetics out in detail.

Mr. FLOOD. Who would do that—you or somebody else?

Dr. DAVIS. I suspect that when we get precise enough definitions and means of diagnosis of asthma, that it could be done.

Mr. FLOOD. Isn't it about time we have?

Dr. DAVIS. We think it is. We think we are now at a stage where we are going to move ahead very rapidly in the study of asthma, because we now have so much more fundamental knowledge about what the mechanism is than we have ever had before.

Mr. FLOOD. There are different kinds of asthma, or different degrees of asthma?

Dr. DAVIS. There are really different degrees of asthma, but it can be triggered by a number of different kinds of things.

Mr. FLOOD. Virus?

Dr. DAVIS. Yes. When people, particularly children, who are susceptible to asthma acquire a viral infection, a cold or other respiratory infection, they very frequently come down with quite severe cases.

In some research patients, cromoglycate has produced clinical improvement and has reduced dependence on corticosteroid drugs. In fact, some patients were taken off steroids. Early trials have indicated that disodium cromoglycate may become an effective treatment in certain cases of severe asthma.

Mr. FLOOD. Would it follow that severe asthma, emphysema and black lung, most probably could cause heart attacks?

Dr. DAVIS. You are quite right, Mr. Chairman, asthma puts a very severe strain on the cardiovascular system.

Knowledge already gained in the way this new class of drug acts in the body should enable scientists to design other drugs for control of severe asthma in man.

ALLERGIC DISEASE CENTERS

In view of findings such as these examples, the Institute is establishing a limited number of allergic disease centers this year where clinical aspects of allergic disorders can be studied in conjunction with existing superior programs in immunologic research. In these research settings, well-trained physician-scientists will study ambulatory patients with allergic conditions. They will be directing their efforts primarily at the diagnosis, prevention, and treatment of asthma, hay fever, skin allergies, and food sensitivities. At the NIH Clinical Center, we began to expand our clinical allergy program in 1968. We are slowly increasing that capacity as resources become available.

Mr. FLOOD. You are establishing a limited number of allergic disease centers. Have you selected the sites?

Dr. DAVIS. These sites have been reviewed. The applications were reviewed by the Council in March. We are now making the awards. Seven will be awarded located in different parts of the country.

Mr. FLOOD. Will you put in the record where they will be? We would like to know.

Dr. DAVIS. Yes.

(The information referred to follows:)

ALLERGIC DISEASES

Approximately 31 million Americans--or 15 of every 100—suffer from one or more significant allergies. This estimate covers three categories of individuals: those who suffer from hay fever, from asthma, and from certain other allergies. The "other allergies" category includes such conditions as allergic eczema angioedema (a swelling of body tissue), urticaria (hives on the surface of the skin), food allergy, drug allergy, and bee sting allergy. The estimate does not include the millions of Americans with contact dermatitis (such as poison ivy, oak or sumac) and those who in recent years reported allergic reactions to detergents with enzyme additives.

Except for asthma—which claimed 3,800 victims in 1969—allergies cause a relatively small number of deaths. But all allergic conditions are costly in terms of days lost from work or school and payments made for medical care and drugs. In 1967, asthma/hay fever victims had 85 million days of restricted activity, of which nearly 33 million were spent in bed. In fact, at any given time, the activities of more than 1.2 million people are limited due to allergic disorders. Time lost from work by adults with allergic diseases amounted to over 6 million days in 1967. For those of school age, this meant almost 9 million days lost from studies.

One study estimated that more than 38 million patient visits were made to private physicians for allergic conditions in 1969. Based on an average patient visit charge of $6.89, the cost to the patients has been estimated at more than $264 millions. Prescriptions for allergic disorders were reported to cost $135 millions in 1967, and the Pharmaceutical Manufacturers Association estimates that $50 millions are spent each year on antihistamine medications alone.

During the past 15 years, fundamental knowledge applicable to allergies has been uncovered by investigators in the disciplines of biochemistry, immunology, and pharmacology. This new information has had a beneficial impact on current allergic research. Scientists today have a better understanding of how the immune system works under normal conditions and of what causes allergic and immunologic disorders. New drugs are being developed to block the immunologic process that results in an allergic reaction. Tests are being devised to detect susceptibility to such conditions as asthma and pencillin sensitivity. And, during the last 15 years, a cadre of clinical allergists who are superbly trained in the basic sciences has emerged.

Since its inception in 1955, the National Institute of Allergy and Infectious Diseases has provided the bulk of Government-financed support for scientist-originated, free-ranging investigations that probe for new facts or methods in clinical allergy and immunology. In fiscal year 1970, it provided $2.7 millions for 55 research grants to hospitals and universities throughout the Nation. Over the last 15 years, it also has provided support for the training of more than 1,800 individuals in clinical allergy immunology.

Since 1968, the Institute has had a small study on aspirin allergy—often a life-threatening reaction—at the NIH Clinical Center in Bethesda. And within the Institute's collaborative programs, a contractor has been preparing bulk quantities of an active ingredient of the ragweed pollen, known as Antigen E. This purified material is being made available to qualified investigators for allergic and immunologic studies.

Last year, advisors to the Institute agreed that the scientific base of knowledge of allergic diseases was sufficiently advanced to give promise of the fruitful application of preventive and therapeutic procedures within a few years. The plan was to establish a number of allergic disease centers where clinical aspects of allergic diseases could be studied in conjunction with high quality immunologic research. The studies would be directed at immediate hypersensitivities such as asthma, hay fever, and food allergies.

This year the Institute is establishing allergic disease centers at the following seven institutions: Robert B. Brigham Hospital, Boston; National Jewish Hospital and Research Center and the Children's Asthma Research Institute and Hospital, both of Denver; Washington University, St. Louis; John Hopkins University, Baltimore; University of Wisconsin, Madison; and the Scripps Clinic and Research Foundation, La Jolla, Calif.

ORGAN TRANSPLANT IMMUNOLOGIC STUDIES

Dr. DAVIS. Institute-supported scientists continue to build on basic immunologic findings related to organ transplantation and the rejec-

tion phenomenon. Use of tissue matching techniques and methods to suppress the body's immune defense system—such as drugs and biological preparations known as ALS——

Mr. FLOOD. What is ALS?

Dr. DAVIS. That is antilymphocyte serum—has resulted in an increasing number of successful transplants. To date, more than 5,000 kidney transplant operations have been performed. Actually, Mr. Chairman, I would like to make a correction here because of a recent report just released. It's something over 6,000 now.

Mr. FLOOD. 6,000 kidney transplants?

Dr. DAVIS. Right.

Mr. FLOOD. That is not generally known.

Dr. DAVIS. In the world.

Mr. FLOOD. Oh, in the world.

Dr. DAVIS. The number that were performed last year were more than twice those done the year before. Most of these have been done in the United States. With the exception of heart transplants, the number of other transplanted organs—liver, bone marrow, lung, and pancreas—though still small compared to kidney transplants, has increased over last year's figures.

Mr. FLOOD. Liver?

Dr. DAVIS. Yes.

Mr. FLOOD. Very many?

Dr. DAVIS. The record shows that 134 liver transplants have been performed. Of these, unfortunately, only 12 are surviving.

Mr. FLOOD. It's a pretty delicate thing to fool with?

Dr. DAVIS. It's a difficult thing.

One of the most promising areas of tranplantation is that of bone marrow, the tissue that makes blood cells. Since January 1968, 86 bone marrow transplants have been carried out in transplant centers on patients with leukemia or certain kinds of anemia. Twenty-five patients survive, and the longest survivor to date received transplanted bone marrow more than 2 years ago.

Mr. FLOOD. By the way, with reference to the liver transplants, you gave us the number attempted and the surviving. Will you give us the age bracket of the survivors, for the record, if you don't have it offhand?

Dr. DAVIS. Most of these are in young children.

(The information referred to follows:)

134 INDIVIDUALS RECEIVING LIVER TRANSPLANTS, 12 SURVIVE AS OF MAY 10, 1971

	Sex	Diagnosis	Length of survival (months)
Age at time of transplant:			
4 years	M	Biliary atresia	33
44 years	F	Carcinoma	27
11 years	M	Wilson's disease	20
51 years	M	Carcinoma	16
4 years	F	Biliary atresia	15
5 months	M	Hepato-blastoma	14
62 years	M	Carcinoma	9
28 years	F	Chronic active hepatitis	9
56 years	M	Secondary tumor in liver	8
4 years	F	Biliary atresia	7
3 years	F	do	7
49 years	M	Hepatoma	6

Note: These figures were obtained from the American College of Surgeons/National Institutes of Health Organ Transplant Registry, located in Chicago.

INCIDENCE OF INFECTIONS

The "killer" diseases related to this institute's program are those caused by viruses, bacteria and other micro-organisms. Although the classic epidemic infectious diseases—such as smallpox, bubonic plague, and typhoid fever—no longer threaten our country, approximately 100,000 Americans die each year from various infections. But deaths alone do not give a true picture of the burden of infectious diseases. Each year the average American suffers at least one such illness which requires medical attention—a heavy cold, the "flu", an intestinal "bug." On the average, each illness results in 2 days of confinement and curtails the patient's normal activities for 4 or 5 days. Of all lost workdays associated with acute conditions, almost 60 percent are due to infectious illnesses—representing an annual loss of more than $4 billion.

Mr. FLOOD. Would you have any figures to indicate days lost, and costs, that result from the so-called common cold?

Dr. DAVIS. Yes.

Mr. FLOOD. For the record, please. We don't need them now.

Dr. DAVIS. Yes.

(The information follows:)

COMMON COLD

There were 167,257,000 workdays lost in 1968 because of infectious, parasitic, and respiratory diseases among the currently employed labor force.[1] Twenty percent of the total—or 32,730,000 workdays [2]—were lost because of the common cold alone. This represents an estimated loss of $851,188,000.[3]

RESEARCH TO DEVELOP A PNEUMONIA VACCINE

Dr. DAVIS. Three years ago, the institute began a program to produce a safe bacterial vaccine capable of preventing most pneumococcal pneumonia cases in the general population. It has been estimated that approximately 300,000 persons are hospitalized for pneumococcal pneumonia in the United States each year and 25,000 to 40,000 die.

Mr. FLOOD. Why do so many people who enter a hospital catch pneumonia while in the hospital?

Dr. DAVIS. There are two reasons. Probably the most important one is that they acquire some kind of an infection when they are in the hospital, often an organism which is resistant to drugs.

The other is, that they are immobilized while they are in the hospital for some illness, an operation for example.

Mr. FLOOD. Their resistance is down, and so on?

Dr. DAVIS. Right. They acquire the infection just by being in the hospital, primarily because they are immobilized and lie on their backs.

A successful pneumococcal vaccine would prolong the lives of thousands of persons in the older age groups, those suffering from debilitating illnesses, such as asthma and heart disease and those in certain high risk groups, such as American Indians.

---

[1] From Vital and Health Statistics Data, National Health Survey, Series 10, No. 60, Current Estimates from the Health Interview Survey, United States, 1968 (National Center for Health Statistics, Health Services and Mental Health Administration, PHS, DHEW).

[2] Unpublished data provided by National Center for Health Statistics.

[3] Work loss cost based on average income of full-time workers, all industries, 1968, $6,454 annually, or approximately $26 per day for 256 working days. Department of Commerce, National Income Division, Personal Income Section.

Mr. FLOOD. What do you mean high risk group?

Dr. DAVIS. There are certain groups in the population which seem to have higher attack rates of pneumonia than others.

Mr. FLOOD. You are speaking of pneumonia?

Dr. DAVIS. Yes.

Mr. FLOOD. I see.

Dr. DAVIS. It would also save $50 to $100 million in hospitalization costs.

Surveillance studies are determining which of the many types of pneumococcus organism are most prevalent. Experimental lots of vaccine are being produced, and preliminary clinical trials of these vaccines are under way in selected adult groups to determine potency.

Mr. FLOOD. Then there is no one thing which is pneumonia? There are many pneumonias, just as they are many cancers?

Dr. DAVIS. That is right. They are caused by many different organisms. Many different types of the pneumonococcus. In fact, there are about 14 types that are the most common causes of pneumonias. It's important to differentiate those types.

Mr. FLOOD. When the average person says cancer, that is that. When they say pneumonia, that is that. They have no idea of the many varieties of each condition.

Dr. DAVIS. You are correct.

As data from these trials accumulate, a single combined vaccine will be formulated to protect against the dozen or so predominant types of the pneumococcus bacteria. Although there have been unexpected technical production problems, we would hope that mass vaccination trials could begin within the next 2 years.

CENTERS EVALUATING VACCINES AGAINST DISEASE IN CHILDREN

Institute-supported vaccine evaluation centers are concerned with other experimental vaccines against a deadly bacterial disease affecting children—meningitis due either to the meningococcus organism or *Hemophilus influenzae*. Scientists at the Walter Reed Army Institute of research have been successful in developing effective vaccines against two types of meningococcus in military personnel and are working on the third type.

Mr. FLOOD. Why is meningitis so widespread among military personnel vis-a-vis the same age brackets among civilians?

Dr. DAVIS. It's probably because these young men are brought together. Many of them are actually carriers of the organism, and they spread it to others. It is just by the more intimate closer contact in the barracks and in training activities that makes this disease spread as it does.

Reports from our evaluation centers may soon justify the institute's undertaking a civilian program to tailor the Army vaccines for use in children. An institute grantee, with support from community funds, is conducting small-scale studies of an experimental vaccine against meningitis in young infants due to *Hemophilus influenzae*. Here again, if early trials are successful, our institute could assist in developing a licensed vaccine.

NEW ANTIBIOTIC FOR TREATING URINARY INFECTIONS

I would like to call your attention to an experimental drug—actually a derivative of penicillin—called carbenicillin. Institute grantees and other investigators appear to have established carbenicillin's therapeutic value in selected instances of bacterial infections of the urinary tract, meningitis, and burn infections due to pseudomonas, proteus and enterobacter.

Mr. FLOOD. Urinary tract infection would be, of course, male and female?

Dr. DAVIS. That is right. These infections are difficult to treat and are increasingly common in hospitalized patients; therefore the medical community welcomes this new antibiotic.

Mr. FLOOD. Why on hospitalized patients?

Dr. DAVIS. For essentially the same reason we mentioned before, that patients who come into the hospital are likely to develop urinary stasis. This results in infections.

SUCCESSFUL RESULTS FOR TWO RESPIRATORY VACCINES

Three years ago, I reported the success of a vaccine for an acute respiratory disease caused by adenovirus type 4. This disease was particularly prevalent in military recruit training camps, and epidemics resulted in hospitalization that ranked next to accidents as a cause of lost manpower. The vaccine against that virus, developed by institute investigators working with Army scientists and a private pharmaceutical firm, has now been administered to more than 750,000 military recruits with great success. More recently, another collaborative effort with the Army found a preventive measure against another adenovirus—type 7. This new vaccine has now been administred to more than 30,000 recruits who simultaneously received adenovirus type 4 vaccine. Both vaccines appear to be 95 percent effective against natural adenovirus disease.

In addition to the traditional methods of vaccine preparation, a promising new aspect of vaccine research is gaining momentum. This is the development of variant strains that grow only at temperatures slightly below body temperature. These strains are called temperature-sensitive mutants. Scientists at our institute have developed such strains of the respiratory syncytial virus, the cause of 5,000 infant deaths a year. They are now trying to isolate and produce temperature-sensitive mutants of other respiratory organisms such as the parainfluenza viruses, the cause of croup, for use in immunizing preparations. Scientists reason that since the nose has a cooler temperature than the less-exposed respiratory tract areas, a temperature-sensitive mutant incorporated into a vaccine and administered directly into the nose might increase immunity in the nasal area and prevent disease. Such a strain presumably would not invade the lungs which maintain a higher temperature, less favorable to this variant. Temperature-sensitive mutants immunize experimental animals and are being evaluated as a vaccine in adult volunteers.

COMMON COLD VIRUSES AND VACCINES

The common cold is caused by many different viruses. The rhinoviruses—a group of 89 different types—are most frequently the culprits. These agents are usually isolated from cold sufferers during the September-October "cold season" but appear to cause few of the colds which occur during winter months. In their search for other viruses associated with winter colds, scientists found several different from rhinoviruses. These have now been shown to belong to a new group, called coronaviruses because they are shaped like crowns. Fifteen of the 23 coronaviruses identified so far have been isolated by institute scientists in Bethesda. It is now believed that these recently discovered coronaviruses may be an important cause of adult colds occurring from December through February.

Although scientists have not yet solved the problem of the multiplicity of cold-causing viruses, they have learned that the route of immunization plays an important role in determining whether a vaccine will be effective. By administering an experimental vaccine in the form of nosedrops or as a nasal spray, investigators found that a significant number of vaccinated individuals resisted infection. The same vaccine offered little protection when given intramuscularly.

Mr. FLOOD. And you do have vaccines which attempt to attack and prevent the common cold?

Dr. DAVIS. There are experimental vaccines. The problem is that there are so many different kinds of viruses. I mentioned 89. There may be even more.

Mr. FLOOD. Just as was found with cancer, there are some hundred different kinds of cancers. When you talk about the common cold, you might be talking about a hundred things.

Dr. DAVIS. That is right. The difficult problem is to have one that will cover all of these. We are a long way from that.

INTERFERON

Although some virus diseases can be prevented through the use of vaccines, others—including the common cold—do not lend themselves to this form of control. As a result, scientific interest has turned to interferon—a natural antiviral substance produced in the body's cells in response either to virus invasion or chemical inducers.

Mr. FLOOD. We have only become recently acquainted with that, within the last few years.

Dr. DAVIS. Yes. This has received a great deal of attention in the last 3 or 4 years.

The Institute has established a collaborative program on interferon and its inducers, as part of a larger targeted research effort on antiviral substances.

HEPATITIS-ASSOCIATED ANTIGENS

Last year I reported on significant findings in the long search for the cause of hepatitis. A protein, known as Australia antigen or "the hepatitis-associated antigen", has been discovered in the blood of patients with serum hepatitis. Since then, our Institute has been preparing and distributing highly purified Australia antigen reagents for laboratory study.

Using these reagents, scientists soon began to gather increasing evidence that the Australia antigen—originally thought to be of only one type—actually appears to have several subtypes. Hepatitis investigators believe this explains to a degree why certain screening tests now performed on the blood of hepatitis patients do not always react to available reagents. Challenged by these new findings, a group of leading hepatitis experts who met with our staff earlier this year were in general agreement that an intensive program is warranted to study these subtypes, particularly in view of the national need for sensitive reagents to screen blood for transfusions.

SUMMARY OF THE BUDGET

In conclusion, Mr. Chairman, the 1972 request for the National Institute of Allergy and Infectious Diseases is $99,342,000. This is a net increase of $1,218,000 over the 1971 operating level of $98,124,000.

Mr. FLOOD. Doctor, yours is another one of the Institutes which has nothing but minuses as far as program changes are concerned. On top of that, you got hit pretty hard by this so-called equitable distribution of the management fund.

That is costing you $670,000. How was it calculated that you owe $670,000 more? Do you know how that was done? How did they calculate that?

Dr. DAVIS. Owed to the management fund?

Mr. FLOOD. Yes. How was it done? Let me ask the second question. When you tell me how it was done, then tell me do you agree that this additional $670,000 charge was accurately calculated. First, how was it calculated. Then, what do you think about the accuracy of the calculation.

Dr. DAVIS. My understanding is that these are funds which were taken out of the Institute appropriations for the central services, including the Clinical Center of the NIH. This was determined to be our share in recognition of the increased costs of management and increased costs of taking care of patients at the Clinical Center.

Mr. FLOOD. Do you people think this was accurately calculated?

Dr. DAVIS. I suspect so. I don't disagree that this is fair.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH

Mr. FLOOD. Take a look at page 18. There you say that the program of the International Centers for Medical Research and Training was broadened in 1971 to offer scientific opportunities for investigators from all United States medical schools and schools of public health.

To what extent are these investigators taking advantage of these new opportunities that you are talking about?

Dr. DAVIS. Originally the awards were made to four universities, which sent only members of their own staff to foreign locations. We realized that this limited the opportunity of research investigators working in other universities throughout the country. So we broadened the program by retaining some of the funds needed, rather than disbursing it all in grants. We advertised among universities for young men who wanted to have overseas research opportunities. We have had some eight or ten applicants. I believe we will send some seven of these men to one or more of the four centers.

Mr. FLOOD. Seven? Is that big or small, good or bad?

Dr. DAVIS. I think it's about the right number for the number of people who are interested and the opportunities which the centers offer.

Mr. FLOOD. You say you are broadening your program. How much additional funds are involved?

Dr. DAVIS. This is just the same amount as the year before.

Mr. FLOOD. Oh?

Dr. DAVIS. This is a rearrangement, a readjustment within the program.

Mr. FLOOD. It's costing a little more than $2 million a year.

Dr. DAVIS. Right.

Mr. FLOOD. What information can you give us to show that we are getting our $2 million worth?

Dr. DAVIS. I think we are. The primary purpose, the purpose is to provide an opportunity for American scientists to have experience with exotic diseases, with foreign diseases. This was the purpose under the International Health Act of 1960.

We are doing that. We are sending some, I would say the exact number is probably about 25 or 30 people, overseas all the time.

SCHOOLS INVOLVED IN THE INTERNATIONAL CENTERS

Mr. FLOOD. Place in the record the names of these four American universities and where they are located that are involved in this program, along with the names of the cooperating foreign universities and where they are located. Then for the record give us a brief statement on what each one of these partnerships are specializing in.

Dr. DAVIS. We can do that very easily.

(The information referred to follows:)

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING (ICMRT) PROGRAM

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

NATIONAL INSTITUTES OF HEALTH

The ICMRT program is a research grant supported activity which operates under the authority of Public Law 86-610: Four centers currently receive NIAID funds:

U.S. sponsoring institution:

1. The University of California, San Francisco Medical Center.

Participating foreign institutions:

Kuala Lumpur, Malaysia.—The Institute for Medical Research, and the University of Malaya Faculty of Medicine.

The scientific program of this ICMRT focuses upon human arbovirus diseases, especially the dengue hemorrhagic fever group; parasitic diseases with an emphasis upon the biologic control of schistosomiasis; blood genetics; and sociocultural research and medical anthropology.

U.S. sponsoring institution:

2. The Schools of Hygiene & Public Health and of Medicine, Johns Hopkins University, Baltimore, Md.

Participating foreign institutions:

Calcutta, India.—The Calcutta School of Tropical Medicine, the All India Institute of Hygiene and Public Health; the Postgraduate Institute for Medical Education and Research and the Indian Statistical Institute.

The Johns Hopkins ICMRT supports respiratory and arbovirus studies; intensive biochemical, pathophysiological, and clinical investigations of human

cholera; parasitological research with an emphasis upon hookworm disease; and several animal ecology projects.

U.S. sponsoring institution:

3. The University of Maryland School of Medicine, Baltimore, Md.

Participating foreign institutions:

Lahore, West Pakiston: The Institute of Hygiene and the Pakistan Medical Research Council.

The University of Maryland's ICMRT, designated the Pakistan Medical Research Center (PMRC), conducts important genetic studies of the mosquito vector of Japanese Encephalitis Virus; has a mycobacterial research project encompassing both tuberculosis and leprosy; supports a long-term study of hepatitis and cirrhosis of the liver; and participates in several clinical projects concerned primarily with bleeding disorders.

U.S. sponsoring institution:

4. School of Public Health and Tropical Medicine, Tulane University, New Orleans, La.

Participating foreign institutions:

Cali, Colombia: Universidad del Valle.

The Tulane University ICMRT conducts individual research projects of varying size within the following six categories: nutrition and metabolism, parasitic diseases and their vectors, infectious diseases and epidemology, experimental pathology, social and behavioral sciences, and environmental health. A new health services research project will soon be initiated.

INFLUENZA EPIDEMIC RECURRENCE

Mr. FLOOD. On page 29 with regard to influenza, you refer to "the expected epidemic outbreak in the late 1970's".

How accurately can these outbreaks be predicted? There are certain things you can predict in cycle. What about this? How accurately can you predict the outbreak?

Dr. DAVIS. We will know at that time. The reason for our prediction and the reason for our action is that history shows that about every 10 years there has been an influenza epidemic in this country and in the world. I refer you to the Hong Kong influenza epidemic of 1968.

Mr. FLOOD. And of course there are different kinds of influenza.

Dr. DAVIS. There are two main kinds of influenza. The one I am talking about is one kind—epidemic influenza—In 1957 we had the Asian flu. In 1947 there also were epidemics, though not as severe as later epidemics, but it was a distinctly different epidemic. Then we had one in 1933 and 1934.

Mr. FLOOD. What year was the Spanish flu epidemic?

Dr. DAVIS. It was in 1918.

The trouble with our studying influenza in the past——

Mr. FLOOD. It was quite a killer.

Dr. DAVIS. The epidemic of 1918 was one of the greatest medical disasters we have ever had. 20 million people died in the world and 500,000 in the U.S. at a particularly critical time.

It was different from the subsequent epidemics, in that the fatality rates were very high, particularly in young adults.

NAMING INFLUENZA EPIDEMICS

Mrs. REID. Would you yield at that point, Mr. Chairman?

Mr. FLOOD. Yes.

Mrs. Reid. These different types of influenza—you mentioned Spanish flu and Asian flu—are there different symptoms for each? Why are they called by different names?

Dr. Davis. They are all the same symptoms and essentially the same disease. They are called by different names because when an epidemic first appears there is an impression that it comes from some particular place. Actually, this is a misnomer. That is the place where it was first identified. For instance, in the case of Spanish influenza, when we look back at the record, the first cases that had been identified were in Bukhara in southern Russia. But the name Spanish influenza was attached to it when it came to this country.

The Asian flu of 1957 was first identified in Asia. This is true of the Hong Kong influenza of 1968 also.

Both of these probably had their origin in southern China. But we have such poor communication and medical intelligence from China that we don't have any real record of that. Although in 1957, later records did show that there were epidemics in southern China which might have been the original source.

DEVELOPMENT OF EFFECTIVE INFLUENZA VACCINES

Mr. Flood. Do you have anything new to tell us about the development of vaccines for influenza?

Dr. Davis. The present influenza vaccines seem to be quite effective in military populations. The problem is that the vaccines have to be given every year. We found that these are really not good vaccines for the civilian population because it's very difficult to vaccinate every year. The experience has been that it hasn't made very much difference in civilian populations anyway.

The problem also is that by the time the new epidemic arrives and you isolate the virus and make vaccines, so much time is taken up that the epidemic is over. This happened both in the Hong Kong influenza in 1968 and the Asian influenza of 1957.

What we are concerned about is starting now to prepare for an epidemic in the late 1970's with the hopes that we can get some better way of handling this, a better vaccine, or else some other method of handling the disease, may be better treatment.

Studies on influenza in the last few years have shown that the virus is made up of a number of different kinds of antigens, that is the proteins in its coat. It's our hope that by studying those antigens we might identify ones that are significant and recombine those in such a way that we will have a vaccine which can be useful.

This approach could also be used by recombining a strain of virus which we know grows well in eggs and a new strain that suddenly appears. This should shorten the time of making the vaccine.

DEVELOPMENT OF COMMON COLD VACCINES

Mr. Flood. That makes me ask you the next question, which would be with reference to the common cold. Are we getting any closer to a vaccine or better kind of treatment?

Dr. Davis. The most progress we have made with the common cold is the identification of the viruses which cause it. Vaccines at the moment don't hold much hope because there are so many different

strains and we haven't found a common antigen, that is, a common vaccine that will affect all of them. If we could do that, then we might have a good vaccine. And studies on inferferon, either treating or preventing a cold, are still in the developmental stage.

WORK ON TUBERCULOSIS VACCINE

Mr. FLOOD. What about other kinds of vaccines, tuberculosis, hepatitis, venereal disease, and so on?

Dr. DAVIS. Tuberculosis vaccine is one which we have studied for many years, particularly at the Rocky Mountain Laboratory in Montana, where we have been working on a vaccine made from the cell wall. It's a purified vaccine, as distinct from the commonly used BCG, that is the Bacillus Calmette-Guerin, which is an attenuated live vaccine.

The studies at the Rocky Mountain Laboratory on the cell wall vaccine are proceeding slowly. We do have an immunizing agent which is quite effective in small animals and it's being tested in monkeys at the present time. It shows considerable promise. But it has been a long and difficult task.

HEPATITIS VACCINE DEVELOPMENT

Mr. FLOOD. What about hepatitis?

Dr. DAVIS. The hepatitis story, of course, is very interesting, with the discovery of the Australia antigen. Dr. Saul Krugman of New York University has made an immunizing agent from human blood which has the Australia antigen in very high titer. He reported before a scientific gathering at New York University and also before the American Epidemiological Society the results of his work.

Mr. FLOOD. It could be a very dramatic thing, couldn't it?

Dr. DAVIS. This would be a very dramatic thing. It points the way and gives us hope that we can move ahead now quite rapidly, because we have shown that the Australia antigen will produce immunity. Dr. Krugman's experiments actually protect individuals who were later exposed to the disease.

TREATMENT AND VACCINATION FOR V.D.

Mr. FLOOD. What about venereal disease?

Dr. DAVIS. Of the two kinds of venereal disease, gonorrhea is the most common. There are over 500,000 cases of gonorrhea reported every year in this country.

Mr. FLOOD. It is becoming epidemic.

Dr. DAVIS. It is. There is no question about that.

As you know, the control of the disease has been by direct treatment which until a few years ago seemed to be going along very well. Some of us are beginning to wonder now whether or not there might be a place for a vaccine particularly in individuals who already have had one attack. Patients can have several attacks.

We need to know much more about the bacteria itself. We really know very little about the bacteria of gonorrhea, the gonococcus. We don't know much about the biochemistry of it, about the biology. Actually we are beginning to divert some funds to this to try to develop a program which will interest research workers in the organisms, in its

biochemistry, its structure, and what antigens are present. Perhaps this will give us a lead.

Mr. FLOOD. And the treatment is not 100 percent effective, as many people think.

Dr. DAVIS. That is right. Even though the treatment could be adequate if managed right, in actual practice frequently it is not.

Mr. FLOOD. What about syphilis?

Dr. DAVIS. Syphilis, of course, is still an important disease but there are not nearly as many cases and probably the incidence isn't rising so fast. I think we have actually about $300,000 worth of grants in syphilis and gonococcal infections.

There is work leading toward a vaccine. This is directed toward uncovering and identifying the different antigens present in the organism.

Mr. FLOOD. As of the last 2 years, syphilis by no means is as near an epidemic as gonorrhea is?

Dr. DAVIS. No.

DRUG RESISTANCE, INTERFERON AND TRANSPLANT IMMUNOLOGY

Mr. FLOOD. Will you for the record devote some attention to drug resistance in infectious organisms, and more on interferon than was on your original statement. Also, develop at reasonable length developments in the area of transplantation immunology. There is great interest in that.

Dr. DAVIS. Yes, sir.

(The information follows:)

DRUG RESISTANCE

Once considered conquered by sulfa drugs and antibiotics, some bacterial diseases have reasserted their serious threat to health. The large number of organisms which have become resistant to antibiotics has seriously limited the effectiveness of many of these drugs.

Fortunately, an arsenal of efficacious synthetic drugs continues to expand. These are being used more judiciously than in the early days in order to minimize the occurrence of resistant strains. Special effort is being exerted to protect individuals with lowered resistance from becoming victims of hospital-acquired infections. Development of protective vaccines is being pursued and use of specific antisera as a treatment is being explored.

The appearance of drug resistance in a previously susceptible strain was originally thought to be due to a spontaneous gene mutation. It is not known that the resistance trait may also be acquired by two other mechanisms: *transformation* and *transduction*. *Transformation* is the process by which a bacterial cell incorporates from its environment one or more genes formed by another cell. In *transduction*, genes formed by another cell are also incorporated but they are introduced into a recipient cell by a bacterial virus. In some organisms these "foreign" genes are eventually lost spontaneously and the strain reverts to its drug sensitive state. To date, no clinically practical suggestion for accelerating this loss of resistance phenomenon has been made.

INTERFERON

Interferon, a protein produced by body cells in response to a virus attack, was once thought of, exclusively as an antiviral weapon. However, results of recent research have indicated that interferon—in animals—is also effective against certain protozoal parasitic infections, such as malaria, and against many tumors.

Scientific interest in interferon is still focused most sharply on its ability to assist in an animal's recovery from viral infections. Control of the wide spectrum

of human illnesses caused by viruses is a special concern of the National Institute of Allergy and Infectious Diseases.

A major barrier to clinical use of interferon has been the general inability of most interferons produced by one species to be effective in another. This has limited the possibility of producing in laboratory animals interferon which could be extracted and used in treating humans. Unfortunately, human and monkey cells grown in laboratory cultures for the purpose of producing interferon useful in treating human diseases have only a moderate output and require a great deal of care.

Because of these problems, scientists are turning their efforts to the study of substances other than viruses that stimulate an individual's body to make extra amounts of its own interferon. Most encouraging is research that has been carried out using RNA's (ribonucleic acids)—fundamental chemicals present in all living cells.

Attention of many investigators has been focused on a synthetic RNA—poly I. poly C—which has been shown in animals, and, to a limited extent, in man, to have the ability to induce interferon and cure some viral infections.

In an effort to coordinate and complement interferon research being conducted and supported by the National Institutes of Health, NIAID has launched a collaborative program of specific studies of interferon and interferon inducers. These investigations are part of the Institute's targeted research effort on antiviral drugs. The new program is concerned with problems of standardization of interferon and interferon inducers and with the development and supply of research materials known as reference reagents. Use of these substances by NIH investigators and others enable scientists to make more valid comparisons of results of their studies.

TRANSPLANTATION IMMUNOLOGY

INTRODUCTION

In 1964, when kidney grafts were medical rarities and the first heart transplant still a dream, the National Institute of Allergy and Infectious Diseases (NIAID) embarked on a program of contracted research and development in the field of transplantation immunology. The plan for the new program—as outlined by a committee of consultants—included coordination of effort between various laboratories to reach a common goal, concentration of effort in tissue typing, and special emphasis in areas where more work was needed.

Today this program includes more than 25 contracts with a total value of approximately $1,800,000. Research and development studies are carried out in such areas as tissue typing reagents and immunosuppression, focusing on those problems which—at this time—best lend themselves to a planned attack.

Research results emanating from NIAD's transplantation immunology programs have played a major role in recent progress in organ transplantation. For example, during 1969, U.S. scientists—using research materials provided by NIAID—reported the transplantation of more than 1100 kidneys. Five years ago, only about 200 such operations were performed. Survival rates are up, too. In some medical centers, when kidneys are transplanted between siblings, the expectation of survival of the organ at the end of one year is now over 90%. When the donor is unrelated, the rate is more than 50%.

Other U.S. transplants in 1969 included 13 livers, 24 hearts, 5 bone marrow, 1 lung, and 4 pancreas.

OBLIGATIONS FOR PROGRAMS IN ORGAN TRANSPLANTATION [1]

NIAID.—1968; $6,096,000. 1969; $8,306,000. 1970; $8,445,000. 1971 (est.); $7,712,000. 1972 (est.); $7,957,000.

THE PROBLEM OF REJECTION

Surgically, it has been possible for years to remove an organ from one body and implant it in another. In animals it was shown that the transplanted organ might even function for a while—the kidney would secrete urine, the heart would pump blood—but sooner or later, unless donor and recipient were identical

[1] Includes research grants, laboratory and clinical research, and collaborative research; excludes training grants and fellowships.

twins, a biological phenomenon known as "immune response" would take over and the new kidney or heart would be rejected.

The immune response is made up of all those reactions of cells and tissues which, ordinarily, protect the body against disease-causing organisms, such as viruses and bacteria. These reactions can be enhanced through immunization against infectious agents—the familiar vaccines against measles, diphtheria, and polio, for example. In transplantation of organs, it is necessary to do just the opposite. The immune response must be suppressed, at least partially, if a body is to accept an organ that ordinarily it would recognize as "foreign" and, therefore, injurious.

Transplantation immunologists have devised a number of immunosuppressive "tricks" to achieve graft acceptance; but these manipulations (described later in this report) have not yet been perfected. The first concern, still, of most transplantation experts is selection of an organ for a prospective recipient that will be so closely "matched" to his tissues that his immune response will be minimized.

TISSUE MATCHING

A number of years ago scientists discovered that certain substances, or antigens, on the surface of red blood cells identified persons as belonging to one of 4 major blood types. Now investigators have learned that other antigens are present on other body cells (including white cells known as lymphocytes) and that individuals can be typed for these histocompatibility (tissue-compatibility) antigens in much the same way they are typed for their blood group. Usually, if these antigens of the donor and recipent are not closely matched, transplanted tissue will be rejected.

Histocompatibility antigens are inherited from one's parents and—on the basis of present knowledge—it is believed that possible combinations number in the thousands. Genetic studies have shown, however, that in the offspring of any two parents no more than 4 combinations of antigens will be found. Thus, though the chance of tissue matching is low between two unrelated individuals, it is better than 25% between brothers and sisters.

Laboratory methods have been developed which enable scientists to recognize histocompatibility antigens and thus select donor-recipient matches that will best enable a transplant to survive. The NIAID collaborative program, administered by the Transplantation and Immunology Branch, has played a crucial role in the development and increase use of techniques in which cells from the donor and recipient are tested against serum samples of known antigenic make-up. These sera (called typing reagents) must be carefully obtained and characterized. Scientists from around the world contribute to and receive sera from NIAID's serum bank at Flow Laboratories, Rockville, Md. During the first 6 months of 1970, 12,700 cc of reagents were shipped to 148 scientists—a one-third increase over the comparable period in 1969.

Eight current contracts of the Institute's collaborative program provide scientists with financial support for evaluation of various aspects of histocompatibility matching. Many of these laboratories are engaged in studies which compare the utility of different techniques. In addition, two of the laboratories are conducting studies comparing the results of kidney cell typing vs. blood lymphocyte typing. A few studies have shown that, in some cases, where good white blood cells are not available, kidney cell typing may provide valuable information.

Eight contracts provide facilities for a program to screen potential serum donors, to characterize antibodies (substances formed in the body in response to antigens), and to collect and ship to the Institute's serum bank quantities of material needed for its typing reagents program.

Two contractors are involved in the organization and coordination of a number of satellite transplantation facilities. These are area typing centers which maintain registries of waiting organ recipients and, by means of computers, attempt to select from cadaver organs, as they become available,the best "matches". These organs are then forwarded to the appropriate surgical center for transplantation.

An interesting adjunct of the European tissue typing contract has been the typing of a large number of chimpanzees, using both human and chimpanzee reagents. Recently, NIAID made it possible for contract personnel to type U.S. chimp colonies at Holloman Air Force Base, New Mexico, Bionetic Laboratories, Kensington, Md., and the U.S. Naval Hospital, Bethesda. The information collected in these typings on over 350 chimps is being analyzed. Preliminary results suggest strongly that certain antigen groups are shared with the human system. There is general agreement, today, that tissue typing for transplantation of

organs between siblings is extremely worthwhile. Many immunologists believe that typing for cadaver donors is beginning to be useful, although this has not definitely been established.

As part of its program, NIAID's Transplantation and Immunology Branch prepares an annual updating of a tissue typing catalog, which lists serum in NIAID's serum bank and provides information concerning the specificity and utility of individual reagents. A manual of tissue typing techniques is also published each year and is widely used in tissue typing training sessions and workshops, some of which are supported by NIAID.

This year's 600-page catalog reflects a significant increase in the quantity and quality of sera available for typing although good monospecific serum, which types for only one antigen, is still in short supply. Improvements in service to investigators are also evident. For example, attempts are being made to develop methodology for freeze-drying (lyophilization) of typing sera. At present it must be stored at —70° C and shipped in dry ice—an expensive and sometimes uncertain procedure. Freeze-drying methods developed for handling bacteria and viruses are, unfortunately, not applicable to histocompatibility sera, so scientists supported by NIAID are investigating the best rates and temperatures for lyophilization and are evaluating the shelf life of the product. Information, to date, indicates that a procedure has been developed which results in a product of sufficient stability to enable it to be exposed to 38° C temperatures for one month without losing its effectiveness. The ultimate aim, of course, is to develop a method which will make it possible to ship, via air mail, to any place in the world, sera which can withstand, en route, brief exposures to varying temperatures.

In addition to studies of bulk serum lyophilization, investigations are under way to permit similar preparation of very small quantities of sera in trays. This would make it possible to ship via air mail without refrigeration preloaded freeze-dried typing trays containing quality sera. Use of NIH trays of carefully characterized frozen sera in micro quantities is already making it possible for a number of laboratories to carry out uniform typing and, thus, to exchange tissues between cities.

Since tissue typing is, at best, a tedious process, one NIAID contractor has been at work developing automated methods. A prototype machine has now been built which will be put to work in a laboratory and its performance compared with results obtained by technicians using conventional equipment.

IMMUNOSUPPRESSION

Even when donor and recipient tissues have been matched as closely as possible, steps to suppress the body's immune response must usually be taken also. These may include use of radiation, certain drugs, and biologic preparations known as antilymphocyte sera (ALS).

Five contracts for studying drugs and antilymphocyte sera are currently funded by NIAID. Some of the drugs are among those used to treat cancer and must be handled with care as they produce unpleasant and potentially serious side effects. However, one such drug, Syclophosphamide, has been found especially effective in preventing graft rejection in bone marrow transplants in both animals and humans.

Antilymphocyte sera and purified fractions of these preparations, known as antilymphocyte globulin (ALG), are of great interest, currently, as means of preventing and reversing rejection. ALS is prepared by first injecting human lymphoid cells in an animal (horse or rabbit, for example). The animal makes antibodies to these cells, which seem to be the ones most involved in the rejection process. Serum containing antibodies is then withdrawn from the animal and used to treat patients.

One of the major difficulties encountered in the use of ALS is determining the potency of various serum products produced by different transplantation centers for use in their own patients. The Transplantation and Immunology Branch has now established a facility for testing ALS and ALG. At present, potency of preparations is measured by their ability to prolong skin grafts in monkeys. Using this test, scientists at the NIAID facility have screened more than 140 preparations, many of which are currently being used in treating patients. As a result of these studies, it has been possible to demonstrate that cells taken from the thoracic duct or the thymus are the most effective producers of ALS.

Other studies have demonstrated the superiority of one preparation—rabbit antihuman thymus ALS—in the prolongation of Rhesus and chimpanzee skin

grafts. A program is now underway to produce sufficient quantities of this material to support clinical trials.

The high cost of using primates for testing ALS has prompted a search for effective *in vitro* (test tube) techniques. Using coded samples of ALS provided by the Transplantation and Immunology Branch, scientists are comparing a number of laboratory tests to see if they correlate with monkey skin graft survivals. If these preliminary studies indicate the efficacy of *in vitro* techniques, such procedures will be utilized as a primary screening method to determine which products warrant testing in sub-human primates.

The long-range goal of scientists studying ALS and ALG is to develop an effective product, to demonstrate its efficacy, and to provide data concerning production and purification methods and treatment regimens. With this knowledge, commercial laboratories could more easily make available effective ALS for use by the transplant surgeon.

TOLERANCE

All methods of suppressing the immune response, as described above, pose a risk for the patient. As his body is "tricked" into accepting a graft, it loses, as well, its ability to recognize potentially harmful infectious agents. For this reason, scientists have been anxious to develop some means of inducing the body to accept a transplanted organ, even in the presence of an otherwise intact defense system. Such a selective immunological phenomenon is known as "tolerance". It can be achieved in animals in regard to certain antigens, under special circumstances.

Transplantation immunologists hope that, eventually, the histocompatibility antigens can be separated from tissues and obtained in such pure form that they can be used to induce specific tolerance to a donated organ in a prospective recipient. In October 1970, NIAID sponsored a meeting of experts to consider the state of the art in obtaining soluble transplantation antigens needed for immunological research. There was general agreement that, though induction of tolerance represents a valid and hopeful goal, much more laboratory and animal work must be done before clinical use of soluble antigens to achieve this goal can even be predicted. Three NIAID contracts are presently supporting the processing of lymphoid tissue to obtain soluble antigenic fractions. However, current techniques for cell fragmentation, together with the low yield of the purification processes has, to date, made it impossible to collect sufficient soluble antigen fragments for intensive study.

DIAGNOSING REJECTION

To determine the efficacy of histocompatibility matching, it is, of course, essential that scientists evaluate clinical data accurately. Recent reports of rejection in well-matched kidney patients may well be due to confusion between true rejection and the occurrence of pathological changes caused by old or new disease. Since the number of kidney rejections seen in individual hospitals is low, NIAID has established a contract facility for the study of "rejected" tissues. In addition to identifying true cases of rejection, careful evaluation of clinical data may also lead to determination of which of the presently recognized histocompatibility antigens are most important. Techniques for evaluation are difficult and standardized reagents are necessary, but with clinical trials of ALS in the offing, such a service will be badly needed.

OTHER INVESTIGATIONS

NIAID'S collaborative program in transplantation immunology is an outgrowth of the results of research carried out by scientists working in NIH laboratories and grantee institutions. This work continues and is constantly providing new leads for the coordinated research which is the hallmark of the collaborative program. Today, transplanted organs are making possible normal lives for many individuals once doomed to invalidism and early death. Tomorrow, when problems sketched in this report are solved, "construction surgery" may be applied to others.

THE IMPORTANCE OF VD CONTROL

Mr. FLOOD. Mr. Michel?

Mr. MICHEL. Thank you, Mr. Chairman.

I am glad to hear your comments, Doctor, on the last line of questioning of the chairman with respect to venereal disease and your shop getting into the act to do something. Before in the hearings, we

have made the point we were particularly concerned; and a couple of years ago we put a half million dollars in the bill over the budget to do something more about it.

I don't recall in the last 10 or 12 years bringing up the subject during NIH hearings to the degree to which you testified. I think we ought to start building a record here and next year come back asking you some questions about what progress we have made in the past year. If we don't start making progress very soon in view of the growth of the problem, we may well be in more serious trouble than anyone realizes is in the offing.

NATURE AND INCIDENCE OF MONONUCLEOSIS

Turning to another subject, isn't mononucleosis infectious?

Dr. DAVIS. Yes.

Mr. MICHEL. From what I have heard, it seems that within the last year there has been an increase in the number of instances of that disease among some of the younger people. Is that nationwide?

Dr. DAVIS. Yes, that is right. You are quite right it occurs in young adults. Its cause hasn't been fully established at the present time. A virus known as the EB virus has been associated with this disease but the evidence I think is not all in that this really is the cause of this disease.

People who have this disease usually show antibodies against this virus. There is evidence it may be the cause, or it may be a similar virus.

It is an infectious disease which is apparently transmitted by personal contact. It is jokingly called the kissing disease. It is a disease which has no serious consequences. The youngsters are sick for 2 or 3 weeks, pretty sick, and then have a long convalescence.

But as far as we know there is no permanent damage. During the disease they may have mild hepatitis, tenderness over the liver and sore throat, and sometimes a rash. It has varied symptoms.

Mr. MICHEL. Do you have any statistics that would show in the past year, for example, how many were afflicted with mononucleosis?

Dr. DAVIS. The record for 1969 shows there were 10,059 reported, and there were 14 deaths ascribed to it.

STATISTICS ON MAJOR INFECTIOUS DISEASES

Mr. MICHEL. You are obviously reading from some prepared list. Is that a list of the major infectious diseases in the country?

Dr. DAVIS. Yes.

Mr. MICHEL. How many are those?

Dr. DAVIS. How many different diseases?

Mr. MICHEL. Yes.

Dr. DAVIS. I suppose there are about 30 or 40.

Mr. MICHEL. If we haven't had that in the record, I think we should have it now. I assume those would be the most prevalent ones then?

Dr. DAVIS. Yes, except that these are the ones that are reported by physicians or by health departments. Influenza, for instance, is not reported here because it is so difficult to diagnose in many cases. So it is impractical. But the ones that can be identified clearly——

Mr. MICHEL. Why don't you put that in the record and also those that can't very practically be reported but are of real concern as you have said here such as influenza and the common cold.

(The information follows:)

National Institute of Allergy and Infectious Diseases

Statistics covering the annual number of deaths and reported illnesses caused by selected diseases dealt with in the National Institute of Allergy and Infectious Diseases are presented in Table I. Only those deaths and new cases reported by professional health personnel are included. Table II reports annual disability and estimated cost to the Nation of infectious and parasitic, and respiratory diseases.

Table I

Category	Morbidity 1969	Mortality 1968
I. Parasitic Infections		
Amebiasis	2,915	51
Malaria	3,102	7
Trichinosis	215	0
Schistosomiasis	205 (3) 1/	0
Ascariasis	418 (6)	7
Toxoplasmosis	63 (7)	0
II. Bacterial Diseases		
Brucellosis	235	1
Diphtheria	241	30
Leptospirosis	89	9
Meningococcal Infections	2,951	741
Pertussis (whooping cough)	3,285	36
Salmonellosis (excluding typhoid)	18,419	70
Tularemia	149	1
Tetanus	192	86
Tuberculosis	38,650	6,292
Typhoid Fever	364	7
Strep sore throat and scarlet fever	450,008	28
Rheumatic fever	3,229 (37)	363
Septicemia (Blood Infections)	Unreported 2/	2,991
Shigellosis	11,946	0
Venereal Disease (new cases)		
Syphilis	92,162	586
Gonorrhea	534,872	1
Other	1,778	6
III. Rickettsial Diseases		
Typhus (including Rocky Mountain Spotted Fever)	534	2
IV. Viral Diseases		
Chickenpox	97,329 (43)	99
Encephalitis (Acute)	1,613	744
Hepatitis	54,325	877
Influenza	Unreported	7,062
Measles (Rubeola)	25,826	24
Mumps	90,918	25
Mononucleosis	10,059 (33)	14
Poliomyelitis	20	130 3/
German Measles (Rubella)	57,686	24

1/ Figures in parenthesis indicate number of states reporting, if less than complete.

2/ Though widespread, some diseases must be listed as "unreported" because accurate diagnosis depends on laboratory tests generally not carried out. However, in the period July 1967-June 1968, an estimated 80.2 million conditions were reported as "influenza-like illnesses".

3/ Many of these deaths occurred at least 1 year after the disease was contracted.

Table I. (Continued)

Category	Morbidity 1969	Mortality 1968
V. Fungal Diseases		
Actinomycosis	13 (9)	16 3/
Coccidiodomycosis	903 (12)	58
Blastomycosis	30 (10)	111 3/
Histoplasmosis	158 (14)	58
VI. Multiple or Unspecified		
Acute Respiratory Infections	447,498 (18)	784
Bronchitis	Unreported	7,637
Pneumonia	Unreported	66,430
Gastroenteritis (in persons 4 weeks of age and over)	Unreported	2,219
VII. Allergic Disorders		
Asthma	Unreported	3,862 4/
All Others	Unreported	51
TOTALS	1,952,400	98,549

4/ Adjusted to reflect changes in International Classification of Diseases.

Morbidity statistics taken from Annual Supplement, Summary 1969, MORBIDITY and MORTALITY Weekly Report, Vol. 18, No. 54, Center for Disease Control, Atlanta, Georgia.

Mortality Statistics were furnished by the Mortality Statistics Branch, Division of Vital Statistics, National Center for Health Statistics, Rockville, Maryland.

Table II

Cost to the Nation's Populace - 1968

ITEM	Combined Total: Infectious, Parasitic & Respiratory Diseases		Infectious & Parasitic	Respiratory
	Number	Percent of all Acute Conditions		
Number of cases	280,067,000	70.1	41,592,000	238,475,000
Restricted activity (days)	1,032,716,000	60.9	164,025,000	868,691,000
School loss (days)	155,892,000	81.3	33,209,000	122,683,000
Work loss (days)	167,257,000	59.3	18,119,000	149,138,000
Work loss (cost)	$4,348,682,000	59.3	$471,094,000	$3,877,588,000

From VITAL AND HEALTH STATISTICS Data from the National Health Survey, Series 10, Number 56, Current Estimates from the Health Interview Survey -- United States -- 1968. National Center for Health Statistics, Health Services and Mental Health Administration, PHS, DHEW.

Work loss cost based on average income of full-time workers, all industries, 1968, $6,454 annually or approximately $26 per day for 256 working days. Department of Commerce, National Income Division, Personal Income Section.

INFLUENZA

~~Also~~, we have difficulty in obtaining morbidity figures for influenza, mycoplasma pneumonia, bronchitis, septicemia and gastroenteritis.

According to the Center for Disease Control, a review of the influenza experience in 1966-67 showed that at no time did national pneumonia-influenza mortality (reported by 122 cooperating cities) show an excursion above the epidemic threshold. In fact, it indicated a decrease in deaths attributed to pneumonia and influenza when compared with the 1965-66 season.

However, in 1968, an outbreak of A2 influenza occurred in Hong Kong and subsequent laboratory studies showed that the virus had undergone a major antigenic shift within the A2 classification. The result -- according to CDC Influenza-Respiratory Disease Surveillance for 1968-69 -- was a widespread epidemic in the United States with a single large and sharp wave of excess mortality. In 1970, some outbreaks of influenza B were reported -- primarily among school children -- with no evidence of excess mortality.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

RESPIRATORY VACCINES

Introduction

At a time when vaccines and "wonder drugs" are available for the prevention and cure of many infections, one is often led to assume that acute respiratory diseases have been conquered. Yet illnesses, such as "flu," colds, and pneumonia, remain important public health problems and continue to exact a tremendous physical and economic toll from our country.

Some respiratory illnesses, such as the "common cold," result in nothing more than transient discomfort; others, such as influenza, pneumonia, and RS (respiratory syncytial) disease of infants, can be killers. Over 70,000 people each year die from respiratory infections, accounting for more than half of all deaths caused by infectious diseases.

Through the management of a collaborative (contract) research program, support of a research grant program, and conduct of intramural research efforts in its laboratories at Bethesda, Maryland, the National Institute of Allergy and Infectious Diseases (NIAID) is responsible for the Government's main efforts to solve the problems of acute infectious respiratory disease in this country.

Table of Obligations - Respiratory Vaccines*

	1968	1969	1970	1971 (est.)	1972 (est.)
NIAID	2,719,000	3,308,000	3,512,000	3,611,000	3,611,000

Adenovirus Vaccines

At one time epidemics of acute respiratory disease, severe enough to require hospitalization, would sweep through military recruit training camps every year. These epidemics ranked next to accidents as a cause of lost manpower. Today, through a collaborative research effort involving the NIAID, pharmaceutical houses, and the military, vaccines are available to protect against adenovirus types 4 and 7 -- two of the major causes of acute respiratory disease in military recruit populations.

The live adenovirus vaccine success story began in 1965 with the results of the first field trials of an adenovirus type 4 vaccine, developed by NIAID and produced by Wyeth Laboratories. This vaccine, taken in capsule form, represented not only a successful means of preventing massive and expensive epidemics at boot camps, but also represented a new concept in immunization against respiratory disease.

A special coating on the capsule prevented the vaccine from being released until it reached the intestinal tract. The live vaccine, thus,

* Includes laboratory and clinical research, and collaborative research; excludes research grants, fellowships, training grants.

bypassed the normal site of adenovirus infection, the respiratory tract. Once in the intestinal tract the vaccine caused a symptom-free infection that was sufficient to stimulate the production of protective substances known as antibodies. This vaccine has now been successfully administered to over 750,000 military recruits.

With knowledge gained from the development of type 4 vaccine and with new epidemiologic data gathered at military camps, a new collaborative effort was begun to find a preventive measure for another common adenovirus culprit -- this time adenovirus type 7.

Now, an adenovirus 7 vaccine, also prepared by Wyeth Laboratories, has been administered to over 30,000 recruits who, simultaneously, received the type 4 vaccine. Both vaccines appear to be 95% effective against natural adenovirus disease and no untoward reactions have occurred. Data from a recent study carried out by the military have shown that the two vaccines, administered simultaneously, do not interfere with the protection afforded by each. This means that two more disease deterrents are available for use at the first sign of an outbreak. Routine immunization, however, must await further study of how eradication of these viruses will affect the presence or emergence of other adenovirus strains.

Presently, NIAID is supporting preliminary testing of a vaccine against a third common offender -- adenovirus type 21. Vaccines against types 1, 2, and 5 also appear promising.

Basic studies of the biology of adenoviruses are continuing. Scientists hope that these studies will enable the development of purer vaccine preparations.

Common Cold Studies

The National Center for Health Statistics reported that during a one year period beginning July, 1967, Americans suffered more than 90 million colds. These illnesses resulted in some 234 million days of restricted activity and a loss of 36 million school days, and 32 million work days.

Statistics, however, do not even begin to reflect the true toll these illnesses take in reduced vitality, decreased efficiency, below standard productivity and personal discomfort.

Known as "the common cold", the syndrome is common only in symptoms and frequency of occurrence. Almost all colds are believed to be caused by viruses, but only 1/2 of these illnesses can be blamed on a specific organism. In fact, there are now at least 89 officially recognized rhinoviruses (34 more than were reported last year) and some 23 corona viruses. These have all been demonstrated as causes of the common cold. Many of these viruses were isolated in NIAID laboratories and in Institute-supported rhinovirus typing centers and research laboratories throughout the world.

Efforts to identify cold agents, determine their prevalence, and group them according to shared characteristics are continuing, but the problems of common cold research are labyrinthine.

Early in the study of colds it was suggested that a "cocktail" vaccine might be developed against the most common rhinoviruses. But, the great number of rhinoviruses and the absence of any one or any few major cold-causing viruses has made the possibility of producing such a combined vaccine extremely unlikely.

Although scientists have not yet solved the problem of the multiplicity of cold-causing viruses, they have learned that the route of immunization plays an important role in determining whether a vaccine will be effective. One vaccine administered intramuscularly offered little protection against experimental infections. When researchers administered the vaccine in the form of nosedrops or as a nasal spray, however, a significant number of the vaccinated individuals resisted infection.

Knowing at least some of the causes of the common cold allows scientists to look for cures as well as means of prevention. In addition to preparing vaccines, NIAID scientists and contractors are seeking substances that inhibit the ability of a virus to take over the cell's genetic processes. One antiviral substance that is under intensive investigation is interferon -- a natural body substance produced in response to virus invasion. New methods are being sought to stimulate, artificially, the body's ability to produce large amounts of interferon when it is needed. Polyinosinic polycytidylic acid (poly I.poly C) has been shown to be a good chemical inducer of interferon in laboratory animals. A few carefully controlled studies have been initiated to determine the usefulness of this inducer in man. Antiviral substances and their inducers are now under intensive study. New concepts in the treatment of viral and viral respiratory infections may well be formulated in the near future.

Scientists are also studying factors which affect susceptibility to colds. One NIAID research team, for example, has studied a popular belief concerning the cause of a cold. Using volunteer subjects, the scientists showed that chilling, exposure, or overheating apparently has little effect on the development or seriousness of a cold. If a rhinovirus or coronavirus infects the body, a cold usually develops, and the importance of other factors has not been demonstrated.

Pneumococcal Pneumonia

Although antibiotics -- such as penicillin and tetracycline -- cure bacterial pneumonia, the death rate from influenza and pneumonia continues to rise. This rise, in the face of reliable cures and proven treatment, has been attributed to the increasing number of elderly in the population, and to the fact that hospital admissions of the elderly since the advent of Medicare has permitted more accurate reporting of the causes of illness and death. In 1955, there were 28.5 million Americans over 55; today there are 37.7 million and it has been predicted that by 1980, the number will reach 46 million.

The elderly are not the only pneumonia victims. For many people the shock of a major infection is frequently fatal, even after antibiotics rid their bodies of bacteria.

In 1967 the Infectious Disease Branch of NIAID began conducting a program of surveillance studies to identify the types of bacterial pneumonia most prevalent and the population groups at highest risk. Presently, the program has expanded to include some 400,000 persons in the United States.

In 1968, on the basis of early findings, a contract was awarded to the Eli Lilly Company for production of vaccines to provide effective immunity against the most common types of pneumococcus -- a group of organisms known to cause pneumonia.

Small clinical trials of these vaccines have begun and will be expanded in 1971. As data from these tests accumulate, work will begin on the formulation of a single vaccine effective against more than one strain of the pneumococcus organism.

Armed with new epidemiologic data and sophisticated laboratory methods for developing vaccines, NIAID and cooperating contractors eventually hope to be able to prevent fatal pneumococcal pneumonia in susceptible population groups.

Mycoplasma Infections

Organisms comprising the Mycoplasma family are becoming of increasing concern to the scientific and medical communities as evidence accumulates implicating them as a cause of acute respiratory disease.

For many years these organisms, which share many biologic characteristics with both viruses and bacteria, were of greater concern to veterinarians than to those working on human medical problems. It was not until 1942 that Dr. Monroe D. Eaton grew in eggs an organism (first known as Eaton's agent) from a case of primary atypical pneumonia. In 1961, a group of NIH and other scientists demonstrated that this unknown agent was Mycoplasma pneumoniae and that it was an important cause of human disease.

Although there are an increasing number of human mycoplasma being isolated, M. pneumoniae seems to be the only strain which produces disease in man. It has been implicated in infections of the nose and throat, the bronchial tubes leading into the lung, and even the small alveoli found deep in the lung tissue. It has also been associated with skin rashes, with some cases of severe meningo-encephalitis, and with hemolytic anemia.

The illness caused by M. pneumoniae varies. Sometimes infection is symptom-free. Dr. Thomas Grayston, NIAID contractor at the University of Washington, discovered that more than 70% of family contacts he examined had clinically detectable pneumonia although they did not feel ill enough to seek medical care.

Although few M. pneumoniae infections are life-threatening and death rarely occurs, infections can be severe. Outbreaks in military and civilian populations have resulted in large numbers of hospitalized patients. Investigations, involving both humans and animals, have shown that certain broad antibiotics, such as tetracycline, significantly reduce the symptoms and shorten the duration of hospitalizations.

Other studies however, have indicated that the usefulness of these drugs in preventing spread of the disease is limited. For this reason, attempts have been underway to produce a safe and effective vaccine using either live or inactivated M. pneumoniae organisms.

An inactivated vaccine was produced in 1967 through the collaborative efforts of NIAID scientists, contractors, and grantees. However, this vaccine and the one produced shortly thereafter, when clinically tested, proved to be only partially effective in preventing illness.

Now a more promising vaccine against M. pneumoniae has been produced from a strain of organism isolated at Children's Hospital in Columbus, Ohio. Using a new technique worked out by NIAID contractor Dr. Norman Somerson and

associates, scientists can now grow the fastidious organisms with relative ease on the walls of glass bottles in a medium using cow serum for nourishment. This has eliminated the necessity of growing the organism in horse serum which can cause potentially explosive allergic reactions in sensitive persons.

Preliminary evaluation data accumulated on vaccine developed by this technique appear quite promising. When tested in 45 volunteers in Texas, the vaccine produced antibodies in the blood of all the volunteers. The investigators must now determine whether these ordinarily protective substances will, in fact, be protective against the mycoplasma pathogen and for how long.

Many questions on the basic nature of the mysterious mycoplasma organism remain to be answered. For example, what role do mycoplasma play in chronic respiratory disease? What role might they play in birth defects, in neurological disorders, and in arthritis?

Other Respiratory Vaccines

Alongside traditional methods of vaccine preparation (the use of live-weakened or killed organisms) a promising new aspect of vaccine research is gaining momentum -- the development of temperature-sensitive (ts) mutant strains. Intrigued by the isolation of strains of RS (respiratory syncytial) virus, able to grow and reproduce only at low temperatures, scientists at the NIAID and elsewhere are now trying to isolate and produce temperature-sensitive mutants of rhinovirus, parainfluenza virus, and M. pneumoniae for use in immunizing preparations. Since the nose has a cooler temperature than the less-exposed respiratory tract areas, scientists reason that a mutant respiratory disease agent, incorporated into a vaccine and administered directly into the nasal tract, might increase immunity in this area and prevent disease. Such an agent would also not invade the lower respiratory tract which maintains a higher, less favorable temperature.

At Children's Hospital in the District of Columbia, a live attenuated strain of RS virus vaccine has been given to infants -- the traditional target of the RS virus. These children are now being watched carefully as they pass through seasonal epidemics of RS infection.

Ts mutants of other live virus strains are presently undergoing extensive testing in tissue culture and animals before being produced and evaluated in humans. Progress in the development of ts mutant strains of mycoplasmas is also being made.

With the steady improvement in research techniques yielding increased knowledge of the biology and ecologies of various respiratory pathogens, it is hoped that the Institute can continue to contribute to the solution of the many problems associated with respiratory illness in this country.

62-645 O - 71 - pt. 3 - 52

RESEARCH GRANT PROGRAM

Mr. MICHEL. How many research grants would be made by your shop in a given year?

Dr. DAVIS. We supported in 1971, 1,198 research grants at a cost of $47,439,000.

Mr. MICHEL. That was 1971?

Dr. DAVIS. That is right. The estimate for 1972 based upon this budget is 1,239.

Mr. MICHEL. And the amount of money?

Dr. DAVIS. $48,856,000.

Mr. MICHEL. Is that a reduction?

Dr. DAVIS. This is an increase in funds from 1971.

Mr. MICHEL. And the increase in the number of grants is what—for continuing projects, and for new projects?

Dr. DAVIS. The increase in the number of grants is 41. The increase in the amount of money for grants is $1,417,000. Most of this actually are the increases for ongoing grants, grants that have been committed in the past. We will not have enough money to pay as many new grants next year as we did in 1971.

Mr. MICHEL. Is that serious?

Dr. DAVIS. It is a reduction of about $1,484,000 less than we had last year.

Mr. MICHEL. Is that a serious matter to you as a professional man in this field?

Dr. DAVIS. Yes.

Mr. MICHEL. Does that concern you?

Dr. DAVIS. Yes, it does. It reduces the amount of new research we can get underway next year.

Mr. MICHEL. Looking through the crystal ball, in 1973 do you suppose that might take a different turn?

Dr. DAVIS. My crystal ball is pretty cloudy at this point, sir.

TRAINING GRANTS

Mr. MICHEL. In training grants, you are just holding your own dollarwise, aren't you?

Dr. DAVIS. Yes, we have the same amount of money, but because of the increase in costs we are not able to support as many as we did last year.

Mr. MICHEL. What do those training grants run individually? Are they all the same?

Dr. DAVIS. They average about $60,000.

Dr. MARSTON. There is a considerable variation in the training grants on the basis of the job to be done and the assessment of what the cost will be of doing that job. They vary in size, in terms of the numbers of trainees, in various institutions in the country.

VARIATIONS BETWEEN INSTITUTES REGARDING SIZE OF TRAINING GRANTS

Mr. MICHEL. While you are responding, Dr. Marston, I would like to get that figure for each of these institutes, not only an average but a low and a high. Is that pretty uniform through all the institutes?

Dr. MARSTON. About half of all the NIH training grants are in the Institute of General Medical Sciences. The big accumulation of training grants is there. There are some differences depending on the nature and the substance of the Institute's mission. But in general they tend to be for the same general purposes and at roughly the same costs.

We would be glad to supply for the record the variations, Institute by Institute, showing the number and cost and average cost and the range and if there is any special reason for differences to put a footnote to that effect.

Mr. MICHEL. Fine.

(The information follows:)

TRAINING GRANTS—1971 RANGE

	Low cost grant	High cost grant	Average cost of grant
Cancer	$7,454	$370,376	$68,624
Heart	2,500	225,000	48,000
Dental	8,000	182,000	59,000
Arthritis	13,000	310,000	56,863
Neurology	1,000	174,000	60,000
Allergy	500	136,000	46,400
General Medical Sciences	13,230	563,175	83,770
Child Health	4,000	310,000	72,000
Eye	21,000	145,000	63,000
Environmental Health	13,000	236,000	85,000
Research Resources	35,000	64,000	39,000

UNFUNDED NIH TRAINING GRANT APPLICATIONS

Mr. MICHEL. While we are on that subject, Dr. Marston, would you place in the record the number and dollar amount of training grant applications that have been approved but cannot be funded.

Dr. MARSTON. Yes.

Mr. MICHEL. Dr. Marston, would it be true that you are only able to fund about one-third of the competing training grant applications that are approved?

Dr. MARSTON. That is the general range. We have had as you know, for a number of years, a fixed number of dollars. At the same time, we have had an increase in the number of medical schools and other institutions involved in research and research training.

So we have had a combination of an increased demand for training grants, and a fixed dollar budget which, considering inflation means decreased support. This has been one of the areas, across the board at NIH, that has had a squeeze. I think you will find that the percentage in Dr. Stetten's Institute may be even lower than this. Dr. LeVeck tells me it is 25 percent in Child Health. We will provide this Institute by Institute.

(The information follows:)

TRAINING GRANTS, 1971 COMPETING

[Dollar amounts in thousands]

	Number	Dollars	Funded percent of approved number	Funded percent of approved dollars
Cancer:				
Approved	71	$4,819	48.0	52.0
Funded	34	2,525		
Unfunded	37	2,294		
Heart:				
Approved	61	4,232	92.0	86.0
Funded	56	3,660		
Unfunded	5	572		
Dental:				
Approved	8	507	38.0	27.0
Funded	3	135		
Unfunded	5	372		
Arthritis:				
Approved	83	4,781	60.0	59.0
Funded	50	2,841		
Unfunded	33	1,940		
Neurology:				
Approved	141	8,323	45.0	40.0
Funded	63	3,353		
Unfunded	78	4,970		
Allergy:				
Approved	67	3,328	31.0	40.0
Funded	21	1,328		
Unfunded	46	2,000		
General medical sciences:				
Approved	166	14,373	53.0	43.0
Funded	88	6,210		
Unfunded	78	8,163		
Child health:				
Approved	106	7,312	19.0	31.0
Funded	20	2,239		
Unfunded	86	5,073		
Eye:				
Approved	13	990	38.0	24.0
Funded	5	242		
Unfunded	8	748		
Environmental health:				
Approved	11	1,220	91.0	84.0
Funded	10	1,026		
Unfunded	1	88		
Research resources:				
Approved	2	105		
Funded				
Unfunded	2	105		
Total, Institutes/Divisions:				
Approved	729	49,990	48.0	47.0
Funded	350	23,559		
Unfunded	379	26,325		

VIRAL RESPIRATORY DISEASES

Mr. MICHEL. What is the most troublesome infectious disease today in this country?

Dr. DAVIS. I think acute respiratory viral infections as a whole. It is the most common disease for which patients go to their doctors, whether it is a child being taken to the pediatrician or an older person going for some respiratory disease or an older person who has pneumonia.

But as a whole the viral respiratory diseases.

A lot of work is going on in these areas and has been for a long time, and we have a number of very good leads.

A disease which all of us feel is at a stage where we are going to move ahead is the one I mentioned a while ago, hepatitis, and we think we are really on the edge of some advances in this. This is troublesome not only because of its danger in transfusion but also

because epidemic infectious hepatitis—which is a different kind—occurs sporadically around the country. It is spread by food or drink often and is a very troublesome disease requiring extended hospitalization and loss of time.

There are something like 40,000 to 50,000 cases a year of infectious hepatitis reported and we estimate the true incidence is several times that.

Mr. MICHEL. That is all, Mr. Chairman. Thank you.

Mr. FLOOD. Mr. Natcher.

Mr. NATCHER. No questions.

Mr. FLOOD. Mrs. Reid.

HEPATITIS AMONG DRUG USERS

Mrs. REID. Doctor, while we are talking about hepatitis, I read an article the other day saying there had been numerous cases of hepatitis among young people taking dope caused by needles that were contaminated.

Dr. DAVIS. They are contaminated, yes. This is essentially the same situation where we have transfusion hepatitis. The infecting agent is in the blood of the person who is infected and he may or may not know he has the infecting agent. Most of the time he does not.

So if his blood is given to somebody in a blood transfusion without knowing it is infectious, that person runs the risk of acquiring infectious hepatitis. This is the same thing that happens when a needle used by one dope addict is not properly cleaned and sterilized and then is used by another one; the agent is transmitted through this improperly sterilized needle.

Mrs. REID. We hear about the use of drugs being more prevalent now. Do you find there have been more cases of hepatitis because of this?

Dr. DAVIS. The number of cases in hepatitis among drug users is very high. It seems to be increasing. So there is no question but what this increased use of drugs is attended by an increased incidence of serum hepatitis.

NIAID AND OTHER INSTITUTES DOING HEPATITIS WORK

Mrs. REID. What is the difference in the research you are doing regarding infectious hepatitis in comparison to the work of the Division of Biologic Standards and the Institute of Arthritis and Metabolic Diseases?

Dr. DAVIS. Let me tell you what we are doing now and what we would like to do in hepatitis.

Mrs. REID. And whether this overlaps the work in these other institutes.

Dr. DAVIS. If I can answer your last question first, I think that Dr. Marston in his opening statement did indicate that a task force had been established at the National Institutes of Health among the institutes which have a concern for hepatitis, and there are four or five, to be sure there was no overlap, and to be sure there was adequate communication between the scientists doing the work.

It is very clear that the job is so big it can be done by quite a number of different people. So in our institute, Allergy and Infectious Diseases, we have outlined for ourselves several tasks.

One is to purify and characterize the hepatitis associated antigen. This is the Australia antigen. This is done best by the use of a zonal centrifuge which is a very high speed centrifuge.

If we can purify this substance which seems to be a protein, we will have a material with which to work. This hasn't yet been fully accomplished. We need to develop and evaluate an assay test to test for antibodies in patients.

We need to do animal studies particularly in the chimpanzee which is the animal most susceptible to this infection, and we need to produce the specific antisera against this agent and against the various subtypes of this agent.

The Division of Biologic Standards, I won't try to speak particularly on this, except they are concerned with blood and blood products and the safety of blood products.

We in NIAID are trying to do some underlying fundamental work which will give us a better understanding of what this disease is all about.

CROMOGLYCATE, AN ASTHMA DRUG

Mrs. Reid. Is the new drug, cromoglycate, in capsule form?

Dr. Davis. Yes.

Mrs. Reid. How do you expect this to be used?

Dr. Davis. This is still in the stage of evaluation in a number of clinics. It has been used in England for some 4 or 5 years, but it is not yet licensed in this country. I am not sure whether it is licensed in England or not, but the English allergists feel this has considerable merit.

The mechanism of its effectiveness is different and new from the other drugs which previously have been used in asthma.

Mrs. Reid. Why has this had greater development in England than here in the United States?

Dr. Davis. I am not sure why they have developed this. They have very skillful pharmacologists and physiologists in England. They have found this drug and have evaluated it there. So it has come to this country that way. It is now being extensively evaluated here.

AVAILABILITY OF PNEUMONIA VACCINE

Mrs. Reid. How soon do you feel the vaccine for pneomococcus pneumonia will be available for general use?

Dr. Davis. We won't get into mass trials for another 1 or 2 years and then it would take several years after that before an evaluation can be done.

Mrs. Reid. Do you think this will be available like Salk vaccine so the average person could receive it?

Dr. Davis. It would seem to me this would be extremely useful for physicians to give their patients as a preventive measure, particularly those over 50 years of age when the disease begins to increase in incidence.

I can see a physician using this vaccine the same way as he prescribes vitamins or an anti-hypertensive drug, or any other drug he does in caring for the patient. It probably would not be useful in younger people unless they were in certain high risk groups. As I

mentioned, the American Indian is one group. There might be other special groups which could be benefited by it.

The vaccine is a very good vaccine because it lasts a long time, it doesn't have to be given every year. It can be given once every 5 or 10 years or even longer than that in order to retain its effectiveness. This is why we feel it does have promise as another preventive measure which physicians can have at their disposal.

Mrs. REID. Will it be very expensive?

Dr. DAVIS. No. It is a simple compound.

LOCATIONS OF THE ALLERGIC DISEASE CENTERS

Mrs. REID. In what areas will the allergic disease centers be located?

Dr. DAVIS. I can give you these. We are in the process of negotiating these and awards are being made. One is being made to Johns Hopkins Medical School in Baltimore, one to Robert Breck Brigham Hospital in Boston, one to Washington University in St. Louis, University of Wisconsin in Madison. There will be two in Denver, one to the National Jewish Hospital and one to the Children's Asthma Research Institute and Hospital.

There will be one at Scripps Clinic, LaJolla, Calif. They are well distributed throughout the country.

Mrs. REID. Thank you very much.

Mr. FLOOD. Are there other questions?

Mr. CASEY. What were you just naming?

Dr. DAVIS. I was just saying we have established a new program in the Institute of Allergic Disease Centers.

Mr. CASEY. You were naming where the centers are to be located?

Dr. DAVIS. Yes.

FUNDING THE ALLERGIC DISEASE CENTERS

Mr. CASEY. Did you say there were about 18 applications pending?

Dr. DAVIS. We had 18 applications which were received for these centers.

Mr. CASEY. They have been awarded?

Dr. DAVIS. Yes. Ten of those were approved by the study section and council and we have enough funds to finance 7 of them.

Mr. CASEY. What do you have allocated to this, $450,000 total for the seven?

Dr. DAVIS. Yes. This is what is budgeted for this first year.

Mr. CASEY. When you split that seven ways, that isn't much is it?

Dr. DAVIS. That is a little less than $70,000 a piece, but this is something to start with. There are programs which we wanted to have for a long time. We think it is an appropriate thing to start. We were able to reprogram moneys from other areas, particularly from some of the transplantation research centers which had acquired sources of funds that they had not had originally. That is why we were able to reprogram this money.

Mr. CASEY. These centers are just now getting started?

Dr. DAVIS. They will be started this summer. The awards are just being made now out of 1971 money.

Mr. CASEY. You had the same amount last year, $450,000.

Dr. DAVIS. That is what we reprogramed and we are requesting the same amount. That is all we have in 1972.

Mr. CASEY. There isn't any new money in 1972. You are just using the money left over from last year?

Dr. DAVIS. There is no money except that we reprogramed from other areas within the institute.

Mr. CASEY. The Senate report suggested this shall we say.

Dr. DAVIS. Yes.

Mr. CASEY. Let's see how you get along with them on that amount of money.

Are these centers used for training purposes?

Dr. DAVIS. They will provide a very excellent place for training, particularly clinical training.

Mr. CASEY. Will they use additional funds where they have something in the way of training programs? Will additional funds come out of your training grants?

Dr. DAVIS. The institution which is host to the centers can apply for a training grant or research grant, and we hope that they can supplement the center concept with these other funds.

Mr. CASEY. The thing is if we start some of these centers and don't give them very much money, the next thing the roof falls in on us. "You started these centers and won't even support them. You are not giving them adequate support."

The next thing you know our mail will be loaded.

Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Patten.

REACTION OF SINUSES TO TEMPERATURE CHANGE

Mr. PATTEN. Has anyone mentioned the word "sinus" here today?

Dr. DAVIS. I don't think I heard it today.

Mr. PATTEN. You were talking about respiratory diseases. I thought you would talk about sinuses. What about this modern air conditioning? We have one chairman that won't allow the air conditioning to be used. You haven't mentioned temperature. My own impression is that temperature is a very important factor, especially a sudden change. You can almost predict people sneezing sometimes if the air changes quickly. Your sinuses tighten up and you start sneezing. We haven't said anything here about quick changes. You don't emphasize this in your work, you are looking for bugs and parasites and fungi and the like. My own reaction would be I think change of temperature at the present time is a big factor.

RESEARCH IN NUCLEAR MEDICINE

You don't mention nuclear radiation. I had a fellow in food research outside of Princeton tell me through the use of nuclear radiation we won't need an icebox in our house 5 years from now. They will preserve any food from bacteria growth. Even take a ship and send corn and wheat to India in bulk, and it won't be subject to the present destruction.

Dr. DAVIS. I think we might very well, but at the present time we are not at that stage and we are not doing that kind of work. We are using and virologists commonly use radioactive elements.

Mr. PATTEN. That is what I mean.

Dr. DAVIS. Particularly for diagnostic development. It is a very sensitive diagnostic technique. The radio immune assay test for hepatitis is based on radioactive material which is incorporated into the test agent, which makes it much more sensitive than the normal serologic methods of precipitation or agglutination. The whole field of nuclear medicine has much to contribute to our field.

PRIVATE RESEARCH ON THE COMMON COLD

Mr. PATTEN. The insurance companies collect billions of dollars. They think they can save money by watching our health and they do some research. How much is done in the private sector to try to pin down the common cold?

Dr. DAVIS. The drug industries have invested money into it. We also have had a number of contracts with the various drug firms for the development of vaccines against these respiratory viruses. We also have grants going to universities and medical centers throughout the country, but in addition to that they invest some of their own money.

I think I can give you a figure here. I have a figure for how much money this institute is spending on respiratory viruses which is $5.6 million. I don't have the figure for money that is spend from the private sector on this.

Mr. PATTEN. Do you think it might approach the amount of work the Government is doing?

Dr. DAVIS. No.

Dr. MARSTON. The overall figure is that private industry put into health research and development about 25 percent of the total amount that is invested in the country as a whole. This is mostly from the pharmaceutical industry and for mostly work that is done within the pharmaceutical industry.

Mr. SMITH. Is that on basic research or on research on how to market the products?

Dr. MARSTON. These figures always run into the problem of definition like that, but we have tried to limit it to biomedical research itself, not research on marketing, not research on packaging. It does include both the developmental aspects as well as the basic research. It is about $700 million a year from private industry.

Mr. SMITH. Thank you.

THE PREVENTIVE CAPABILITIES OF FACE MASKS

Mr. CASEY. On my one trip to Tokyo I noticed a lot of the Japanese wear masks. Is that a status symbol or is it really for medicinal purposes? Or do you know?

Dr. DAVIS. Yes, that is the common thing in Japan. They believe that this reduces the chance of inhaling viruses which are in the environment and there is a debate whether or not this has any affect or not.

We know that when viruses from the respiratory tract are disseminated from the nose or the mouth, they go relatively a small distance,

a foot or two. Within that distance they are quite highly infectious but it is very difficult to show that they are highly infectious beyond a short distance.

I know people and scientists in this country feel this is not useful.

Mr. CASEY. Thank you.

AMOUNT SPENT FOR RESPIRATORY DRUGS

Mr. PATTEN. Mr. Chairman, your budget let's say is $100 million. What are we spending on pills for colds? I will bet everybody in the room has two or three pills. Every place I look I see all kinds of pills. What do you think the public is spending in the United States?

Do you think we are spending 10 times what you are spending?

Dr. DAVIS. In 1966 the records show that $556 million was spent for respiratory pharmaceuticals.

Mr. PATTEN. I am not going to ask you to comment about how valuable they are. That is all, Mr. Chairman.

Mr. FLOOD. Mr. Conte.

SURVIVAL RATES IN KIDNEY TRANSPLANTS

Mr. CONTE. Of the 5,000 kidney transplant operations that have been performed throughout the world, how many can be termed a success?

Dr. DAVIS. Since approximately 40 percent of all kidney transplants have been performed only during the past 2 years, not enough time has elapsed for proper evaluation of the "success" of many of them. The latest survivor figures for kidney transplants are those in the "Eighth Report of the Human Kidney Transplant Registry," published in the March 1971 issue of Transplantation. They show that of the 3,645 kidney transplants reported through January 1, 1970, those from related living donors have a 78-percent 1-year survival rate and a 75-percent 2-year survival. Kidneys from cadaveric donors have a 52-percent 1-year survival and a 41-percent 2-year survival. In the years 1967–69, 56 percent of all kidneys transplanted were from cadaver donors.

INCIDENCE OF PNEUMONIA IN INDIANS

Mr. CONTE. How widespread a problem is pneumococcal pneumonia among the American Indians?

Dr. DAVIS. In the Navajo Indian study, the incidence of overall pneumonia is four times as great among Indians as in the general public. We don't know for sure how much of this is pneumococcal pneumonia, but there appears to be more pneumococcal pneumonia among the Navajos than among the general American population.

PNEUMONIA AND MENINGITIS VACCINES

Mr. CONTE. What have your preliminary clinical trials of the pneumonia vaccines indicated as to their potency?

Dr. DAVIS. As expected, they are potent.

Mr. CONTE. What were the unexpected technical problems that you experienced in the production of the vaccines?

Dr. DAVIS. There are 14 different polysaccharide pneumococcus vaccines. The method for growth and purification for one type of polysaccharide is not always applicable to other types. So several different procedures had to be developed.

Mr. CONTE. If trials of the meningitis vaccines prove successful, how long will it take to develop a licensed vaccine for general use?

Dr. DAVIS. An estimate would be 3 years from now.

INCIDENCE OF RESPIRATORY DISEASE IN MILITARY CAMPS

Mr. CONTE. What accounts for the fact that the acute respiratory disease described on page 6 was particularly prevalent in military recruit training camps?

Dr. DAVIS. Military recruits always have had problems with acute respiratory diseases. The recruit camp is an ideal setting for outbreaks of contagious disease when you consider the continual influx of healthy "carriers," stressful situations, and men living in close quarters.

Mr. CONTE. Are there any other diseases that are heavily concentrated in such camps? Every now and then, I read about an outbreak of meningitis on some military installation. Are preventive measures being taken to lessen the possibility of this occurring in the future?

Dr. DAVIS. Other diseases would include rubella or German measles, mumps, and meningococcal meningitis. I understand that when an outbreak of group C meningococcal meningitis occurs in a military camp, vaccine is administered.

VITAMIN C TREATMENT OF COLDS

Mr. CONTE. There has been a lot of play in the press recently about the effects heavy doses of vitamin C have or don't have in preventing colds. Has the Institute conducted research in this area? If so, what are its findings?

Dr. DAVIS. The Institute has not supported any research on the effect of heavy doses of vitamin C in preventing colds. No research grant applications have been received. So far, emphasis within the Institute has been on the identification of the causes of the common cold and potential development of vaccines.

Mr. CONTE. That is all, Mr. Chairman.

Mr. FLOOD. Thank you, Doctor.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation

	1971 Estimate	1972 Estimate
Appropriation	$102,249,000	$99,342,000
Real transfer to:		
"Departmental Management"	-31,000	---
Real transfer from:		
"National Institute of General Medical Sciences" (Proposed transfer for increased pay costs.)	119,000	---
Comparative transfers to:		
"Office of the Director"	-746,000	---
"National Heart and Lung Institute"	-802,000	---
"National Institute of Arthritis and Metabolic Diseases"	-1,023,000	---
"Health Manpower"	-1,642,000	---
Total, obligations	98,124,000	99,342,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
13	Research	---	$56,052,000	---	$56,919,000	---	+$867,000
	General research support grants	---	(5,044,000)	---	(4,494,000)	---	(-550,000)
	Categorical clinical research centers	---	(1,266,000)	---	(1,266,000)	---	(---)
	International centers for medical research and training	---	(2,263,000)	---	(2,263,000)	---	(---)
	Scientific evaluation	---	(40,000)	---	(40,000)	---	(---)
21	Fellowships	---	3,579,000	---	3,334,000	---	-245,000
23	Training	---	7,280,000	---	7,280,000	---	---
	Direct operations:						
24	Laboratory and clinical research	576	17,329,000	576	17,745,000	---	+416,000
28	Collaborative research and development	36	11,661,000	36	11,729,000	---	+68,000
34	Review and approval of grants	43	1,627,000	43	1,714,000	---	+87,000
34	Program direction	32	596,000	32	621,000	---	+25,000
	Total obligations	687	98,124,000	687	99,342,000	---	+1,218,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	687	687	---
Full-time equivalent of other positions	18	18	---
Average number of all employees	705	705	---
Personnel compensation: Permanent positions	$8,488,000	$8,974,000	+$486,000
Positions other than permanent	136,000	180,000	+44,000
Other personnel compensation	150,000	150,000	---
Total personnel compensation	8,774,000	9,304,000	+530,000
Personnel benefits	876,000	919,000	+43,000
Travel and transportation of persons	350,000	350,000	---
Transportation of things	85,000	85,000	---
Rent, communications, and utilities	270,000	278,000	+8,000
Printing and reproduction	60,000	60,000	---
Other services	1,248,000	1,253,000	+5,000
Project contracts	10,567,000	10,372,000	-195,000
NIH Management fund	6,283,000	6,452,000	+169,000
Supplies and materials	2,300,000	2,336,000	+36,000
Equipment	400,000	400,000	---
Grants, subsidies, and contributions	66,911,000	67,533,000	+622,000
Total obligations by object	98,124,000	99,342,000	+1,218,000

Summary of Changes

1971 estimated obligations	$98,124,000
1972 estimated obligations	99,342,000
Net change	+1,218,000

	Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase costs	---	---	---	+$368,000
2. One additional day of pay	---	---	---	+33,000
3. Within grade pay increases	---	---	---	+150,000
4. FTS rate increase	---	---	---	+8,000
5. Wage board pay raise	---	---	---	+23,000
6. Non-competing research grants	---	---	---	+2,901,000
B. Payments to the "National Institutes of Health management fund" for centrally furnished services	---	$6,283,000	---	+169,000
Total, increases	---	---	---	+3,652,000
Decreases:				
A. Program:				
1. Research grants	---	56,052,000	---	-2,034,000
2. Fellowships	---	3,579,000	---	-245,000
3. Laboratory and clinical research	576	12,039,000	---	-155,000
Total, decreases	---	---	---	-2,434,000
Total, net change	xxx	xxx	xxx	+1,218,000

Explanation of Changes

Built-in Increases--These increases will provide $368,000 for annualization of 1971 pay increase costs; $33,000 for one additional day of pay in 1972; $150,000 for within grade pay increases in 1972; $23,000 for wage board pay increases; $8,000 for increased costs in 1972 for use of the Federal Telecommunications System and $2,901,000 for 46 additional non-competing research grants.

Program decreases:

Research grants -- The decrease of $2,034,000 reflects a decrease of $1,484,000 in low priority regular research grants, and will provide a net total of $48,856,000 to fund 1,239 awards in 1972. The request also includes a decrease of $550,000 for general research support grants, a program included in each NIH appropriation containing research grant projects, but administered separately by the Division of Research Resources.

Fellowships -- The decrease of $245,000 will provide a total of $3,334,000 and approximately 186 awards, or 17 below the 1971 level.

Laboratory and clinical research -- The decrease of $155,000 will provide a total of $11,874,000 and 576 positions for intramural research, and is a reduction in contractual support of this research.

Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1971 Senate Report	
Special grants	
1. The Committee believes that the launching of these units (clinical allergy research centers) is a necessary next step in translating the results of research at the laboratory bench into practical application by physicians treating allergic patients, and must not be delayed. (Page 42)	1. The Institute has established a special grant program for the support of allergic disease centers. Eighteen applications will be reviewed by the March Council for possible payment. The expected funding of this program is about $450,000.
2. As in many other areas, the Committee does not feel that enough is being done to develop new training programs for physicians assistants especially trained in allergy treatment. The Committee will expect future budgets to reflect attention to these needs. (Page 42)	2. It is expected that establishment of allergic disease centers in various parts of the United States will provide the opportunity for improved training of all levels of medical care and research for the prevention and treatment of allergic disorders. The present budget provides the same level of effort for the allergic disease centers as that of 1971.

Authorization Legislation

Legislation	1972 Authorization	1972 Appropriation requested
Public Health Service Act of 1944:		
Section 301 -- Research and Investigation, in general.....	Indefinite	$99,342,000
Title IV, Part D -- National Institute of Allergy and Infectious Diseases.....	Indefinite	99,342,000

PUBLIC HEALTH SERVICE ACT

The legislative authority which provides for the award of grants for research, research training, and fellowships is included in section 301 of the Public Health Service Act.

The Public Health Service Act, Title IV, Research Institutes, Part D, National Institute on Arthritis, Rheumatism, and Metabolic Diseases, National Institute of Neurological Diseases and Blindness, and other Institutes.--

"Sec. 431 (b) The Surgeon General is authorized with the approval of the Secretary to establish in the Public Health Service one or more additional institutes to conduct and support scientific research and professional training relating to the cause, prevention, and methods of diagnosis and treatment of other particular diseases or groups of diseases (including poliomyelitis and leprosy) whenever the Surgeon General determines that such action is necessary to effectuate fully the purposes of section 301 with respect to such disease or diseases."

"Sec. 433 (a) Where an institute has been established under this part, the Surgeon General shall carry out the purposes of section 301 with respect to the conduct and support of research relating to the disease or diseases to which the activities of the institute are directed, through such institute and in cooperation with the national advisory council established or expanded by reason of the establishment of such institute. In addition, the Surgeon General is authorized to provide training and instruction and establish and maintain traineeships and fellowships, in such institute and elsewhere, in matters relating to the diagnosis, prevention, and treatment of such disease or diseases with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he may deem necessary, and in addition, provide for such training, instruction, and traineeships and for such fellowships through grants to public and other nonprofit institutions. The provisions of the subsection shall also be applicable to any institute established by any other provision of this Act to the extent that such institute does not already have the authority conferred by this subsection."

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer to:		
Departmental Management	-$31,000	For consolidating within the Office of the Secretary, DHEW, certain construction activities through the establishment of the Facilities Engineering and Construction Agency.
Real transfer from:		
National Institute of General Medical Sciences	119,000	Proposed transfer for increased pay costs which could not be absorbed by the receiving appropriation.
Comparative transfers to:		
Office of the Director	-76,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director for establishing the Office of Contracts and Grants.
Office of the Director	-670,000	To provide an equitable distribution of the Management Fund in 1972.
National Heart and Lung Institute	-802,000	Transfer of regular research grants for the pulmonary research program.
National Institute of Arthritis and Metabolic Diseases	-1,023,000	Transfer of regular research grants for the malnutrition research program.
Health Manpower	-1,642,000	Transfer of institutional support to Health Manpower.

62-645 O - 71 - pt. 3 - 53

National Institute of Allergy and Infectious Diseases

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
1962	$48,322,000	$52,182,000	$60,000,000	$56,091,000
1963	59,342,000	62,142,000	68,142,000	66,142,000
1964	69,226,000	68,723,000	69,226,000	68,723,000
1965	68,600,000	70,100,000	70,400,000	70,100,000
1966	74,987,000	74,987,000	77,987,000	77,987,000
1967	85,702,000	88,670,000	90,670,000	90,670,000
1968	94,422,000	94,422,000	98,922,000	94,422,000
1969	98,562,000	95,119,000	99,119,000	96,840,500
1970	102,389,000	102,389,000	105,000,000	103,694,500
1971	99,219,000	102,249,000	102,749,000	102,249,000
1972	99,342,000			

Justification

National Institute of Allergy and Infectious Diseases

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	687	$9,650,000	687	$10,223,000	---	+$573,000
Other expenses.....	---	88,474,000	---	89,119,000	---	+645,000
Total.....	687	98,124,000	687	99,342,000	---	+1,218,000

General Statement

The Institute conducts and supports broadly based research on the causes, characteristics, prevention, control, and treatment of diseases believed to be caused by infectious agents including bacteria, fungi, viruses, and parasites--or by abnormalities in the body's immune mechanisms such as allergies. In its attack on infectious and allergic diseases, the Institute is focusing attention primarily on important problems that demand increased research efforts. Two types of programs - nationally organized research programs and special emphasis research programs have been set up to deal with these problems.

The nationally organized research programs are collaborative, contract-financed, institute-coordinated efforts carried on by many laboratories to attain a common goal. They are conducted in partnership with industry, university research centers, and other institutes of NIH. The special emphasis research programs are designed to intensify investigations of critical disease problems in urgent need of increased effort. Special emphasis research programs are also aimed at promoting the exchange of information to help identify and evaluate avenues of research that should be followed. The Institute also supports a large body of free-ranging investigator-inspired research.

The National Institute of Allergy and Infectious Diseases is requesting a total of $99,342,000 for 1972, a net increase of $1,218,000 above the 1971 level. This net increase is to be directed toward the following areas: (1) research grants +$867,000; fellowships -$245,000; and (2) laboratory and clinical research +$416,000; collaborative research and development +$68,000; review and approval of grants +$87,000 and program direction +$25,000.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Research projects.....	$47,439,000	$48,856,000	+$1,417,000
Special programs.....	8,613,000	8,063,000	-550,000
Total research grants.....	56,052,000	56,919,000	+867,000

Introduction:

The Extramural Programs of the National Institute of Allergy and Infectious Diseases provide research grant support to investigator initiated research projects in public or other nonprofit institutions as part of a coordinated attack on allergic, immunological, and infectious diseases of man. These programs seek to establish, expand, and improve research and training activities in disease problems of national importance. A number of urgent disease problems have been identified for special support. The Institute and its advisors selected these special programs not only because of the importance of the disease problem, but also because of recently identified research opportunities in these fields.

Allergy and Other Immunologic Disorders:

Transplantation Immunology

This special emphasis area is concerned principally with identification of the mechanisms of cellular immunity, without which the full potential of clinical transplantation cannot be realized. The basic components of this area are the isolation and characterization of the cell membrance histocompatibility antigens that determine the career and fate of lymphocytes; knowledge of the regulatory mechanisms that determine the transformation, by specific antigens, of quiescent small lymphocytes into new biosynthetic activities; and identification of the mediators of cellular immunity systhesized by immune lymphocytes following contact with antigen.

Impressive progress is being made in these three segments of this field, the majority of developments being promptly applicable to urgent clinical problems. This area is unique in the convergence of basic research and the solution of practical medical problems relative to autoimmune disease states, tumor immunity, homograft rejection, immunity to intracellular parasitism with bacteria, viruses and fungi.

This program area will be funded at a level of approximately $3,386,000 in 1971, and $3,429,000 in 1972, an increase of $43,000.

Allergic and Immunologic Diseases

This special emphasis area is concerned with primary immunological deficiency diseases that are genetically controlled abnormalities in the maturation of the immune system, and secondary immunological deficiencies resulting from naturally occurring diseases involving a mature immunological system. Failure of immune

competence can involve antibody deficiency syndromes or defects in the thymus-dependent cellular system. Loss of natural tolerance can occur and be expressed as autoimmune responses. Tissue injury with major consequences can develop following in vivo antigen-antibody reactions; i.e., immune complex disease.

There is continuing recognition of diseases with immunologic concomitants and the establishment of immunologic etiology for heretofore obscure disease states - particularly the immunologic consequences of chronic viral infection. It is now clear that immunologic diseases constitute a major segment of modern medicine.

This program area will be funded at a level of approximately $9,156,000 in 1971, and $9,274,000 in 1972, an increase of $118,000.

Viral Diseases and Problem Areas:

Interferon and Other Antiviral Substances

Diseases of viral origin constitute the largest single cause of morbidity in this country. In addition, there is accumulating evidence that many diseases of unknown etiology eventually may be shown to be of viral origin.

The great diversity of virus types necessitates the employment of broadly based alternative approaches in combating virus diseases. Drug screening, largely empirical, has revealed no drugs (with a few isolated exceptions) useful in combating viral diseases.

Interferon is an antiviral substance elaborated by the host cell in response to viral attack. It can also be induced by non-pathogenic agents or chemicals which stimulate the cell to manufacture this substance. We have current interest in the class of such compounds known as synthetic RNAs which induce interferon production in the cell. The use of these compounds represents one of the most interesting current advances in the search for antiviral substances. If certain problems of compound toxicity can be overcome, these substances may ultimately play a role in preventing and perhaps even treating viral infections in man. The induction of interferon through the use of these compounds is an illustration of how an understanding of the basic molecular biology of nucleic acids can contribute a practical method of coping with viral infections through disruption of the growth of the virus.

In the past the role of basic research in the development of antiviral substances has been limited, due largely to the lack of detailed information concerning viral protein structure and viral nucleic acid structure. This in turn has precluded the development of precisely defined modes of attack on the problem of selective inhibition of viral synthesis or function.

More recently, the increasing knowledge of the structure and metabolism of nucleic acid and protein syntheses has provided a large resource base of interest and an opportunity for new studies on antiviral activity through molecular biology. Additional information is needed concerning virus-specific features of viral macromolecules.

This program area will be funded at a level of approximately $4,949,000 in 1971 and $5,012,000 in 1972, an increase of $63,000.

Chronic and Degenerative Diseases

These diseases, because of their slow development and protracted course, are recognized as significant public health problems. Such problems as chronic renal diseases, degenerative diseases of the central nervous system (CNS), chronic vascular disease and connective tissue disorders all are part of this Special Emphasis area. Newer knowledge in this area tends to substantiate the role of infectious agents and immunologic aberrations as being of prime importance in their causation. Of basic importance in developing knowledge of these diseases are a number of natural and experimental animal diseases which, although not substituting for direct human studies, parallel the chronic and degenerative diseases of man. Scrapie, a degenerative CNS disease of sheep caused by a "slow" virus infection, has a direct bearing on demyelinating diseases of man such as multiple sclerosis. Equine infectious anemia, equine viral arteritis, and encephalomyocarditis of mice are research areas also being funded as model systems with great potential for understanding similar human diseases. Rapid progress in research on chronic and degenerative disease has been hampered by the inability to establish some of the infectious agents in tissue culture systems and in suitable animal models. It is gratifying to note a considerably increased interest and activity in this admittedly difficult research area. This Institute will continue in its efforts to stimulate further research and interest in chronic and degenerative diseases.

This program area will be funded at a level of approximately $1,563,000 in 1971, and $1,583,000 in 1972, an increase of $20,000.

Infectious Hepatitis

Infectious hepatitis is a disease of major public health importance, with approximately 45,000 cases being detected and 900 deaths occurring each year in the United States. Although this disease has been the target of intensive research by many capable investigators, only limited success has been achieved thus far; much more remains to be done in the study of this difficult disease entity. One new and very promising area in the field of hepatitis research is the recent discovery of the so-called Australia antigen, or the "hepatitis-associated antigen." Many research workers now believe that this virus-like agent, found in the serum of hepatitis patients, may be the actual causative agent, or an infectious entity closely related to it. As a result of this recent work, renewed interest in this area of research has been stimulated.

More sensitive and rapid methods for detection of the Australia antigen are being developed. It is hoped that these tests will be useful for detection of "carriers" of the agent in blood bank operations, thereby eliminating one major source of the disease. New research grant applications in this area are continuing to come to this Institute for funding as evidence of a renewed interest in hepatitis. It is the desire of this Institute to continue to stimulate and support such projects to the greatest extent possible.

This program area will be funded at a level of approximately $97,000 in 1971, and $101,000 in 1972, an increase of $4,000.

Parasitic Diseases and Problem Areas

Research on diseases caused by animal parasites seek new means of treatment

or control of parasitic infections. Animals serving as models produce information which is applied to research on such important human diseases as malaria, amebiasis and schistosomiasis.

Immunity to Animal Parasites

This special emphasis area encourages research leading to vaccination against many diseases which are caused by animal parasites. Present methods of treatment for these diseases are not satisfactory and many obstacles prevent development of drugs for large scale parasite control. It is therefore important that new means of immunization against parasites be investigated.

This program area will be funded at a level of approximately $1,503,000 in 1971, and $1,515,000 in 1972, an increase of $12,000.

Transmitters of Disease

Many human diseases, especially those caused by animal parasites or by viruses, are transmitted by insects, mites and ticks, or by snails. Research activity in this area seeks to control certain diseases by interrupting the transmission.

This program area will be funded at a level of approximately $1,700,000 in 1971, and $1,715,000 in 1972, an increase of $15,000.

Biological Regulation of Vectors

Recent publicity on dangers of using DDT and certain other insecticides emphasizes the need for research on control of such disease vectors as insects and snails. This area has been designated as one for special emphasis to encourage research on chemicals determining vector behavior, hormones affecting vector development, and genetic regulation of vectors.

This program area will be funded at a level of approximately $1,510,000 in 1971, and $1,524,000 in 1972, an increase of $14,000.

Bacterial and Mycotic Diseases

Streptococcal Diseases and Sequelae--Studies on the relationship of the biological and epidemiological characteristics of group A streptococci to their role in the pathogenesis of acute rheumatic fever, rheumatic heart disease and acute glomerulonephritis should be intensified. Many gaps remain in our knowledge of the various components and products of these organisms. The mechanisms by which these infections result in serious non-suppurative complications are not clear. Consequently, ways to improve control of the diseases remain uncertain.

Accumulating epidemiological and immunologic evidence suggests that certain strains are nephritogenic while others are rheumatogenic. Perhaps there are strains which have the potential to be involved in both of these sequelae and some that cause neither. Clarification and extension of our fundamental knowledge of streptococcal infections is highly important.

This program area will be funded at a level of approximately $984,000 in 1971 and $1,013,000 in 1972, an increase of $29,000.

Drug Resistance--Bacterial and fungal infections, once considered a minor problem on the verge of extinction as a result of the new antibiotics, have become extremely troublesome, and in many situations life-threatening. Many of these very serious infections arise in patients undergoing immunosuppressive therapy or suffering from naturally altered immune responses.

Hospital acquired infections are now a worldwide problem, with an increasing annual frequency. In large city hospitals, for example, 15% of infections are hospital-acquired, either through the airborne route or through medically necessary manipulative procedures. The financial and medical resources thus wasted are cause for concern. The pathogenic organisms involved are primarily common opportunistic pathogens, normally of little significance except to the seriously ill or to the immunologically compromised patient. It can be expected that staphylococcal strains and fungal organisms in hospitals, resistant to the newer drugs, will emerge; therapy for these common hospital-acquired infections will therefore become more difficult.

Continuing research to combat these drug-resistant microorganisms and to understand the nature of hospital-acquired infections will continue to be one of the Institute's major goals.

This program area will be funded at a level of approximately $6,396,000 in 1971, and $6,478,000 in 1972, an increase of $82,000.

Special Programs

General Research Support Grants--A level of support of $4,494,000 is proposed for 1972, a reduction of $550,000 from the 1971 level of $5,044,000.

These funds represent the Institute's proportionate share of the proposed budget for this program.

Categorical Clinical Research Centers--$1,266,000--The same level of support, $816,000 is continued from 1971 to 1972 for centers participating in multidisciplinary investigations brought to bear on disease areas of critical need, including transplantation immunology and allergies.

During the 1971 hearings before the Committee on Appropriations the need for Allergic Disease Centers was explained and justified. At the strong recommendation of the Committee the Institute has established an Allergic Disease Centers program.

Asthma and other allergic disorders affect at least 31 million Americans - asthma alone causes 4,000 deaths a year and disables many thousands more. Significant advances in new knowledge of the immunological events related to these disorders have been made in recent years. The time is opportune to extend this capability to improved prevention, diagnoses and treatment. Accordingly the Institute is broadening its clinical allergy program in 1971 by the establishment of a small number of Allergic Disease Centers which purposely combine high scientific competence in immunology and experienced clinical expertise to develop better methods of management of allergic disorders. Such Centers under the Categorical Clinical Center Program will also provide unique training opportunities for clinical investigators and will upgrade the quality of health care provided patients with these diseases. In 1971 five Centers will be established at a total cost of $450,000. In 1972, it is planned to continue these Centers and possibly increase the number of Centers.

International Centers for Medical Research and Training--This program promotes research and research training of United States scientists in selected foreign settings under the sponsorship and direction of four American universities and with cooperating foreign institutions and investigators. During 1971 the Program was broadened to offer scientific opportunities for investigators from all U. S. medical schools and schools of public health. The Centers now in operation provide unusual experience and exceptional biomedical research opportunities for American physicians and scientists for the long range interests of the United States. This program area will be funded at a level of $2,263,000 in 1971 and 1972.

Research Grants Program Analysis

Fields	1971 Estimate	1972 Estimate	Increase or Decrease
Allergy and other immunologic disorders	$12,542,000	$12,703,000	+$161,000
Transplantation immunology	(3,386,000)	(3,429,000)	(+43,000)
Bacterial and Mycotic diseases	16,401,000	16,611,000	+210,000
Streptococcal diseases and sequelae	(984,000)	(1,013,000)	(+29,000)
Drug resistance	(6,393,000)	(6,478,000)	(+82,000)
Viral diseases and problem areas	12,223,000	13,191,000	+968,000
Infectious hepatitis	(97,000)	(101,000)	(+4,000)
Chronic and degenerative diseases	(1,563,000)	(1,583,000)	(+20,000)
Antiviral substance	(4,949,000)	(5,012,000)	(+63,000)
Parasitic diseases and problem areas	6,273,000	6,351,000	+78,000
Biological regulation of vectors	(1,510,000)	(1,524,000)	(+14,000)
Immunity to animal parasites	(1,503,000)	(1,515,000)	(+12,000)
Transmitters of disease	(1,700,000)	(1,715,000)	(+15,000)
Subtotal	47,439,000	48,856,000	+1,417,000
General research support	5,044,000	4,494,000	-550,000
Scientific evaluation	40,000	40,000	---
Categorical clinical research centers	1,266,000	1,266,000	---
International Centers for Medical Research and Training	2,263,000	2,263,000	---
Total, research grants	56,052,000	56,919,000	+867,000

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Noncompeting	788	$29,792,000	834	$32,693,000	+46	+$2,901,000
Competing	410	17,537,000	405	16,053,000	-5	-1,484,000
Supplementals	(8)	110,000	(8)	110,000	--	---
Subtotal regular programs	1,198	47,439,000	1,239	48,856,000	+41	+1,417,000
General research support		5,044,000		4,494,000		-550,000
Scientific evaluation	(1)	40,000	(1)	40,000		---
Categorical clinical research centers	8	1,266,000	8	1,266,000		---
International centers for medical research and training	4	2,263,000	4	2,263,000		---
Subtotal special programs	12	8,613,000	12	8,063,000		-550,000
Total research grants	1,210	56,052,000	1,251	56,919,000	+41	+867,000

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Total fellowships.....	$3,579,000	$3,334,000	-$245,000

The primary objective of the Fellowships Program is to increase the availability of trained professional researchers in research areas within the categorical interests of the Institute. The Program is an integral portion of the research grant and training activities which are supported by the Institute.

The postdoctoral fellowships support postdoctoral training for PH.D's and those holding other equivalent degrees. Special fellowships are for those who can justify that additional training is needed to increase their value as independent investigators. Research career development awards are for support of young investigators who plan to pursue careers in independent research and teaching and who need further experience and training.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting....	144	$2,932,000	135	$2,625,000	-9	-$307,000
b. Competing.....	5	44,000	5	44,000	--	---
2. New.....	54	603,000	46	665,000	-8	+62,000
Total.....	203	3,579,000	186	3,334,000	-17	-245,000

Fellowships (by type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Postdoctoral.....	72	$620,000	61	$520,000	-11	-$100,000
2. Special.....	31	369,000	25	299,000	-6	-70,000
3. Research career:						
a. Career.....	17	530,000	17	530,000	--	---
b. Development...	83	2,060,000	83	1,985,000	--	-75,000
Total.....	203	3,579,000	186	3,334,000	-17	-245,000

Fellowships Program Analysis

Fields:	1971 Estimate	1972 Estimate	Increase or Decrease
1. Allergy and Immunology.....	$1,039,000	$967,000	-$72,000
2. Bacteriology and Mycology.....	964,000	897,000	-67,000
3. Biochemistry and Physiology....	610,000	570,000	-40,000
4. Parasitology and Medical Entomology.....	358,000	333,000	-25,000
5. Virology and Rickettsiology....	608,000	567,000	-41,000
Total.....	3,579,000	3,334,000	-245,000

Training Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Total Training Grants.....	$7,280,000	$7,280,000	---

The Institute's Graduate Training Grant Program assists qualified public and non-profit institutions to establish, expand and improve training opportunities in the fields of allergy, immunology, infectious diseases, tropical medicine parasitology, and other areas of special research emphasis of the Institute. A highly trained and well-qualified pool of manpower is produced to insure the necessary scientific base for future research in these biomedical specialties. The number of individuals well-qualified for careers in teaching and related patient-care activities is also increased.

Distribution of Training Grants

	1971 Estimate			1972 Estimate			Increase or Decrease		
	No. FTE	No. Proj.	Amount	No. FTE	No. Proj.	Amount	No. FTE	No. Proj.	Amount
1. Continuations:									
a. Noncompeting..	774	129	$5,746,000	738	123	$5,625,000	-36	-6	-$121,000
b. Competing.....	108	18	997,000	120	20	1,081,000	+12	+2	+84,000
2. Supplementals....	(36)	(6)	60,000	(48)	(8)	60,000	--	--	---
3. New.....	78	13	427,000	84	14	464,000	+6	+1	+37,000
4. Scientific evaluation.....		(1)	50,000		(1)	50,000	--	--	---
Total, Training Grants.....	960	160	7,280,000	942	157	7,280,000	-18	-3	---

Training Grants (by type of program)

	1971 Estimate			1972 Estimate			Increase or Decrease		
	No. FTE	No. Proj.	Amount	No. FTE	No. Proj.	Amount	No. FTE	No. Proj.	Amount
1. Graduate.....	960	160	$7,230,000	942	157	$7,230,000	-18	-3	---
2. Scientific evaluation.....		(1)	50,000		(1)	50,000	--	--	---
Total, Training Grants.....	960	160	7,280,000	942	157	7,280,000	-18	-3	---

Laboratory and Clinical Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	576	$7,899,000	576	$8,307,000	---	+$408,000
Other expenses.....	---	9,430,000	---	9,438,000	---	+8,000
Total.....	576	17,329,000	576	17,745,000	---	+416,000

Introduction

The research effort of the intramural program of this Institute is wide ranging. Laboratory scientists and clinical investigators, representing many disciplines, direct efforts to the discovery and exploitation of new knowledge leading to the eventual prevention and treatment of diseases caused by infection with microorganisms or abnormal immunological mechanisms. The program embraces both basic and applied research. Emphasis is on those problems difficult to accomplish under the research grant mechanism. New infectious agents are discovered, the role of new or previously recognized agents in human disease evaluated, new or improved diagnostic technics developed, host-parasite relationships studied, and therapeutic agents evaluated in animal models and human subjects.

The Institute's intramural scientific program constitutes a vital bridge between the basic research of academic institutions and applied research and technical development as represented in the Institute's collaborative research program. Collaborative programs often originate in intramural laboratories and the scientists act as both technical advisors and project officers on contracts implementing the collaborative program.

The research of intramural scientists forms an important element of the national health effort and is transmitted to the biomedical community in the more than 300 scientific publications annually contributed by the professional staff, at national and international meetings and in a wide variety of smaller meetings and seminars. In past years these contributions have made possible the solution of many problems such as epidemics of adenovirus infections and mycoplasma pneumoniae in military recruits, and Rocky Mountain Spotted Fever in civilian populations; have led to the discovery in our own laboratories of over one-half of the viruses known to cause acute respiratory infections in man, opening up the current efforts of vaccine development; have discovered and provided a method for the control of Bolivian Hemorrhagic Fever; and have provided new diagnostic and therapeutic methods to the medical profession.

Infectious diseases no longer are the major cause of death in the United States but continue to be major causes of morbidity and are responsible for a major percentage of medical costs to the public. Viruses are responsible for a high proportion of the acute illnesses. The more recent evidence for viral persistence as the underlying cause of such problems as mental retardation, progressive neurological and other degenerative diseases, and for certain types of cancer has directed the attention of intramural scientists to the difficult

problems of how to diagnose and treat such viral infections. In addition to the extensive studies on slow virus diseases in animals which are models for the chronic diseases which may be caused by some viruses in man, NIAID scientists are engaged in studies of the control of viral replication using various chemical compounds or enzymes to alter the process, and as to how new immune mechanisms may be involved to halt viral damage to the host. Interferon, a naturally occurring antiviral substance in man and animals is being intensively studied and Institute scientists have led the effort to study mechanisms for inducing interferon in man and as to whether this may provide an effective means of prevention or treatment.

Immunology has been the most rapidly developing branch of biomedical science in recent years and again the scientists of this Institute have played a major role in bringing advances to bear on the problem of infection, showing that ineffective vaccines can cause an infection to worsen and that immune mechanisms at the cell surface instead of in the blood are necessary in the prevention of some virus infections. Immunological studies also support the transplantation immunology collaborative program and are beginning to define a number of the fundamental mechanisms of hypersensitivity and allergic reactions and allergy.

Laboratory and clinical research of this Institute continues to maintain field stations in Honolulu, Hawaii; Hamilton, Montana; Atlanta, Georgia; and the Panama Canal Zone. In these field locations unique opportunities are available for special epidemiological and/or laboratory studies utilizing the special environments. At the Pacific Research Section in Honolulu, studies on parasites and viral diseases are being conducted. Its special capabilities have also made it possible to initiate investigations on the biological control of mosquitoes that transmit disease. The Rocky Mountain Laboratory in Montana provides special facilities not available in Bethesda for the study of hazardous agents such as Q-fever, tuberculosis, and "slow" viruses. Atlanta provides opportunity for therapeutic studies on drug resistant malaria which has been of military, as well as civilian, importance. The Middle America Research Unit in the Panama Canal Zone affords special field opportunities to work with insect-transmitted diseases and their animal reservoirs.

The Institute also has the delegated responsibility for the Pakistan-SEATO Cholera Research Program and the Pakistan-SEATO Cholera Research Laboratory (PSCRL) in Dacca, East Pakistan. Significant advances in the understanding of the epidemiology and immunology of cholera have been achieved at PSCRL as well as testing of standard and experimental vaccines. The SEATO Cholera Research Program, coordinated with the U.S.-Japan Cholera Research Program in NIAID, is developing a toxoid which may neutralize the toxin responsible for the lethal diarrhea and afford a prolonged immunity. One of the most significant advances for the developing countries has been development of a method for oral fluid therapy which enables the intravenous fluids required to be reduced by 70 to 80 percent. Even in countries which have no capability for manufacture, distribution and administration of intravenous fluids, oral therapy by the methods, demonstrated now in several thousand patients, will afford significant reduction in mortality and has been adopted by the World Health Organization.

Program Plans in 1971 and 1972

Program plans for 1971 and 1972 are for continued redirection of the program

towards those infections and immunologic disorders which are major problems.

Clinical Allergy and Immunology

The research program in allergy will be expanded as young scientists trained under Institute auspices both at the NIH and in academic centers can be enlisted to enhance the effort. An additional senior clinical investigator with expertise in the problems of clinical allergy is under recruitment and research on the problems of asthma, hayfever, and other allergies will be accelerated as rapidly as resources allow. This joint effort by the Laboratory of Clinical Investigation and the Laboratory of Immunology is being mounted in recognition of the opportunities which have been created by advances in fundamental knowledge regarding hypersensitivity which should enable many of the problems of allergy to be solved or at least minimized during the decade of the 70's. These laboratories along with the Laboratory of Microbial Immunity will continue their work to better define the mechanisms involved in the immune rejection of organ transplants and in the better understanding of the immunological processes by which tumors, infectious agents, and parasites are controlled and/or destroyed in the host. Recent findings indicating that the polysaccharides from pneumococci which are under development as a vaccine stimulate immune mechanisms differing from those of other vaccines will be accelerated because of the importance to the vaccine effort.

Twenty senior scientists and 27 junior scientists are carrying on a total of 38 distinct research investigations in these efforts and nearly 25% of the Institute's intramural financial resources are involved in their support. This represents an approximate 5% increase in level of effort over the past two years and will gradually further increase during the next year. Institute scientists also cooperate in research towards the immunoprophylaxis or immunotherapy of cancer since this is closely related to the mechanism by which the body combats other foreign organisms or abnormal cells. Promising leads are being pursued in the prevention of leukemia through immunization.

Viral, Mycoplasmal and Rickettsial Disease

Because viral infections remain a major cause of sickness and medical workload in civilian medical practice as well as being a significant cause of more serious disease, the Institute will continue to give emphasis to the unsolved problems including those of isolating the still elusive viruses responsible for many respiratory infections, a major part of the acute hepatitis cases, epidemic gastroenteritis and "slow" virus diseases. Also since there is a pressing need for effective treatment, the Institute will continue to emphasize its efforts to develop therapeutic methods.

Methods for attenuating viruses causing acute respiratory diseases have been developed which restrict the growth of these viruses to the nose. Respiratory syncytial (RS) viruses damage the lungs, causing serious illness and death in babies. Exploration of attenuated RS viruses will be continued in collaborative studies to find one which can create immunity in infants without causing illness. Similar efforts are underway and will be continued with parainfluenza viruses (the cause of croup), influenza viruses, and mycoplasma.

Studies on epidemic gastroenteritis will be continued. Infectious material

blood leukocyte, the role of these in the immunosuppressed patient is being studied. Infections are major problems in cancer patients undergoing chemotherapy or extensive irradiation and in patients under immunosuppression after transplant. Susceptibility may reside in preventable defects in the defense system and this will be actively pursued since antibiotic resistant organisms are the major cause of these infections in hospitals.

Parasitic Diseases

The breakthrough which will enable definition as to whether the domestic cat is responsible for the high rate of toxoplasmosis in man in the United States is being followed up, as are studies on how the disease may be eliminated from the cat.

Several parasitic diseases are of interest to allergy research because of the marked degree of hypersensitivity which marks the disease. These are being explored as possibly providing animal model systems.

The level of effort in both bacterial and parasitic diseases is expected to remain the same or decline slightly from their present level of utilizing about 20% of the Institute's intramural financial resources.

The net increase of $416,000 includes $27,000 for one additional day of pay in 1972; $125,000 for within grade increases; $23,000 for wage board pay increases; $8,000 for Federal Telecommunications system (FTS) increased costs; $274,000 for annualization of 1971 pay increase costs; and $114,000 to the National Institutes of Health Management fund for centrally furnished services, and a decrease of $155,000 in lower priority contractual support.

Collaborative Research and Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	36	$600,000	36	$663,000	---	+$63,000
Other expenses.....	--	11,061,000	--	11,066,000	--	+5,000
Total.....	36	11,661,000	36	11,729,000	--	+68,000

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 immunologic and infectious diseases. It conducts and supports developmental research in the prevention, control and treatment of diseases caused by infectious agents including bacteria, viruses and parasites, and by abnormalities in the body's immune mechanisms. These activities are carried out through research contracts with industry and other Federal and non-Federal institutions. The research areas presently encompassed by the Collaborative Research Program are Transplantation and Immunology, Infectious Disease, Research Resources, and Geographic Medicine.

The primary priority of the Transplantation and Immunology Program has been to determine the utility of histocompatibility matching in the selection of tissues for human transplantation. Studies of the tissue types of donors and recipients and the continuing evaluation of recipients of typed tissues indicate the utility of matching and the relative importance of the number of tissue antigens in the organs of transplant donors and recipients. There has been a continuing increase in the utilization of the tissue typing reagents and the development of the NIH trays has provided a rapid, accurate convenient method for donor-recipients matching at transplant centers.

The Infectious Diseases Program has been broadened so that the original emphasis on developing vaccines against virus diseases now includes an attack on virus diseases through the use of antiviral substances and on bacterial diseases with vaccines against pneumococcal, streptococcal, hemophilis and influenza infections.

While the original mission of the Research Resources Program was to produce, test and distribute virus reagents, the activities now include reagents for mycoplasma, allergens and the Australia antigen which is associated with serum hepatitis. The Research Resources Program is also responsible for the management of the NIAID Molecular Anatomy Laboratory, which is designed for the purification, concentration and analysis of viruses, vaccines and reagents.

The U. S.-Japan Cooperative Medical Sciences Program is a scientific collaborative effort concerned with diseases of substantial health importance to Asian countries. The diseases or categories of diseases are 1) cholera, 2) leprosy, 3) malnutrition, 4) parasitic diseases and 5) tuberculosis and viral diseases.

known to contain a virus will be intensively studied by new technics or organ culture and viral concentration. This virus may become a candidate for a vaccine since the disease follows closely the respiratory diseases in morbidity in children.

"Australia Antigen" although patently related to acute hepatitis has not been proven to be a virus or cultured in vitro. Again, intensive efforts with organ cultures and other new technics for viral recovery will be pursued to identify the actual virus so that efforts on a vaccine can start. Work to improve diagnostic tests will be continued until the subtypes are identified and practical methods developed for use in blood banks and other diagnostic laboratories. Efforts to identify the still unknown viruses which cause other types of hepatitis will also be continued.

Work on influenza will be reoriented during the year to focus more clearly on the expected pandemic outbreak in the late 1970's and to develop methods that will enable the Department to offer better solutions to the public than has been possible in the past. This research will explore methods for creation of new influenza strains for use in vaccines, for immunological enhancement and non-specific immunity as mechanism for obtaining better protection, and for new treatment methods. The interferon system and means of enhancement of interferon production are currently under study both from the standpoint of prevention and treatment of influenza in man. These studies will be continued during the coming year using new methods of induction of interferon.

Much of the basic research in virology in the Institute's laboratories relates directly to the problem of virus induced cancer. This includes not only the studies on the mechanisms by which certain viruses are able to render normal cells malignant but cooperative studies on the role of poly I: poly C in the treatment of human cancer, work growing out of original studies by an Institute scientists in animals.

Nearly 50 of the senior professional staff of the Institute are involved in virological research conducting a total of about 62 distinct investigative efforts and consuming about 30% of the total resources available to the Institute's intramural program. The level of effort is expected to remain relatively stable during the next year.

Bacterial and Mycotic Diseases

Work on the non-living tuberculosis vaccine is now concentrated on a biochemical effort to separate the fraction responsible for protection from the rest of the cell wall of the tubercle bacillus. The whole cell wall cannot be used in an acceptable vaccine because of reactions in the lung of animals which are not related to the protective factor. New methods have been developed for the separation process and considerable progress should be made in study of the various fractions.

Effective use of pneumococcal vaccines will require the development of new tests for immune response in recipients of the vaccine. Several new methods are under study and one or more should be developed to the point of practical use during the next year.

Since major defenses against bacterial infections reside in the cell and the

Program Plans in 1971 and 1972

Allergy and Other Immunologic Disorders:

The primary mission of the Transplantation Immunology Program is to develop and manage a program designed to apply knowledge in immunology toward facilitating the transplantation of human organs and to develop and improve methods to diagnose, treat and prevent immunologic diseases.

Major emphasis will continue to be placed on the acquisition and distritubion of high-quality matching sera. Continued support will be provided for the search for new histocompatibility specificities and, with the development of improved technics for quality control, more reliable monospecific histocompatibility typing sera will be obtained. Freeze-dried sera, packaged in bulk and in preloaded trays, will be distributed to qualified investigators, thus permitting a more rapid performance of the typing procedures. Data concerning the utility of the trays and the outcome of transplants will be obtained by the program to determine the relative importance of various histocompatibility antigens. More sophisticated quality-control techniques will be used to check the stability of sera in clinical usage and the accuracy and the reproducibility of the typing results of various laboratories. A limited number of program-supported research laboratories will be funded to conduct research in the efficacy of typing and to develop and compare a variety of new technics. Support will not be provided for the operation of typing service laboratories. In a joint NIH effort, support will be provided for the collection of clinical and immunological data on a variety of human organ transplants.

An increasingly larger percentage of the budget will be spent in the development of facilities to test and evaluate the efficacy of new immunosuppressive therapies. More potent drugs, antilymphocyte sera and soluble antigens preparations will be studied first in sub-human primates and eventually in human transplant patients. The ultimate goal of this program is to provide safe and more effective means of preventing and treating graft rejection.

The Institute will continue to support, on a small scale, investigations into the immunological consequences of transplantation. These include: studies of the reoccurrence of primary disease in immunosuppressed patients, graft versus host disease, and a systematic evaluation of some of the more rare immunological changes seen in transplant patients. These studies will lead to a more thorough understanding of the mechanisms of graft rejection and may be useful in the early diagnosis of complications in transplant patients. Studies in the solubilization of histocompatibility antigens, their characterization and biologic testing will be expanded. Soluble antigens obtained will be used to produce specific histocompatibility antisera and also study the induction of specific tolerance in animals.

Through the Research Resources Program the Institute has produced and is now prepared to distribute a highly purified ragweed pollen known as Antigen E. This material will be evaluated both in the research laboratory and in clinical research in human allergic disorders. Other ragweed antigens including Antigen K and RA-3 will be purified, tested and distributed for research in allergic disorders. Efforts in developing and evaluating purified allergy reagents and improved allergy test systems are closely linked to the Institute's developing program for support of centers for research in allergy.

Viral, Mycoplasmal, Bacterial and Rickettsial Diseases:

The Infectious Diseases Branch will be concentrating on 3 major areas for development: (1) Virus Vaccines - The Institute will continue to develop and evaluate vaccines designed to protect pediatric populations, in particular against respiratory diseases due to Respiratory Syncytial virus, parainfluenza and adenovirus. Efforts will continue in the comparative studies on various methods for immunizing against smallpox for the purpose of finding a vaccine strain and method of injection which will lessen the risk of adverse reactions. The Institute will develop a program to utilize existing knowledge and promote needed research for the purpose of lessening the impact of the expected pandemic outbreak of influenza. (2) Bacterial and Mycoplasma Vaccines - The Institute will evaluate on an increasing scale the vaccine which it has had produced against pneumococcal pneumonia. After safety and efficacy testing is complete the pneumococcal vaccine will be field tested in populations in which pneumococcal infections are a serious health problem. Studies and surveys to date indicate that pneumococcal infections are a serious health problem in selected populations causing pneumonia, otitis media and meningitis and having considerable economic impact because of the hospitalization required in patients.

The Institute plans to conduct safety and efficacy studies on a vaccine against meningococcal meningitis. Two strains of this vaccine have already been produced for military use and the Institute will evaluate the same vaccine in young adults and children. Should these preliminary tests be successful, the Institute will procure additional lots of vaccine, including quantities representing a third strain.

The Institute will initiate testing and possible scaled up production for a vaccine against meningitis due to H influenzae. This is a serious crippling disease of children that is probably preventable by immunization.

Among the important causes of pneumonia is the organism Mycoplasma pneumonia. A new vaccine being developed through the Institute's Collaborative Research Program is expected to provide an effective means of control. Small lots have been prepared, tested and demonstrated to be capable of producing protective antibody. It is planned that developmental studies will lead to scaled up production and evaluation efforts in 1972. (3) Antiviral Substances - As a result of research efforts supported to a large measure by NIAID grants and a strong intramural base, a systematic contract program has been launched to develop and test a variety of chemical and biological materials having potential use in preventing and treating viral diseases. Greatest potential application for the antiviral substances is in diseases not readily preventable through vaccines. The Institute plans on moving from a materials-production phase to new phases, including evaluation of the antivirals in animal models; theraphy of human disease; improved production purification and assay methods; a search for means of enhancing effectiveness and reducing toxicity of materials; and investigation of potential antivirals.

Through the Research Resources Program, the NIAID will continue to distribute and evaluate the interim reagents which it has produced for the Australia Antigen (Au) associated with serum hepatitis. These critically needed reagents will be supplemented with reagents that are even more sensitive in detecting Au antigen-containing blood. Elimination of Au positive blood donors has already reduced hepatitis acquired through blood transfusions. Concerted efforts will be made to purify the Au antigen and elucidate its physical, chemical and biological nature, this is actively being carried out in the Institute supported AEC-NIAID Molecular

Anatomy Laboratory. It is planned to support efforts to propagate hepatitis virus in cell culture and animal model systems, recognizing that only through breakthroughs in this area can a vaccine against hepatitis be realized.

The Geographic Medicine Branch manages a research program designed to study diseases affecting the health of millions of people in the world. The various projects are supported by a carefully coordinated grant and contract program. Data reported at Workshops, Conferences, and Joint U.S.-Japan Meetings indicate advances in each of the disease categories being pursued.

In cholera research, progress has been made in each of the three major priority areas, including the development of a more effective vaccine, the delineation of the mechanism by which the cholera toxin causes intestinal fluid loss, and the isolation of bacterial exotoxins responsible for non-vibrio, cholera-like disease. Following the initial suggestion that the exotoxin induced electrolyte secretion is mediated by cyclic adenosine monophosphate, it has been clearly demonstrated that gut electrolyte secretion can be initiated by other agents which increase intracellular cyclic adenosine monophosphate levels. As the result of studies in this area, a number of agents known to inhibit intracellular cyclic adenosine monophosphate accumulation are now being investigated to ascertain their possible practical value in rapidly blocking the gut fluid loss in cholera patients. Except during major cholera epidemics, the so called cholera-like diseases result in greater morbidity and mortality than endemic cholera infections. A number of carefully designed studies of the pathogenetic and immunologic aspects of cholera-like diseases are currently underway.

In the field of leprosy investigators continue to make progress in major priority areas including pharmacology of antileprotic drugs, chemotheraphy trials with promising new compounds, cultivation of the leprosy bacillus in vitro and in vivo, and the role of the immune mechanism in this disease.

Recent investigations have shown that the principal metabolite of dapsone (DDS) in plasma, MADDS (monoacety l DDS) is enzymatically acetylated by the same enzyme system which acetylates isoniazid and sulfonamides. Preliminary information obtained from a clinical trial using various doses of clofazimine (B663) indicate that this drug is effective, although long-term follow-up will be necessary before a final evaluation can be made. In an attempt to prevent the emergence of drug resistance, combinations of antileprotic drugs will be used in chemotherapy trials. Specially, a trial is planned using DADDS and rifampin, a drug used successfully in treating tuberculosis. Leprosy patients often demonstrate deficient cellular immunity and attempts now focus on the mechanisms underlying this deficiency.

Additional data confirm earlier reports that severe Malnutrition during the first two or three years of life, even though dietary adequacy is later provided, has a lasting detrimental effect upon intelligence and behavior in later life. It is anticipated that highly sophisticated neuropsychiatric and neurophysiologic methodolgy currently being developed and applied will provide the basis for more exacting quantification of brain functions and allow more precise evaluation of the influence of early malnutrition thereon. Also under investigation in several countries is the prevalence and frequency of iron and protein deficiency in children and of folic acid deficiency in pregnant women. Other research in progress endeavors to explain, and find means of correcting, the poor absorption of iron from cereal grains.

Parasitic disease research is limited to schistosomiasis and filariasis. During the past year, new compounds have been developed and tested against schistosomiasis. One study is exploring the relationship between chemical structure and configuration compared against antischistosomal activity in vitro of heterocyclic compounds. Work is in progress to develop an economical "bait" formulation containing molluscicidal compounds for the snail vectors of schistosomiasis in order to eliminate the environmental contamination resulting from current snail control procedures. Efforts have continued to synthesize antifilarial drugs, which have been thoroughly tested in animal models. Although no compounds have been demonstrated to be more active than diethylcarbamazine, these studies are adding to the limited knowledge in this field.

Tuberculosis research work has been limited to the pathogenic and immunologic aspects of tuberculosis. An important objective of the program is to find a practical animal model which gives results relevant to the immunity that exists in humans against naturally acquired tuberculosis infection. With such a model, improved tuberculosis vaccines, both living and non-living, could be developed for clinical use. In order to encourage and stimulate studies of the immunology of tuberculosis and the basic mechanisms of cellular and humoral responses to infection and disease, special reagents, difficult to prepare and not readily available, have been made available to qualified investigators. These include: living, frozen mycobacterial cells of the Glaxo vaccine strain of BCG; lyophilized PPD tuberculin; a large number of fully characterized mycobacterial strains; and specific rabbit antisera against many strains of mycobacteria. A reference kit, including antigen and antiserum, has been prepared and is being tested by a number of investigators as a possible reference system in the study of mycobacterial antigens.

During the past year, the guidelines of the viral diseases program were revised to limit the areas of scientific involvement to rabies and the arboviruses, with emphasis on dengue and the pathogenesis of hemorrhagic fever. Progress has been been made in these areas and is expected to continue during the coming year.

The increase of $68,000 includes $2,000 for one additional day of pay in 1972, $9,000 for within grade increases, $52,000 for annualization of 1971 pay increase costs, and $5,000 to the National Institutes of Health Management fund for centrally furnished services.

Review and Approval of Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	43	$662,000	43	$703,000	---	+$41,000
Other expenses	--	965,000	--	1,011,000	---	+46,000
Total	43	1,627,000	43	1,714,000	---	+87,000

These funds provide 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 Diseases 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 grant management.

The increase of $87,000 includes $2,000 for one additional day of pay in 1972, $10,000 for within grade increases, $29,000 for annualization of 1971 pay increase costs, and $46,000 to the National Institutes of Health Management fund for centrally furnished services.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	32	$489,000	32	$510,000	--	+$21,000
Other expenses	--	107,000	--	111,000	--	+4,000
Total	32	596,000	32	621,000	--	+25,000

These funds provide for the support of the Institute Director and his immediate staff, including public and scientific information activities, in the overall administration, coordination and direction of all the Institute's activities. The increase of $25,000 includes $2,000 for one additional day of pay in 1972, $6,000 for within-grade increases, $13,000 for annualization of 1971 pay increase costs, and $4,000 to the National Institutes of Health Management fund for centrally furnished services.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Research Grants - (Public Health Service Act, Title IV - Part D.)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$56,052,000	Indefinite	---	$56,919,000

Purpose: The purpose of the Research Grants Program is to support research on the causes, characteristics, prevention, control, and treatment of diseases believed to be caused by infectious agents including bacteria, fungi, viruses, and parasites --or by abnormalities in the body's immune mechanism such as allergies.

Explanation: The Institute sponsors over 1,200 research projects at universities, hospitals, research institutions and other private or non-profit institutions. Grant supported projects vary from the relatively circumscribed activities of an individual scientist to broadly-based programs that integrate the effort of groups of investigators in a variety of scientific disciplines.

Accomplishments in 1971: The Institute continued its efforts to stimulate further research and interest in transplantation immunology, allergic and immunologic diseases, chronic and degenerative diseases, bacterial and mycotic diseases, viral diseases and problem areas, parasitic diseases, and provided special research grant support for the Gorgas Memorial Institute, Categorical Clinical Research Centers and International Centers for Medical Research and Training. Management of the Gorgas Memorial Institute was transferred to the Fogarty International Center in 1971.

Objectives for 1972: The program for 1972 is designed primarily at maintaining the basic research program close to its present level, while increasing selected areas of high priority. Special programmatic emphasis will center on transplantation immunology, viral, bacterial and mycotic, chronic and degenerative diseases, and clinical allergy areas.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Fellowships - (PHS Act, Title IV, Part D.)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$3,579,000	Indefinite	---	$3,334,000

Purpose: The Fellowship Program purpose is to raise the level of competence and increase the availability of trained professional researchers in research areas within the categorical interests of the Allergy and Infectious Diseases Institute.

Explanation: This program supports (a) postdoctoral awards for the training of PH.D's, M.D. and those holding other equivalent degrees, (b) special awards for those who can justify that additional training is needed to increase their value as independent investigators and whose needs are not met by other fellowship programs, and (c) Research Career Development awards for support of young investigators who plan to pursue careers in independent research and teaching and who need further experience and training.

Accomplishments in 1971: This Institute will support approximately 203 fellowship awards in the following areas of concern: Allergy and Immunology, Bacteriology and Mycology, Biochemistry and Physiology, Parasitology and Medical Entomology, and Virology and Rickettsiology.

Objectives for 1972: Funds requested in 1972 would support 186 awards.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Training Grants - (PHS Act, Title IV, Part D.)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$7,280,000	Indefinite	---	$7,280,000

Purpose: The general purpose of these awards is to support graduate training leading toward careers of research related to medicine and health, or toward increased competence in the treatment of diseases of rapidly expanding areas of prime concern, such as immunology and virology.

Explanation: Graduate training grants are awarded to assist public and other nonprofit institutions to establish, expand, or improve training opportunities in the health related sciences for persons interested in careers in research, teaching, and in certain designated areas, clinical service. In addition to providing support of the institutions program, these grants may also provide funds for stipends and allowances awarded by the institution to trainees selected by the institution.

Accomplishments in 1971: The Institute will make approximately 160 separate awards to provide training support for the full-time equivalent of 960 trainees in areas of special interest to the Institute.

Objectives for 1972: Funds requested for 1972 would provide the same dollar level as in 1971 and will support 157 awards and result in the training of approximately 942 trainees.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Laboratory and Clinical Research - (PHS Act, Title IV, Part D.)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
576	$17,329,000	Indefinite	576	$17,745,000

Purpose: This activity involves research performed by scientists and other research personnel of the Institute's intramural staff who are assigned to the Institute's various laboratories and the central clinical facility.

Explanation: The Laboratory and Clinical Research activity is conducted at laboratories in Hamilton, Montana; Honolulu, Hawaii; Atlanta, Georgia; and the Panama Canal Zone, as well as Bethesda, Maryland. These research efforts are directed to the discovery and exploitation of new knowledge leading to the eventual prevention and treatment of diseases caused by infection with microorganisms or by abnormal immunological mechanisms, and embraces both basic and applied research.

Accomplishments in 1971: Attenuated strains of respiratory syncytial (RS) virus were used as a live vaccine in children down to the 2-year old age range in a collaborative research program at Childrens Hospital in Washington without causing illness or other ill effects. A new and more sensitive test system for "hepatitis associated antigen" was validated and enabled demonstration of immunity in both chimpanzees and man which had been missed by previous methods, thus opening new avenues for research in hepatitis. Further progress was made on identification of the active fraction of killed tuberculosis vaccine and in establishing an animal model system for evaluation of live tuberculosis vaccine (BCG.) Toxoplasma gondii, cause of a common U. S. parasitic disease with eye damage, was shown to be a protozoa and the mechanisms by which cats can act as reservoirs demonstrated. Rifampin, an antibiotic, was shown to block the intracellular assembly of some viruses and further work was undertaken to define its potential as an antiviral for man. A program in research on clinical allergy was initiated.

Objectives for 1972: Further development of the research on clinical allergy will be pursued as resources permit. The evaluation of the attenuated RS virus vaccine will be continued as well as efforts to develop better vaccines for other respiratory viruses. Efforts to isolate and identify hepatitis viruses will be expanded as well as research on the subtypes of "hepatitis associated antigen." Work on a killed tuberculosis vaccine will advance. Immunologic research will center more on the problems of allergy and transplantation and more scientists will be used in support of the collaborative programs.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Collaborative Research and Development - (PHS Act, Title IV, Part D.)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
36	$11,661,000	Indefinite	36	$11,729,000

Purpose: This activity has as its mission the translation of significant basic research data into practical achievements of clinical applicability in immunologic and infectious diseases. It conducts and supports developmental research in the prevention, control and treatment of diseases caused by infectious agents including bacteria, viruses and parasites and by abnormalities in the body's immune mechanism.

Explanation: This activity is carried out through research contracts with industry and other Federal and non-Federal institutions.

Accomplishments in 1971: In the transplantation immunology program evidence continues to accumulate as to the value (in man) of tissue typing reagents and (in monkeys) of antilymphocyte serum in prolonging grafts. In the respiratory diseases program evaluation of vaccines against the 14 most common pneumococcal types has begun. In a number of viral diseases nasal antibody now seems to be the most important determinant of resistance to disease. Antiviral substances, specifically interferon and its inducers, are effective in curing or preventing certain diseases in animal model systems. Reagents for viruses, interferon standards, and the Australia antigen (which is associated with serum hepatitis) have been produced and distributed to facilitate research.

Objectives for 1972: Efforts to identify the antigens important in tissue matching will be intensified. Isolation of large quantities may make it possible to induce tolerance to the specific antigens and hence increase the likelihood of successful transplant. Evaluation of a large lot of rabbit lymphocyte globulin will be undertaken with a similar end in view. Preliminary studies will be undertaken of new vaccines against the diseases caused by the bacteria, H. influenza and meningococcus (both frequent causes of meningitis and middle ear infections) and by the smallpox, parainfluenza and respiratory syncytial viruses. The pneumococcal vaccine studies will be expanded to include polyvalent vaccines. Purified interferon will be prepared and tested as an antiviral prophylactic or therapeutic agent.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Review and Approval of Grants - (Public Health Service Act, Title IV, Part D.)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
43	$1,627,000	Indefinite	43	$1,714,000

Purpose: This activity provides for the over-all coordination and administration of the Institute's grants programs.

Explanation: 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 Diseases Council, liaison with appropriate organization 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 grant management.

Accomplishments in 1971: A study was initiated to identify appropriate criteria for judging the health relevance of research projects to the mission of the Institute. Procedures were designed to meet new grantee equipment accountability requirements. Plans were made to convert to a central indirect cost management system.

Objectives for 1972: Increased effort will be made for developing an effective and responsive grants management and evaluation program for the research and training grants and fellowship activities.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Program Direction - (Public Health Service Act, Title IV - Part D.)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
32	$596,000	Indefinite	32	$621,000

Purpose: This activity provides for the support of the Institute's Director and his immediate staff in the over-all administration, coordination and direction of all the Institute's activities.

Explanation: The personnel to support this activity include Personnel Office, Financial Management Office, Travel, Mail and Files, Information, etc.

Accomplishments in 1971: The Biostatistics Unit, staffed by two professional personnel was established in the Office of the Director. It is expected that this unit will conduct in-house and contract activities to develop information on selected disease problems.

Objectives for 1972: To continue to look for better and more effective ways of providing Institute direction through reorganization and initiation of new policies.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

WITNESSES

DR. DeWITT STETTEN, JR., DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ARTHUR E. HEMING, ACTING ASSOCIATE DIRECTOR FOR RESEARCH, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
GORDON J. KLOVDAHL, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
MRS. EMMA LOU AKERS, BUDGET OFFICER, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
GERALD F. MEYER, CHIEF, HEALTH BRANCH, DIVISION OF BUDGET

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Object Classification (in thousands of dollars)

Identification code 09-30-0851-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	2,364	2,449	2,506
11.3	Positions other than permanent	35	44	44
11.5	Other personnel compensation	20	24	24
	Total personnel compensation	2,419	2,517	2,574
12.1	Personnel benefits: Civilian employees	223	254	260
21.0	Travel and transportation of persons	147	161	161
22.0	Transportation of things	7	22	22
23.0	Rent, communications, and utilities	127	156	171
24.0	Printing and reproduction	124	157	157
25.0	Other services	4,979	9,196	5,365
26.0	Supplies and materials	51	60	60
31.0	Equipment	20	22	22
41.0	Grants, subsidies, and contributions	139,993	147,521	141,299
99.0	Total obligations	148,090	160,066	150,091

Personnel Summary

Total number of permanent positions	191	191	197
Full-time equivalent of other positions	5	5	5
Average number of all employees	192	192	200
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0851-0-1-651		1970 actual	1971 est.	1972 est.
	Program by activities:			
	1. Grants:			
	(a) Research	67,140	85,321	87,772
	(b) Fellowships	18,836	18,454	15,142
	(c) Training	44,395	43,746	38,385
	Total, grants	130,371	147,521	141,299
	2. Direct operations:			
	(a) Collaborative research and development	4,167	7,667	3,548
	(b) Training activities	360	290	315
	(c) Review and approval of grants	3,158	3,381	3,611
	(d) Program direction	1,158	1,207	1,318
	Total, direct operations	8,843	12,545	8,792
	Total program costs, funded [1]	139,214	160,066	150,091
	Change in selected resources [2]	8,876	----------	----------
10	Total obligations	148,090	160,066	150,091
	Financing:			
25	Unobligated balance lapsing	119	6,256	----------
	Budget authority	**148,209**	**166,322**	**150,091**

Program and Financing (in thousands of dollars)

Identification code 09-30-0851-0-1-651		1970 actual	1971 est.	1972 est.
	Budget authority:			
40	Appropriation	164,644	166,072	150,091
40	Pay increase (Public Law 91-305)	10	----------	----------
40	Portion withdrawn (Public Law 91-204, sec. 410)	-11,678	----------	----------
41	Transferred to other accounts	-4,767	----------	----------
43	**Appropriation (adjusted)**	148,209	166,072	150,091
46.10	**Proposed transfer for wage-board pay increases**	----------	14	----------
46.20	**Proposed transfer civilian pay act increases**	----------	217	----------
46.30	**Proposed transfer for military pay act increases**	----------	19	----------
	Relation of obligations to outlays:			
71	Obligations incurred, net	148,090	160,066	150,091
72	Obligated balance, start of year	113,242	106,818	110,819
74	Obligated balance, end of year	-106,818	-110,819	-111,831
77	Adjustments in expired accounts	-2,895	----------	----------
90	Outlays, excluding pay increase supplemental	151,619	155,815	149,079
91.10	Outlays from wage-board supplemental	----------	14	----------
91.20	Outlays from civilian pay act supplemental	----------	217	----------
91.30	Outlays from military pay act supplemental	----------	19	----------

[1] Includes capital outlay as follows: 1970, $21 thousand; 1971, $19 thousand; 1972, $19 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $61,102 thousand; 1970, $69,978 thousand; 1971, $69,978 thousand; 1972, $69,978 thousand.

NOTES

Includes $144 thousand in 1972 for activities previously financed from (in thousands of dollars):

	1970	*1971*
Division of Biologics Standards	48	---
National Heart and Lung Institute	---	144

Includes $119 thousand in 1971 and $119 thousand in 1972 for activities previously financed from: Research resources, 1970, $117 thousand.

Excludes $5,811 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	*1971*
Office of the Director	27	21
National Heart and Lung Institute	-----	429
Health Manpower	5,361	5,361

INTRODUCTION OF DR. STETTEN AND ASSOCIATES

Mr. FLOOD. We continue with the National Institutes of Health, and will now take up the National Institute of General Medical Sciences. The presentation will be made by Dr. DeWitt Stetten, Jr., the Director. I believe this is your first appearance isn't it?

Dr. STETTEN. Yes, sir.

Mr. FLOOD. I see we have a biographical sketch of you. Do you have any people you would like to introduce?

Dr. STETTEN. I have Dr. Heming, Acting Associate Director for Research, Mr. Klovdahl, Executive Officer, and Mrs. Emma Lou Akers, Budget Officer, with me.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH OF DEWITT STETTEN, JR.

Name: DeWitt Stetten, Jr.
Position: Director, National Institute of General Medical Sciences.
Birthplace and date: New York City, May 31, 1909.
Education: A.B., Harvard College, 1930; M.D., Columbia University, 1934; Ph. D., Columbia University, 1940.

EXPERIENCE

Director, National Institute of General Medical Sciences, October 1970–present.
Dean, Rutgers Medical School, and director of Medical Center, 1962–70.
Associate Director in Charge of Research, and Chief, Section on Intermediary Metabolism, National Institute of Arthritis and Metabolic Diseases, 1954–62.
Chief, Division of Nutrition and Physiology, Public Health Research Institute of City of New York, Inc., 1948–54.
Assistant professor, Department of Biochemistry, Harvard University, 1947–48.
Associate in medicine, Peter Bent Brigham Hospital, 1947–49.
Assistant, instructor, assistant professor, Department of Biochemistry, Columbia University, 1938–47.
Intern, resident, Bellevue Hospital, New York, 1934–37.

ASSOCIATION MEMBERSHIPS

American Association for the Advancement of Science (Fellow) (VP 1962).
American Society of Biological Chemists.
Harvey Society.
Phi Beta Kappa.
Alpha Omega Alpha.
Sigma Xi.
Society of Experimental Biology and Medicine.
Cosmos Club.
American Institute of Chemists (Fellow).
National Advisory Committee, Oklahoma Fnd. for Medical Research.
Advisory Committee, Department of Biology, Princeton University.
Executive Committee, Division of Medical Sciences, NRC–NAS.
Board of Directors, Foundation for Advanced Education in the Sciences.

SPECIAL AWARDS, CITATIONS, OR PUBLICATIONS

Joseph Mather Smith Prize, 1943.
Albarenga Prize Award, 1954.
Horace Mann Award for Outstanding Alumnus of the Year, 1957.
Banting Medal from the American Diabetes Association, 1957.

Mr. PATTEN. Mr. Chairman.

Mr. FLOOD. Mr. Patten.

Mr. PATTEN. Mr. Chairman, I want to welcome Dr. Stetten who was dean of Rutgers Medical School in our State. I want you to know we have high regard for Dr. Stetten. He has a host of friends in our area, and he has made our medical college an outstanding institution.

GENERAL STATEMENT

Mr. FLOOD. I see you have a prepared statement. How do you wish to proceed?

Dr. STETTEN. I would like to read it.

Mr. FLOOD. Suppose you do.

Dr. STETTEN. I am appearing before this committee for the first time in my new capacity as Director of the National Institute of General Medical Sciences. Because of my very recent exposure to the deanship of a struggling medical school, I am perhaps unusually sympathetic to the problems of our chief clients—the medical schools.

Mr. FLOOD. You just left a very hazardous occupation didn't you?

Dr. STETTEN. Yes.

Mr. FLOOD. Please proceed with your statement.

Dr. STETTEN. It is in our medical schools that much of the medical research, the teaching of physicians and others, and the care of patients take place and interdigitate. I trust that I shall be excused if I repeat some obvious truisms.

In biomedical sciences:

(*a*) Today's research training is tomorrow's research.

(*b*) Today's research is tomorrow's health care.

(*c*) The citizens of 1970 would be totally dissatisfied with the quality of health care of the pre-antibiotic 1940 era. Likewise, the people in the year 2000 will demand a far more sophisticated level of medical attention than is available today.

It is, I believe, the continuing mission of the National Institute of General Medical Sciences to stoke the fires of research, to provide the support needed by those disciplines which are fundamental to the advance of medical science, both in their direct and indirect costs of operation and in their present and future manpower needs. The former we accomplish by research grants and contracts; the latter by training grants, fellowships, and career development awards.

It is incumbent upon us to be alert to those scientific areas of most acute need and greatest urgency. Beyond this, we must continuously assess the scientific "ripeness" of the problem. Not every problem which appears to cry for immediate solution is profitably studied at this time. For any program of research to succeed, a backlog both of information and of technique is required.

PRIORITY BEING GIVEN TO THE STUDY OF GENETIC DISEASE

Judged to be both urgent and ripe for study at this time is the exciting area of human genetic disease. This matter was outlined before this committee in citizen testimony last year by Dr. Joshua Lederberg, Nobel Laureate and professor of Genetics and Biology at Stanford University.

In summary, there is a very large number of diseases, about two thousand now tabulated, which are caused chiefly or entirely by errors in the substance or in the transmission of genetic information from

parent to offspring. Usually but not always these diseases become evident in infancy or early childhood. They vary in severity from trivial to lethal. Although many of the individual genetic defects are quite rare, considered in its entirety, genetic disease is a very important cause of human morbidity, estimated to account for about 25 percent of all hospitalization in this country. It has been claimed that about 7 percent of the population suffers from clinically significant disease present at birth, either genetically determined or resulting from environmental influences during fetal life. Because of the early onset and high mortality of some of these diseases, they produce an enormous impact upon the "future life years lost." Thus in 1967 it was estimated that birth defects accounted for about 36 million future life years lost, whereas heart disease, cancer, and stroke accounted for about 8 million, 4 million, and 3 million respectively. Virtually all organs and organ systems of the body may be affected by diseases of this group, and study of certain specific diseases may therefore fall in the provinces of one or another categorical institute. On the other hand, the mechanisms of transmission, the possible means of prevention, and the pursuit of general methods of treatment which should be common to this entire class of diseases have long been and continue to be major interests of the National Institute of General Medical Sciences.

For over a hundred years, scientists, using peas, flies, molds, bacteria, and viruses, have studied the nature of storage and transmission of genetic information. In no field of science has more rapid progress been made in the past fifteen years. Today we are able to study these processes as they occur in mammals by the use of mammalian cells grown outside the body in tissue culture. We know that genetic information is stored in microscopically visible structures of the cell nucleus, chromosomes, and more specifically in the molecules of deoxyribonucleic acid, DNA, contained in these chromosomes. The processes of the living cell transcribe the DNA message into RNA.

Mr. FLOOD. What do you mean by DNA and RNA?

Dr. STETTEN. DNA, deoxyribonucleic acid is the name of the chemical substance which contains the information of genetics in its ordered structure.

RNA, ribonucleic acid is a similar compound which serves as the template for protein synthesis.

GLOSSARY OF TERMS

At the suggestion of Mr. Klovdahl I have prepared a glossary which I can put in the record.

(The glossary follows:)

HEMOPHILIA

A genetically determined disease of the blood characterized by a tendency to persistent bleeding following minor injury. The common form of the disease is transmitted in a sex-linked genetic pattern by which is meant that it manifests itself only in the male but is transmitted through the female.

LESCH-NYHAN'S DISEASE

A recently described biochemical abnormality in the metabolism of the purines, a group of nitrogen-containing compounds involved in the nucleic acids DNA and RNA. This disease is genetic, sex-linked, having been observed thus far only

in the male. It is characterized by mental retardation, involuntary formless movements of the body, strong aggressive behavior patterns, and an extraordinary tendency to self-mutilation involving biting of the patient's own fingers and lips.

PHENYLKETONURIA

A fairly wide-spread genetic defect in the metabolism of the essential amino acid, phenylalanine. The disease is characterized by severe mental retardation and an inability properly to handle the products derived from the above amino acid. The development of symptoms, if early diagnosis is made, can be minimized by very rigid dietary control.

CYSTIC FIBROSIS

Perhaps the commonest genetic disease, which behaves as a single gene defect. It occurs equally in both sexes; it is characterized by wide-spread damage to many or all secretory glands. The sweat glands produce sweat which is excessively rich in sodium ions. The glands of the bronchial tree produce an abnormally viscous (sticky) mucus, which drains poorly and leads to frequent infections of the lung.

SICKLE CELL ANEMIA

A defect in the manufacture of hemoglobin which is genetically transmitted as a recessive disease. The disease is encountered only among persons with black ethnic background. In its completed form, the patient is subject to very painful seizures called crises, and to episodes of fragmentation of red cells of the blood, with consequent anemia. The carrier of the disease has approximately half of his hemoglobin normal, and the other half of the sickle cell variety. Such individuals are believed to be refractory to certain forms of malarial infection.

TAY-SACHS DISEASE

Characteristic of the Ashkenazi Jews is a recessive genetic disease involving progressive blindness, with a characteristic damage to the retina, and a very severe and progressive mental retardation leading to idiocy and death, usually within two years.

HETEROZYGOTE CARRIER

A disease which is recessive will only be manifest if the genetic information for that disease is derived from both parents and is therefore doubly expressed in the genetic constitution of the patients. An individual who derives genetic information for the disease from only one of two parents is said to be heterozygous and may be totally free of symptoms, hence is called a carrier. Should she mate with another heterozygous carrier, in general one-quarter of the offspring of such a mating will have the disease; that is, will be homozygous for the disease trait.

POMPE'S DISEASE

One of the serious genetic afflictions of childhood in which glycogen—a high molecular weight sugar, the animal equivalent to starch in the vegetable world—accumulates in excessive amounts. The threatening nature of Pompe's Disease results from the fact that the heart is involved in this process, leading to death from congestive heart failure in early years.

ALZHEIMER'S PRESENILE DEMENTIA

An early deterioration of all mental processes, with a concurrent demonstrable deterioration of the cells of the brain (see microtubules below).

THALASSEMIA

An anemia characteristic of people in the Mediterranean Basin, caused apparently by a failure which is congenitally transmitted to manufacture one of the component protein chains of hemoglobin at adequate rate. The disease is often characterized by a tendency to generate red cells of abnormal shape.

MICROTUBULES

These are among the more recently discovered anatomical features of every cell type which multiplies by mitosis. This includes substantially all the cells of the animal and the vegetable world. Microtubules may be observed in the elec-

tron microscope as tubular structures of uniform and small diameter and of varying length. They apparently have a variety of functions in the cell. The hair-like growths of certain cells, the so-called cilia and flagellae, are composed of microtubules. The spindle apparatus which is the prime mover of the process of mitosis is apparently made up of microtubules aligned in a characteristic array. The centrioles about which the two daughter nuclei form as the current nucleus splits are also made up of modules of microtubules. In Alzheimer's Presenile Dementia (see above), the microtubular structure of the axons, the long extensions of nerve cells, is in complete disarray.

Dr. STETTEN. This information is then translated into the structure of a specific protein which in many instances is an important enzyme, a catalyst of body processes.

At any and each stage, this complex series of events may be disturbed, and any disturbance may lead to clinically significant disease. The loss of a chromosome or the appearance of an extra one is a catastrophic event. Single bits of genetic information, called genes, may be lost or deformed, leading to the absence or abnormality of a single protein, and many diseases are recognized today arising from such deficiencies. Among these are hemophilia and Lesch-Nyhan's disease, both sex linked, and phenylketonuria, cystic fibrosis, and sickle cell anemia, which occur about equally in both sexes. Most of the diseases in this group are said to be "recessive," which means that there exists a carrier state, and there are individuals carrying the genetic taint who are themselves symptom free. Identification of such persons is possible for some but not for other diseases today, but such identification is of prime importance since future affected victims may be among their offspring.

TREATMENT OF GENETIC DISEASES

The present status of treatment of these diseases is quite unsatisfactory. In some instances the complications of established disease can be prevented by prompt institution of rigorous diet control, as in galactosemia or phenylketonuria. For the most part, treatment is limited to the corrections of symptoms as these develop, as in the use of antibiotics to control lung infections encountered in cystic fibrosis. Prevention by genetic counseling has been of limited use, and intrauterine diagnosis followed by abortion has to date had only limited application. Relatively few abnormalities can today be diagnosed from the materials secured by amniocentesis, aspiration of fluid and cells from the pregnant uterus. The absence of very specific enzyme normally present in cells of the skin has permitted the positive diagnosis, in early embryonic life, of Tay-Sachs disease by one of our grantees. This condition is uniformly fatal in early life.

Its early diagnosis by amniocentesis has allowed the pregnant woman to consider the option of terminating the pregnancy.

More complex are those heritable disease states which relate to defects in several genes rather than a single genetic site. A prime example of such a "polygenic" defect is the very common disease, diabetes. It genetic pattern is sufficiently complex, in contrast to that of hemophilia, to defy precise analysis at this time. Only by the acquisition of more information can we hope to understand the complexities of the genetics of diabetes. In common with other genetic defects, while the manifestations of diabetes can today generally be controlled with diet and insulin, the disease has so far not been cured.

DETECTION OF CARRIERS OF FAULTY GENES

But the problem of genetics of disease is "ripe" today. Our Institute proposes to establish the study of genetics and genetic diseases as a formal program. We are conducting at present a critical and highly professional review of the entire field. Already in fiscal year 1971 we have provided nearly $30 million in research grant support, and $6 million in training and fellowship support in these areas of medical science. In addition to the all-important continuance of support for the study of basic genetic processes and their anomalies, we propose certain areas for initial targeted concern.

1. To stimulate research directed toward the identification of the so-called heterozygote carrier the apparently well individual who carries in his genetic stock a defective gene which might lead to serious disease in his offspring.

The heterozygote carrier is an individual who carries one but not two genes for a particular disease, the disease being manifest only when both genes for that disease are present. The single gene does make him a carrier, possible parent of the diseased individual even though he does not have the disease.

We think that these people should be more completely identified.

Such identification is today not feasible for most genetic diseases, hindering precise genetic counseling. One of our grantees has recently utilized a novel technique of stimulating enzyme production in cells for the biochemical identification of heterozygote carriers of Pompe's disease, the most dreaded of several glycogen storage diseases.

Mr. FLOOD. After you identify a carrier, what do you do?

Dr. STETTEN. You advise him. In the first place, you can tell him or her what the probabilities are of disease in their children. He or she must then make the ultimate decisions.

RESEARCH ON THE NATURE OF THE CHROMOSOME

2. To proceed with the all important but very laborious task of "mapping" the human chromosomes. Such maps have been developed for the colon bacillus and the fruit fly, but we have barely begun to locate the thousands of known genes on human chromosomes. It has been said that the mapping of the 23 human chromosome pairs, which contain all the necessary information to the structure and function of the body, is surely more challenging and more relevant to human welfare than is the mapping of the moon. This mapping has been initiated in a number of laboratories supported by grants from the National Institute of General Medical Sciences. One of these grantees has had considerable success in the application of hybridization techniques, the fusion, under specified conditions of cells derived from different species. Such hybrids are found to cast off chromosomes serially, permitting allocation of specific genes to specific chromosomes.

RESEARCH ON DNA

These defined targets will be in addition to the more general goals of our genetics program. By way of example, microbial geneticists discovered many years ago that the bearer of genetic information,

DNA, might be transferred from one cell to another by the intervention of an infecting virus. This discovery of so-called "transduction" suggests a possible approach to the therapeutic problem of supplementing a genetically deficient mammalian cell with DNA from another cell line. One might visualize actually curing such a disease if this hope could be realized. It should be mentioned that one of our grantees has indeed made significant strides in this direction. Equally important, however, this relation between microbial and mammalian genetics illustrates the need for continued assault upon genetics on a broad base. There is still much of great usefulness to be learned from studies of bacteria and bacteriophage.

I have concentrated, in this presentation, upon a new stress in our program direction. I have made no mention of our other defined programs in other basic medical sciences, in pharmacology-toxicology, in trauma, in automation of diagnostic laboratory instruments, in the clinical subjects of diagnostic radiology and anesthesiology. The National Institute of General Medical Sciences continues to support research and research training in all of these areas. This committee has heard much about these programs from my predecessors, Dr. Brown and Dr. Stone. Excellent work continues to be done, dependent upon the support of this Institute, and much of it is described in the documentation being submitted.

I deeply appreciate the privilege of being permitted to outline for you some of the horizons of biomedical knowledge as my colleagues, our advisers, and I see them. History of the recent past reconfirms our belief that the expansion of knowledge, followed inevitably by the application of such knowledge, will permit ever-accelerating progress in our ability to cope with human disease.

SUMMARY OF BUDGET

Mr. Chairman, to support the efforts outlined above, the appropriation request for the National Institute of General Medical Sciences for 1972 totals $150,400,000, a decrease of $4,127,000 from the 1971 comparable to the 1972 President's budget. Most of this decrease is in fellowships and collaborative research and development.

Mr. FLOOD. Doctor, how long have you been in this job?

Dr. STETTEN. I came October 1, 1970, 7 months ago.

Mr. FLOOD. I am curious. Your justifications seem to play down genetics and you devoted almost all your presentation to the importance of genetics.

It looks to me like you got hit about the hardest of all the Institutes. Just looking at the overall figures, you are having to absorb increased costs in 1972 and on top of that you are being cut back $4,127,000.

As important as we have been told your activities are, that is pretty hard to believe. But it's true.

Dr. STETTEN. As I mentioned, the cuts occur in places that I hope we can tolerate without too much difficulty.

REDUCTION IN FELLOWSHIP PROGRAM

In the first place, a substantial share of the total predoctoral fellowships program of NIH is borne by this institute. A policy decision was made a year ago or more to phase out the predoctoral program entirely. This has been done in such a way as not to injure the individuals who had been started on a typical fellowship which is usually a 3-year award.

Mr. FLOOD. What do you think personally about postdoctoral fellowships as distinguished from guaranteed loans. For instance, in those cases where, in the medical schools, you train teachers to teach. What is that—academic medicine?

Dr. STETTEN. Yes. We have training grants for this and we have postdoctoral fellows and career development awards. These are all active programs.

RATIONALE FOR INCREASING GRANT STAFF

Mr. FLOOD. Here is something that looks a little strange to us. While there is a reduction of about $3½ million in the funds for grants, you are requesting an increase of $65,000 and three jobs for review and approval of grant applications. How do you put that together?

Dr. STETTEN. We believe that in instituting a new program of genetics this must be staffed. Indeed, we have at this time a minimum of genetics staff on board.

This is a program which I have felt is sorely needed. As a program, it must be organized to a higher degree than it has been to date. It would take additional hands to do this properly.

USE OF FUNDS ADDED BY COMMITTEE FOR GENETICS

Mr. FLOOD. Of course, you weren't around here at the accouchement for the new genetics program. You were not here.

Dr. STETTEN. No.

Mr. FLOOD. Last year this committee—not the Department but this committee—increased your budget request by $17,696,000. The committee earmarked $10 million for a special program in genetics.

Dr. STETTEN. That is right, sir.

Mr. FLOOD. Take a look at page 49 under the heading. "Action Taken or to be Taken." It looks to us like most of it is "to be taken."

This indicates to us that the task force to head up this program hasn't even been named yet. What has been done?

Mr. MARSTON. Could I say something about the $10 million and then let Dr. Stetten talk about what has been done with the moneys that have been released?

Mr. FLOOD. I wish you would.

Dr. MARSTON. The committee did increase and earmark $10 million, of which $7,750,000 actually was made available for this program.

Mr. FLOOD. You know, Dr. Marston, this committee was impressed by the presentation made by a so-called public witness. It couldn't possibly be that you fellows were jealous and sort of played this thing down because of that fact, because it wasn't your idea?

Dr. MARSTON. No, sir. The NIH and the General Medical Sciences Institute were, and continue to be, very enthusiastic about genetics and its possibilities.

The point I wanted to make is that we mounted a major program increase in the area of genetics but—and this is not something that Dr. Stetten had any discretion about—at a slightly lower level than the committee had instructed. It is at a $7,750,000 level rather than the $10 million level that you indicated.

Within the Institute and the other parts of NIH, it has been his responsibility to institute that program, and it has been done very well during the past year.

THE TASK FORCE ON GENETICS

Dr. STETTEN. May I respond?

Mr. FLOOD. Sure.

Dr. STETTEN. The funds that Dr. Marston mentioned were not made available until in February 1971. At that time the task force was assembled under the chairmanship of Dr. Robert Berliner, the Deputy Director for Science, NIH. It had representations of several Institute Directors: Dr. La Veck of the Child Health and Human Development Institute; Dr. Davis of Allergy and Infectious Diseases; Dr. Whedon of Arthritis and Metabolic Diseases; also Dr. Lamont-Havers, who is the Associate Director, NIH, for extramural programs, and myself.

Mr. FLOOD. That helps. Directing your attention again to page 49, you have a caption, "Action taken or to be taken." Apparently that is out of date, because I see in there a task force "To be established by the Director of NIH, and "plans are now being made."

Apparently that is just simply out of date.

Dr. MARSTON. Yes; that is right.

Dr. STETTEN. Yes, sir. The task force is in existence. It has transacted its business for the year. May I review the business, sir?

Mr. FLOOD. Sure.

STATUS OF GRANT AWARDS

Dr. STETTEN. Approximately 159 awards will be made against the funds which were provided. They are distributed among six Institutes. They all relate to problems of genetics and genetic chemistry. The largest share came to our Institute because that is where most of these applications are assigned.

There are 111 awards, totaling $5,632,297 to General Medical Sciences; 21 awards to allergy and infectious diseases; 10 to arthritis and metabolic disease; 13 to child health and human development; three to cancer and one to the Neurological Institute.

LACK OF EMPHASIS ON GENETICS IN THE JUSTIFICATIONS

Mr. FLOOD. In spite of all that, you don't even have a separate section in the justifications on genetics. You have a section for "trauma," one for "diagnostic radiology"; one for "anesthesiology"; "biomedical engineering," and so forth. But genetics is just part of the narrative under the heading, "fundamental sciences."

In view of this subcommittee's very pointed, if I can understate it, interest, why don't you give this more visibility. We thought this was one of the truly important, recent breakthroughs in basic medical research and that it deserves special treatment.

Dr. STETTEN. May I say, sir, that one of the chief charms of this position that was offered to me was Dr. Lederberg's testimony. It was for this reason, too, that I devoted substantially the entirety of my opening statement to this area of disease. It is the area of disease which I personally find at this time most interesting to work with.

THE BUDGET FOR GENETICS

Mr. FLOOD. Just so we know.

How much are you budgeting for genetics research and training in 1972?

Dr. STETTEN. $38,828,000 total.

THE IMPORTANCE OF GENETICS RESEARCH

Mr. FLOOD. I know, from your opening statement, that you think genetics research is important even though that may not be reflected very well in the justifications. I would appreciate it if you would place a more comprehensive statement in the record telling us why you think it is important.

(The additional statement follows:)

A PROGRAM IN HUMAN GENETIC DISEASE FOR NIGMS

Two generally recognized classes of effects—environment and heredity—operate upon each organism, including man, and determine its state of health or of disease. The environment includes the air we breathe, the water and other fluids we drink, the food we eat. It includes the clothing and housing we construct to temper the elements—heat, cold, rain, snow, solar radiation, indeed the complete spectrum of radiant energies; also the pollutants of air, water, food, and soil. In addition there are all the other living organisms, both large and microscopic, with which each organism must cope, including the pathogenic bacteria and viruses.

The hereditary component of health and disease has been rather more difficult to define until recently. We now know that all the information necessary to create man from a fertilized ovum is contained in the ordered sequence of nucleotides in the DNA of the chromosomes. We have learned that portions of this ordered sequence can be copied or transcribed from DNA in the nucleus into RNA which, in the sytoplasm of the cell, serves as a template against which the individual amino acids are arranged in ordered sequence to form specific proteins. This latter process, from nucleotide patterns to amino acid sequences, is termed translation, and we now know the entire dictionary upon which this translation is based. Thus in the past 15 years enormous strides have been made in our understanding of the nature of the storage and retrieval of genetic information to the point where we are now amply prepared to apply this knowledge and the attendant techniques to problems of human health and disease. Up to the present time, well over 2,000 different human disease states have been described which are genetically transmitted; and in some instances, a high degree of chemical definition—identification of the defective protein—has been possible.

The problem is not a trivial one. Whereas some of the individual genetic diseases are relatively infrequent, others are not. Many, though not all, manifest themselves early in life and result either in early death or in protracted invalidism. Some 7 percent of the population of the United States is estimated to suffer significantly from one or another genetic defect, and 25 percent of hospitalizations are accounted for by these diseases. Many genetic diseases are today totally lacking in effective treatment. Only in a few instances can some of the manifestations of the disease be deferred or prevented by drastic dietary treatment or by replacement of the deficient end-product protein as in diabetes. However, in no case thus far has any disease of this category been cured in the sense that there is no longer need of any continued treatment.

There are three predominant goals in the program envisioned here:

(1) Better understanding and hence more effective management of diseases of this class.
(2) Treatment of such diseases by the ultimate pharmaceutical, an appropriate therapeutic bit of DNA administered so that it becomes self-renewing in the cells of the patient.
(3) Prevention of such disease by intrauterine diagnosis and termination of pregnancy or, better still, by the early identification and counseling of the carriers of such disease who are in many cases themselves devoid of symptoms.

THE MAJOR GENETIC DISEASES

Mr. FLOOD. Take a look at page 55:

There are over 1,000 different diseases which are believed to be genetically transmitted or in which genetic mechanisms appear to have a highly significant role.

For the record, would you list, say, about 25 of the more important ones?

Dr. STETTEN. No problem. Many of them have been mentioned.

(The information referred to follows.)

EXAMPLES OF GENETIC DISEASE

Diabetes mellitus.
Glycogen deposition diseases, such as von Gierke's disease and Pompe's disease.
Galactosemia.
Hyperbilirubinemia, which is a genetically transmitted defect leading to jaundice.
Phenylketonuria, a common cause of mental retardation.
Alcaptonuria.
Albinism.
Infantile amaurotic family idiocy, also known as Tay-Sachs disease.
Niemann-Pick disease.
Gaucher's disease.
The adrenogenital syndrome.
Gout.
Lesch-Nyhan's disease.
Wilson's disease.
Hemochromatosis.
Periodic paralysis.
Hereditary pherocytosis.
Drug-induced hemolysis, as in primaquine sensitivity (favism).
Sickle cell disease, and other abnormalities of hemoglobin structure.
Hemophilia, and several other genetic defects in blood clotting.
Cystinuria.
Acatalasia.
Huntington's chorea.
Cerebellar ataxia.
Cystic fibrosis.

The above list includes only a small fraction of the many diseases which have been described that are known or believed to be transmitted genetically. Among those listed are some of the more common diseases and also some which, though rare, have been carefully studied and have yielded valuable information.

CUT IN PREDOCTORAL FELLOWSHIPS

Mr. FLOOD. Your fellowship program really got clipped—from 1,600 this year to 1,140 in 1972. That is a cut of over 25 percent. Why is your fellowship program being cut back more than any other Institute on the campus?

Dr. STETTEN. This is contributed to quite largely by the planned phasing out of the predoctoral fellowships. This happened before my

arrival. It is generally agreed that the support of predoctoral candidates is better accomplished through training grants than through predoctoral fellowships and, in view of the stringencies of the times, the priorities for predoctoral fellowships were low. It was therefore determined to phase them out.

PROGRESS IN AUTOMATING CLINICAL LABORATORIES

Mr. FLOOD. What progress has been made in the area of biomedical engineering, especially automated clinical laboratories? There has been considerable excitement about that for a few years. What has been going on in those fields, especially the automated clinical laboratories?

Dr. STETTEN. If you were to visit Georgetown University Hospital you would see that.

Mr. FLOOD. I will in about 2 hours.

Dr. STETTEN. If you visit Dr. Martin Rubin's laboratory you will see the prototype of an instrument which has now been developed under funding from our institute at Oak Ridge National Laboratory by Dr. Norman Anderson. This instrument is now in commercial operation and represents the culmination of a numbers of years of support. It is an instrument in which we have high confidence that it will not only increase precision and enormously increase the bulk of work that can be accomplished but will also effect very real economies in the operation of a hospital.

This, then, is the type of thing we like to have on our record.

There are other instruments currently under development. There is an instrument also being designed under contract to us from Oak Ridge National Laboratory for the analysis of a very large number of constituents simultaneously in urine samples.

This instrument is presently under study by a committee of six professors of medicine and pediatrics whom I have assembled as an ad hoc group. We will place one of these instruments in each of their departments. We hope over the next 12 months or more to secure from them an appraisal of what the real uses of this instrument will be in the practice of medicine and in research.

Mr. FLOOD. For the record develop this subject a little more.

Dr. STETTEN. Yes, sir.

(The information follows:)

AUTOMATION OF CLINICAL LABORATORIES

The Institute, through a variety of mechanisms, continues to provide broad support for the advancement of the field of biomedical engineering. Its objective is to support the effective introduction of engineering into fundamental and applied biomedical research and quality research training in the area. In a few selected instances, usually arising from the pool of fundamental research supported by the Institute, prototype instrumentation and devices are being developed that will be useful in the improvement of health care.

A general overview places the workload of the clinical laboratories in the United States at approximately one-half billion tests in 1969. It further indicates that this number may double within five years or less. Thus, by 1975, the nation's clinical laboratories will be faced with the performance of some billion tests per year, and a likely insistence that quality be markedly increased and that costs per test be decreased. It is clear that the only solution to this critical problem is to find ways to mechanize and automate the clinical laboratory. The solution is not an easy one as it involves a highly complicated mixture of activities in clinical chemistry, hematology, microbiology, mycology, parasitology, serology, and urinalysis.

Over the past three years, it has become apparent that a variety of bottlenecks and unsatisfactory techniques in instrumentation and data processing are seriously retarding the realization of completely automated systems in all areas of clinical laboratory practice. To help resolve this situation, NIGMS has undertaken a concerted program of research and development in this area.

Its present and planned program represents a consolidated effort to improve laboratory functions through specific research grants and contracts in the areas of:

1. Development and automation of new, more accurate, sensitive, rapid and reliable analytical tools and methods for the clinical laboratory.
2. Development of appropriate computer hardware and software for sample identification, laboratory data processing, control of analytical methods, and identification of abnormal test results.
3. Development of proper laboratory standards (reagent and reference) for use by clinical laboratories to assure the validity and uniformity of their measurements.
4. Definition of normal values by age, sex, geographic location, and other variables.
5. Exploitation of basic research discoveries to provide new diagnostic tests for use in the clinical laboratory.
6. Development of appropriate sets of profile tests suitable for the early detection and evaluation of various diseases.

The major areas being concentrated on at this time are: clinical chemistry, hematology, microbiology, and urine analysis. It would appear that by making progressive improvements in both the hardware and software now available, it should be possible in the next few years to increase by 15 to 20 percent the effective automation of clinical chemistry and hematology. The overall goal is to develop a modular automated clinical laboratory system that can be adapted to benefit all sizes of hospitals from the small community hospital to the large university hospital complex. This program is considered to have singular importance and has a high priority in the order of developmental work that must be undertaken to assure the country of an adequate system for the delivery of health services.

During Fiscal Year 1971, this program supported 58 grants, at a cost of $4,702,000. The distribution of grant monies for various activities within the program is as follows:

AUTOMATION IN THE CLINICAL LABORATORY SCIENCES

	Number of grants	Dollars in millions
Analytical chemicals	14	0.524
Methods and instruments	26	2.186
Automation	9	.552
Computers	9	1.440
Total	58	$4.702

In addition to grant support, approximately $1,200,000 in contracts was awarded. Significant achievements via contracts include:

1. Under an interagency agreement between NIGMS and the Atomic Energy Commission (AEC), conceptually new instrumentation for analytical chemistry has been developed. This "Fast Analyzer" instrumentation has demonstrated its usefulness in clinical and research laboratories during the past year. The principal impact of this instrumentation has been to decrease the cost and increase by manyfold the rate at which analytical chemistry analyses may be performed.
2. Through an interagency agreement between the National Bureau of Standards and NIGMS, the Bureau is developing and producing a number of certified standard reference materials that are of vital importance to clinical chemistry laboratories.
3. In our Body Fluids Analyses Program, also conducted under an interagency agreement between NIGMS and the AEC, automated high resolution analytical systems are being developed for clinical laboratories. Techniques are being studied which will enable the laboratory scientist to identify and quantitate large numbers of the molecular constituents of body fluids, particularly organic compounds of low molecular weight.

4. A new NIGMS-supported computerized system has been developed that rapidly processes and evaluates laboratory diagnostic data. This system has been installed recently in 12 North American hoespitals, with another 12 scheduled to get the system in the next few months. The system is designed to improve patient care by making available to the physician cumulative daily summaries of all laboratory work done on each of his patients.

Recognizing some possible shortcomings, we still must emphasize that the only way to meet the shortage of physicians, scientists, and technical staff in the laboratory is to move in the direction of automation. While going in this direction, it is important to stress that there will be a need for a much larger number of laboratory physicians, laboratory scientists, and technicians than we have today because of the expanding demand for laboratory services arising not only from patients who are sick, but from well people who want to stay that way via health maintenance programs.

TRAINING FOR PHARMACOLOGISTS AND TOXICOLOGISTS

Mr. FLOOD. Mrs. Reid?

Mrs. REID. Thank you, Mr. Chairman. Doctor, how much support are you giving to the program for training pharmacologists and toxicologists?

Dr. STETTEN. For training toxicologists and pharmacologists, the total of fellowships and training comes to $5.2 million in 1971.

Mrs. REID. For the two?

Dr. STETTEN. Yes, for the two.

TRAINING GRANT AND FELLOWSHIP AWARD CRITERIA

Mrs. REID. What criteria do you use in awarding training grants and fellowships and career development awards?

Dr. STETTEN. We have a standing committee which sends consultants to the institutions which have submitted applications to us. The training grant committee meets in full session and reviews the scientific program, the quality of the faculty and students, and the overall quality of the program in terms of the breadth of training provided in appropriate scientific disciplines and the depth of training in a specific research field. Then the award is either disapproved or approved and a priority assigned.

MAJOR RESEARCH CONTRACTS

Mrs. REID. Woud you supply for the record a listing of your major research contracts by institution?

Dr. STETTEN. All institutions?

Mrs. REID. Yes, research contracts.

Dr. STETTEN. Yes.

(The information referred to follows:)

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

COLLABORATIVE RESEARCH AND DEVELOPMENT

Contractor	Contract No.	Total Contract Period	Title and Purpose	FY 1971	FY 1972 Estimated
NATIONAL BUREAU OF STANDARDS	Interagency Agreement	4/22/69-6/30/71	"A Standard Reference Materials Approach to Clinical Chemistry" - Develop standards through which the nation's clinical laboratories may be brought into close control (scientifically).	$ 338,000	$ 340,000
OAK RIDGE NATIONAL LABORATORY	Interagency Agreement	2/14/69-6/30/71	"General Medical Sciences-GeMSAEC Fast Clinical Analyzer." - Exploration of new methods for performing large numbers of analyses on clinical samples rapidly and with precision.	222,000	230,000
OAK RIDGE NATIONAL LABORATORY	Interagency Agreement	6/21/66-3/31/72	"Molecular Anatomy Program: High Resolution Analysis of Body Fluids Analyses" - Conduct a research program consisting of the following: (1) High resolution analysis of urine; (a)the further development and application of semi-portable automated chromatographic systems, (b) the development and application of clinically oriented miniature chromatographic systems, (c) an investigation of separatory materials for chromatographic systems, and (d) the development and application of miniaturized, trouble-free systems for sample processing and analysis; (2) Basic studies on automated bioanalytical systems.	622,500	325,000

Contractor	Contract No.	Total Contract Period	Title and Purpose	FY 1971	FY 1972 Estimated
OAK RIDGE NATIONAL LABORATORY	Interagency Agreement	2/14/69-12/31/71	"NIH-AEC High Resolution Electron Microscopy Program" - This program is concerned with (1) sample purification and preparation; development of a reliable noncrystalline test object; (2) theoretical studies of electron optics; and (3) experimental studies of high voltage stabilization, lens design and performance, field emission, electron beam source, image intensification readout.	100,000	100,000
AMERICAN COLLEGE OF SURGEONS	NIH-69-95	2/14/69-4/30/72	"Transplantation Registry" - Establish and maintain a transplantation Registry for recording data concerning vital organs. (A joint participation financed by NHI, NIAID, NCI, NIAMD, NIDR and NIGMS.)	30,000	30,000
BAYLOR COLLEGE OF MEDICINE	NIH-69-2161	6/23/69-7/31/71	"Development and Use of Analytical Methodology for Pharmacology--the Biochemistry and Pharmacology of the Polyene Macrolides" - The objectives of this work are: (1) the development of new analytical methods, based primarily on gas phase analytical biochemical techniques, for the study of human metabolic changes induced by polyene macrolides, (2) the development of model systems for the study of the enterophepatic circulation of metabolites and drugs in animals and in humans, (3) the study of metabolic changes, including those associated with cardiovascular disease (atherosclerosis) in humans, caused by drugs of the polyene macrolide group, and (4) the clinical study of effects on prostatic and testicular tissue of these drugs.	453,300	250,000

Contractor	Contract No.	Total Contract Period	Title and Purpose	FY 1971	FY 1972 Estimated
RESEARCH TRIANGLE INSTITUTE	PH43-65-1057	6/30/65-7/31/71	"Investigations in Drug Metabolism" - Investigations of the metabolism of steroidal hormones and drugs; development of new techniques for study of drug metabolism, in particular the application of combination of gas chromatography and mass spectrometry techniques.	950,000	900,000
TUFTS UNIVERSITY	PH43-67-1485	6/29/67-7/31/71	"Comprehensive Drug Utilization Program" - This project supports a program in clinical pharmacology which will identify and characterize adverse and hazardous drug reactions, utilizing epidemiological techniques.	735,000	850,000
UNIVERSITIES ASSOCIATED FOR RESEARCH & EDUCATION IN PATHOLOGY, INC.	PH43-66-966	6/23/66-6/30/71	"To Operate a Registry of Tissue Reactions to Drugs" - The Registry shall assemble autopsy, surgical and biopsy specimens from cases of suspected adverse drug reactions; study the material by various methods, solicit scientific counsel as needed, prepare and correlate findings and opinions on such cases. (A joint participation financed by AMA, FDA, and NIGMS.)	20,300	-
NATIONAL ACADEMY OF SCIENCES	PH43-64-44 Task Order 5	5/1/66-4/30/72	"Support of the Drug Research Board" - The Drug Research Board serves as a forum in which the problems, responsibilities and opportunities of academic and professional medicine, of Government and of industry in regard to research on the development of new drugs, can be delineated and integrated toward a more coherent and productive national effort.	95,000	50,000

Contractor	Contract No.	Total Contract Period	Title and Purpose	FY 1971	FY 1972 Estimated
NATIONAL ACADEMY OF SCIENCES	PH43-64-44 Task Order 13	6/11/64-6/25/71	"Biochemical Nomenclature and Specifications" Establish and maintain an office of Biochemical Nomenclature to coordinate information concerning biochemical nomenclature efforts of national and international organizations. Prepare and publish criteria and specifications for biochemical materials used in research.	25,000	25,000
AM. PHARMACEUTICAL ASSOCIATION		6/1/71-5/30/72	"31st International Congress of Pharmaceutical Sciences Symposium" - partial support of the main Symposium, "Optimizing Drug Activity."	5,000	-
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE	NIH-70-2082	3/3/70-2/29/72	"The Use of Deoxyribonucleic Acid as a Therapeutic Agent to Treat Inborn Errors of Metabolism" - To produce a particle consisting of a specific animal gene protected by a virus coat and to demonstrate the biological activity of this gene in correcting the corresponding genetic defect in animals.	88,300	-
COLLABORATIVE RESEARCH, INCORPORATED	PH-43-67-1157	6/5/67-8/4/71	"Synthesis of Polyoligoribonucleotides of known sequence" - To achieve a substantial upgrading of the present methods and potentialities for oligonucleotide synthesis involving primarily: (1) the development of new and more versatile protecting groups; (2) the development of simple practical methods for isolating pure oligonucleotide products. The second phase of the work will be the actual syntheses of a variety of specific oligonucleotide segments of molecules of particular interest. The third phase will be concerned with the assembly of these oligonucleotide segments into larger molecules.	87,000	90,000

Contractor	Contract No.	Total Contract Period	Title and Purpose	FY 1971	FY 1972 Estimated
EXCERPTA MEDICA FOUNDATION	NIH-71-2086	6/30/66-1/31/72	"Translation and Publication of Human Genetics Abstracts" - Approximately 3,200 abstracts in the field of human genetics will be translated where necessary, and published in English. Human Genetics abstracts will be based on material derived from a comprehensive screening of the current world-wide literature in the basic medical and biological sciences, clinical specialties, and related areas such as anthropology, psychology and sociology.	22,500	22,000
OAK RIDGE NATIONAL LABORATORY	Interagency Agreement	5/19/66-6/14/71	"Biological Macromolecular Separations Technology" - Research and development of three scientifically divided problem classes: (1) separation methods for macromolecules; (2) analytical methods; (3) unit operation (productionfacility). The purpose is to develop the technology of preparing macromolecules the present lack of which constitutes a bottleneck to the progress of important areas of biomedical science. Present thrust is on preparation of transfer RNA's. The research program includes the necessary theoretical, physical, chemical, biological, and engineering studies.	565,100	256,000

62-645 O - 71 - pt. 3 - 56

Contractor	Contract No.	Total Contract Period	Title and Purpose	FY 1971	FY 1972 Estimated
OAK RIDGE NATIONAL LABORATORY	Interagency Agreement	6/21/66-6/30/71	"Mammalian Comparative Mutagenesis" - Provides basic information for the estimation of genetic hazards of exposure of human beings to chemical mutagens. The purpose of this program is to explore in detail the mutation process in the mouse, specifically the induction of mutation by various classes of chemicals both combined and individually. The mouse is the mammal of choice because of the detailed knowledge of its genetic structure and because of the mouse genetic facilities available at the ORNL. The studies seek to establish the kinds of mutations which may be used for evaluating the mutagenic potential of drugs and chemicals in mammals and predicting the hazard for man.	77,000	-
NATIONAL ACADEMY OF SCIENCES	PH 43-64-44 Task Order 26	11/17/65-12/31/71	"Evaluative Study of the Training Grant Program" To carry out an evaluative study of the NIGMS Graduate Research Training Grant and Fellowship Programs. The data base built up in the earlier phases of the contract is a valuable foundation for additional work. The present contract provides for (1) maintenance and updating of the Trainee/Fellow file with the NIGMS file; (2)providing reports from the NIGMS file on request; (3) development of a mathematical model of the impact of NIGMS support on bioscience departments; (4) study of the manpower flow in the biosciences, from the baccalaureate through postdoctoral professional employment.	105,000	80,000

Contractor	Contract No.	Total Contract Period	Title and Purpose	FY 1971	FY 1972 Estimated.
NATIONAL ACADEMY OF SCIENCES	PH 43-64-44 Task Order 17	12/8/64-12/31/71	"U. S. National Committee for the International Union of Physiological Sciences" - Partial support to promote research in the physiological sciences in the USA, giving particular attention to those aspects which call for international cooperation.	7,000	-
			TOTAL.	4,548,000	3,548,000

PROGRESS AGAINST HEMOPHILIA

Mrs. REID. Have there been any important new discoveries in regard to the control of hemophilia?

Dr. STETTEN. There are preparations today available of antihemophilic factor, which is manufactured from the blood of normal individuals. Such material is safer and simpler to administer than is whole blood. Its cost, unfortunately, makes it unavailable to many hemophilic patients.

This is not an area in which I claim any particular expertise. These patients today can be adequately controlled, but they had better stay fairly close to medical clinics. In this disease, as in other genetic defects, whereas we have no cure, we can treat the patient by replacement of the deficient product.

TAY-SACHS DISEASE

Mrs. REID. You mentioned Tay-Sachs disease. Is this relatively new insofar as the United States is concerned?

Dr. STETTEN. No, it has been known for a number of years. It was known under the name of amaurotic family idiocy. As sickle-cell disease is peculiar to people with black ethnic background, this is a disease of the Jewish people, particularly of that group known as the Ashkenazi Jews of central Europe.

It is rarely found in families which have no ancestry in this group.

Mrs. REID. That is all, Doctor.

Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Conte?

LONG-RANGE GOALS AND PLANS

Mr. CONTE. It is my understanding that the Institute has been directed to come up with a long-range plan outlining the major problems and goals in its field. Has this been done? If so, would you summarize the major recommendations of this plan and indicate how much it would cost to implement it?

Dr. STETTEN. We have, of course, made within the National Institute of General Medical Sciences long-range plans regarding major problems and goals within our mission. We have developed these plans most completely in the area of genetics where a specific assignment to direct our efforts has been given. Specifically, we consider the following tasks to be necessary and responsive to the directive.

1. The establishment of ten to twelve genetics research and training centers at major medical schools, serving to support both sophisticated research at basic and clinical levels, and the training of various types of specialists needed to implement the program. Among these may be mentioned population geneticists, professional genetic counselors, cytologic technicians, in addition to the more usual cell biologists, microbial geneticists, and enzymologists. Such centers would average $600,000 a year for their total operation for a total cost of $7.2 million.

2. The creation of approximately 15 clinical research and demonstration centers in teaching hospitals throughout the country. These will provide the complete enzymologic and cytologic study of individuals in that geographic area who may be harboring one or another genetic defect. It is here that the local physician can refer special problems in diagnosis and therapy. Such clinical centers may cost $300,000 a year each to operate for a total cost of $4.5 million.

3. Additional funds for individual research projects conducted by qualified investigators in genetics whose needs were not met by last year's appropriation. A total of 50 additional awards averaging $50,000 each would meet this need for a total cost of $2.5 million.

4. For provision of centralized services and resources for use of scientists and clinical investigators. These resources include: the establishment of a bank of surviving mutated human cells for research and diagnostic purposes, and for hybridization studies; the development of more rapid procedures for growth of fetal cells from amniotic fluid to increase the speed of diagnosis; and the establishment of a national registry of genetic diseases to which physicians will be encouraged to report relevant diagnoses. This latter component is important because it will permit ultimately the determination of frequency of each of the several diseases. This would cost about $2 million.

5. The development of truly multidisciplinary attacks on the problems of genetic disease by the provision of additional postdoctoral and special fellowships. These fellowships will be used, for example, to place a biomedical engineer into a genetics center to develop automated techniques of chromosome analysis and automated analysis of enzymes from single cells; or epidemiologists or statisticians into a genetics department to analyze the environmental and genetic components of complex diseases—such as diabetes, hypertension, and many forms of mental illness—in which heredity and environment are both known to have a significant role. Possibly 65 such fellowships could initially be profitably filled, with the number to grow as the program develops at a cost of about $1 million.

The total cost of such a program in its initial complete year of operation would approximate $17.2 million. It is envisioned that additional opportunities exist, and the program could usefully double in magnitude over the ensuing 5 years.

LEVEL OF MEDICAL SERVICE IN 2000 A.D.

Mr. CONTE. What "more sophisticated level of medical attention" do you foresee for the average American by the end of the 20th century?

Dr. STETTEN. Medical science advances so rapidly that it is hazardous to forecast where we shall be in the year 2000. I would assume that enormous advances will be made in skill and rapidity of diagnostic procedure. We have already seen a rapid expansion in the use of radioisotopes in medicine and are now seeing the beginnings of the applications of sonic diagnostic devices, holographic technology, and the use of cell cultures to assist in the attainment of proper diagnoses. With advancing technology, all methods presently in use and those which have yet to be discovered will become both rapid and, hopefully, sufficiently inexpensive to be generally available. The futures in treatment are also difficult to forecast. By the year 2000, many of the today lethal diseases will certainly be curable. Over the past generation, diabetes, pernicious anemia, Addison's disease, subacute bacterial endocarditis, and a host of others have ceased to be life-threatening diseases, because of increasing sophistication and skill in therapy. This progress will surely continue and may well include the major killer diseases, such as cancer, cardiovascular disease, hypertension, and so forth.

ADVANCES IN DIAGNOSIS OF GENETIC DISEASE

Mr. CONTE. What advances have been made over the last several years with regard to detecting the presence of genetic disease in newborn children?

Dr. STETTEN. The major, single advance has probably been the application of the technique of aminocentesis to permit intrauterine diagnosis of genetic diseases. An understanding of the single enzyme defects which occur as a result of genetic disease has permitted the creation of a variety of diagnostic tests which detect these diseases. This has not only permitted the physician to give a far more accurate prognosis than would otherwise have been possible, but has in many instances provided the physician with an immediate means of treatment. Examples of diseases which can today be quite precisely diagnosed include phenylketonuria, galactosemia, the several glycogen storage diseases, the several abnormalities of hemoglobin synthesis, among others.

IDENTIFICATION OF FAULTY RECESSIVE GENES

Mr. CONTE. Would you describe what efforts you are engaged in to improve methods for identifying persons with diseases in the recessive state?

Dr. STETTEN. At this time, a test is hopefully being devised to permit unequivocal identification of the heterozygous carrier of cystic fibrosis. For many of the diseases in this group, we have little in the way of clear-cut results to report. In sickle cell disease, we have long been able to determine the heterozygote. There is every reason to expect, however, that for every identified single protein defect, we should, given adequately sensitive methods, be able ultimately to identify the carrier of this defect.

COMPLETION OF THE GENETICS REVIEW

Mr. CONTE. When will your review of the genetics field be completed?

Dr. STETTEN. Our consultant who is working with us in this area will probably have a quite complete study in hand within the next few months for the consideration of our staff and committees. From this review, a comprehensive plan of action will be developed during the course of the coming year.

ADDITIONAL PROJECTS FUNDED IN FISCAL YEAR 1972

Mr. CONTE. You indicate on page 49 of the justifications that plans are now being made to fund additional projects in genetics. How many will be funded and what are their missions?

Dr. STETTEN. 159 additional applications for research grants in the field of genetics of good to high quality are being funded that would not otherwise have been paid. Projects range from research on the genetics of bacteria and viruses to studies on the process of genetic mutation and possible mechanisms of repair; the detailed structure of the genetic material and of the machinery within the cell which translates genetic information into proteins; the processes of genetic control within the mammalian cell as mediated by hormones and other chemical factors; clinical investigations on human genetic disease at the

level of the patient, the level of the diseased cell in culture, and at the molecular level of the specific nucleic acids and proteins involved; and finally to broad studies relating to population genetics.

STUDIES IN PEDIATRIC PHARMACOLOGY

Mr. CONTE. What have your efforts over the past 2 years to stimulate studies in pediatric pharmacology accomplished? What studies have been initiated and what have they achieved?

Dr. STETTEN. A program project in perinatal pharmacology has been established at Baylor College of Medicine to study the actions of drugs on the infant prior to birth. The accomplishments of this research program include: (1) the finding that nearly all drugs taken by the mother pass to the fetus through the placenta, (2) drugs that pass through the placental barrier can be identified in the infant at birth on two to three drops of blood from the umbilical cord, using highly sensitive analytical techniques, and (3) certain drugs frequently taken by mothers during pregnancy and delivery are highly toxic to the infant. These include several major tranquilizers; barbiturates; morphine, demerol, and other narcotics.

PROGRAMS CUT BY REDUCTION IN COLLABORATIVE RESEARCH AND DEVELOPMENT

Mr. CONTE. What programs are going to be deemphasized as the result of your planned cutbacks in collaborative research and development?

Dr. STETTEN. Instrument development projects in several collaborative research and development programs are nearing completion and the initial prototypes of instruments developed are now ready for industry to put into production. Cuts in the collaborative research and development program will necessarily come in this area.

Mr. CONTE. That is all, Mr. Chairman.

Mr. FLOOD. Thank you, Dr. Stetten.

DR. STETTEN'S QUALIFICATIONS

Dr. MARSTON. If you will permit me, Mr. Chairman, I would like to say, since this is Dr. Stetten's first appearance before this committee, that the filling of this job was one of the most important things that has occurred since I have been Director of the National Institutes of Health. We made a thorough national search for the best person that we could find. I have been particularly pleased that we were able to persuade a distinguished scientist and educator to come back to the NIH after several years away and to become Director of this Institute. He has been of great help, not only in the running of the Institute but in advising me and my staff on the whole broad course of NIH programs.

Mr. FLOOD. I am glad to hear you say that, Dr. Marston. We feel a lot better about the future of research in genetics after hearing your testimony than we did after reading the justifications, Dr. Stetten.

Dr. STETTEN. Thank you, sir. I will bear that in mind next year when I appear.

Mr. FLOOD. We think you will do an excellent job as Director.

Dr. STETTEN. Thank you.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Amounts Available for Obligation

	1971	1972
Appropriation	$166,072,000	$150,400,000
Real transfers to: (Proposed transfers for increased pay costs)		
"National Heart and Lung Institute"	-1,446,000	---
"Health Manpower"	-816,000	---
"Division of Dental Health"	-363,000	---
"National Cancer Institute"	-898,000	---
"National Institute of Dental Research"	-183,000	---
"National Institute of Allergy and Infectious Diseases "	-119,000	---
"National Institute of Child Health and Human Development"	-262,000	---
"Division of Research Resources"	-44,000	---
"National Library of Medicine"	-229,000	---
"Office of the Director"	-236,000	---
"St. Elizabeths Hospital"	-1,282,000	
Comparative transfers to:		
"Office of the Director"	-21,000	---
"National Heart and Lung Institute"	-429,000	---
"Health Manpower "	-5,361,000	---
Comparative transfer from:		
"National Heart and Lung Institute"	+144,000	---
Total obligations	154,527,000	150,400,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
54	Research	---	$87,892,000	---	$87,657,000	---	-$235,000
	General Research support grants		(6,978,000)		(6,218,000)		(-760,000)
	Scientific evaluation grants		(1,487,000)		(1,487,000)		---
	Pharmacology-Toxicology research		(3,593,000)		(3,593,000)		---
	Anesthesiology and Diagnostic Radiology centers		(950,000)		(950,000)		---
61	Fellowships		18,454,000		15,142,000		-3,312,000
65	Training		38,385,000		38,385,000		---
	Direct operations:						
70	Collaborative research and development	---	4,548,000	3	3,607,000	+3	-941,000
72	Training activities	15	354,000	15	373,000	---	+19,000
72	Review and approval of grants	120	3,577,000	123	3,846,000	+3	+269,000
73	Program direction	56	1,317,000	56	1,390,000	---	+73,000
	Total obligations	191	154,527,000	197	150,400,000	+6	-4,127,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions.....	191	197	+6
Full-time equivalent of all other positions.....	5	5	---
Average number of all employees.....	192	200	+8
Personnel compensation:			
Permanent positions.....	$2,530,000	$2,781,000	+$251,000
Positions other than permanent.....	44,000	54,000	+10,000
Other personnel compensation.....	24,000	24,000	---
Subtotal, personnel compensation....	2,598,000	2,859,000	+261,000
Personnel benefits.....	262,000	289,000	+27,000
Travel and transportation of persons..	161,000	172,000	+11,000
Transportation of things.....	22,000	22,000	---
Rent, communications, and utilities...	156,000	171,000	+15,000
Printing and reproduction.....	157,000	161,000	+4,000
Other services:			
Project contracts.....	4,548,000	3,603,000	-945,000
Payment to NIH Management Fund.....	1,675,000	1,772,000	+97,000
Other.....	135,000	81,000	-54,000
Supplies and materials.....	60,000	62,000	+2,000
Equipment.....	22,000	24,000	+2,000
Grants, subsidies, & contributions....	144,731,000	141,184,000	-3,547,000
Total obligations by object.....	154,527,000	150,400,000	-4,127,000

Summary of Changes

1971 estimated obligations	$154,527,000
1972 estimated obligations	150,400,000
Net change	-4,127,000

	Base Pos.	Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase costs	---	---	---	+$125,000
2. Within-grade pay increase	---	$2,517,000	---	+51,000
3. FTS rate increase	---	50,000	---	+15,000
4. Additional day of pay in 1972	---	---	---	+12,000
5. Non-competing continuation grants	---	---	---	+3,498,000
B. Program:				
1. Collaborative research and development	---	4,548,000	+3	+55,000
2. Review and approval	---	2,030,000	+3	+65,000
C. Payment to the "NIH Management Fund" for centrally furnished services	---	1,636,000	---	+97,000
Total, increases	---	---	+6	+3,918,000
Decreases:				
A. Program:				
1. Research grants	---	6,978,000	---	-3,733,000
2. Fellowships	---	18,454,000	---	-3,312,000
3. Collaborative research and development	---	4,548,000	---	-1,000,000
Total, decreases	---	---	---	-8,045,000
Total, net change	---	---	+6	-4,127,000

Explanation of Changes

Built-in Increases: These increases will provide: $125,000 for annualization of pay increase costs effective in fiscal year 1971; $51,000 for within-grade pay increase in 1972; $15,000 for increased rate in 1972 of using the Federal Telecommunications System; $12,000 for an additional day of pay in F.Y. 1972 and $3,498,000 for non-competing continuation of research grants.

Research Grants: The total program decrease of $3,733,000 reflects a decrease of $2,973,000 for competing projects and $760,000 for general research support grants, a program included in each NIH Appropriation containing research grant projects, but administered separately by the Division of Research Resources.

Fellowships: The total program decrease of 460 awards and $3,312,000 reflects a reduction of 414 new awards amounting to $2,726,000, 33 awards in non-competing projects for $385,000, 13 awards in competing awards for $195,000 and $6,000 for supplementals. This represents a reduction of 216 predoctoral awards, 196 postdoctoral, 43 special, 3 development awards, and 2 career awards.

Collaborative Research and Development: The total program decrease of $941,000 includes three positions and $59,000 for costs required to administer the contracts program of the Institute. A decrease of $1,000,000 for contracts is reflected in the area of biomedical engineering and automated clinical laboratories.

Review and Approval: The program increase of three positions and $65,000 will provide additional staff required to effectively develop and administer the genetics program.

Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1971 House Report	
Genetics	
1. The Committee feels that the time has come to recognize the importance of the synthesis of the gene and other equally dramatic developments in the science of inherited human qualities. It is mindful that genetic knowledge ultimately will solve a whole spectrum of diseases. Current knowledge in this field must be brought into focus and the leads at hand developed in an orderly way.	1. The focal point for this effort will be within NIGMS. Each of the categorical Institutes will collaborate through a task force to be established by the Director of NIH. Plans are now being made to fund additional projects in genetics and develop certain knowledge related to genetics.

Authorizing Legislation

Legislation	1972 Authorized	1972 Appropriation requested
Public Health Service Act Section 301--Grants programs.....	Indefinite	$150,400,000
Title IV, Part E, Institutes of Child Health and Human Development and of General Medical Sciences.....	Indefinite	150,400,000

PUBLIC HEALTH SERVICE ACT

The legislative authority in Section 301 of the Public Health Service Act which provides for the award of grants for research, research training, and fellowships is included in the section of the justifications under the tab, "Preamble Paragraph" in Volume IV.

"Sec. 442. The Surgeon General is authorized, with the approval of the Secretary, to establish in the Public Health Service an Institute for the conduct and support of research and research training in the general or basic medical sciences and related natural or behavioral sciences which have significance for two or more other institutes, or are outside the general area of responsibility or any other institute, established under or by this Act."

"Sec. 444. The Surgeon General shall, through an institute established under this part, carry out the purposes of sections 301 with respect to the conduct and support of research which is a function of such institute...."

"Sec. 433. (a) .... In addition, the Surgeon General is authorized to provide training and instruction and establish and maintain traineeships and fellowships, in such institute and elsewhere, in matters relating to the diagnosis, prevention, and treatment of such disease or diseases with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he may deem necessary, and in addition, provide for such training, instruction, and traineeships and for such fellowships through grants to public and other non-profit 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

	1971 Estimate	Purpose
Real transfers to:		
National Heart and Lung Institute	-$1,446,000	Proposed transfers for increased pay costs.
Health Manpower	-816,000	
Division of Dental Health	-363,000	
National Cancer Institute	-898,000	
National Institute of Dental Research	-183,000	
National Institute of Allergy and Infectious Diseases	-119,000	
National Institute of Child Health and Human Development	-262,000	
Division of Research Resources	-44,000	
National Library of Medicine	-229,000	
Office of the Director	-236,000	
St. Elizabeths Hospital	-1,282,000	
Comparative transfers to:		
Office of the Director	-21,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director for establishing the Office of Contracts and Grants.
National Heart and Lung Institute	-429,000	Transfer of regular research grants for the pulmonary research program.
Health Manpower	-5,361,000	Transfer of institutional support funds to Health Manpower.
Comparative transfers from:		
National Heart and Lung Institute	+144,000	To provide an equitable distribution of the management fund in 1972.

National Institute of General Medical Sciences

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
1966	$124,538,000	$124,538,000	$129,388,000	$127,188,000
1967	137,175,000	142,613,000	145,113,000	145,113,000
1968	160,284,000	160,284,000	164,284,000	160,284,000
1969	165,777,000	161,250,000	166,250,000	163,513,000
1970	154,288,000	154,288,000	175,000,000	164,654,274
1971	148,376,000	166,072,000	171,072,000	166,072,000
1972	150,400,000			

Note: Included in "General Research and Services, National Institutes of Health," appropriation prior to 1966.

Justification

National Institute of General Medical Sciences

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	191	$2,860,000	197	$3,148,000	6	+$288,000
Other expenses	-	151,667,000	-	147,252,000	-	-4,415,000
Total	191	154,527,000	197	150,400,000	6	-4,127,000

General Statement

The National Institute of General Medical Sciences supports a broad base of fundamental research that seeks elucidation of those life processes whose alteration or disturbance may lead to disease. In addition the Institute develops and supports research programs on certain major health problems and in certain clinical specialties, the responsibility for which lies beyond the purview of the categorical Institutes. Specific programmed research objectives are to develop new knowledge for safer and more effective use of drugs, to understand the genetic basis of disease, to improve health services through the application of engineering knowledge to medical care; and to develop more effective automated laboratory procedures to improve and speed the diagnosis of disease. The Institute also has principal responsibility for training young medical scientists in some 20 preclinical and clinical disciplines, thus reinforcing strongly the total National Institutes of Health research effort.

The National Institute of General Medical Sciences is requesting a total of $150,400,000 for F.Y. 1972, a decrease of $4,127,000 from F.Y. 1971.

Research Grants

	1971	1972	Increase or Decrease
Research projects.....	$74,884,000	$75,409,000	+$525,000
Special projects.....	13,008,000	12,248,000	-760,000
Total research grants.....	87,892,000	87,657,000	-235,000

Introduction

The NIGMS has a broad mission to support fundamental research in the sciences basic to medicine. The primary goal of these research programs is knowledge and scientific discovery that will lead to a deeper and more comprehensive understanding of life processes--knowledge and understanding that are essential to progress in all areas of medical research and contribute to the advance of the research programs of each of the categorical Institutes.

In addition to the support of fundamental research, NIGMS has two other significant tasks:

a. The selective support of research projects in such fields as anesthesiology, radiology, and general surgery--clinical specialties which do not relate directly to the mission of any of the categorical Institutes and hence have been relatively neglected in the past.

b. The development of research programs dealing with broad medical problems that are not appropriately handled by the existing categorical Institutes. Examples include research on trauma, the problems of pharmacology and toxicology as they arise from the use and misuse of drugs, and research relating to biomedical engineering and the automation of clinical laboratories--all of which have an important bearing on the delivery of health services.

Program Plans in 1971-1972

A special program is being developed on the genetics of disease, with emphasis both on the acquisition of basic knowledge and on clinical aspects of its application. Other areas of the fundamental sciences will continue to receive support on a competitive basis. Ongoing special programs (trauma, anesthesiology, diagnostic radiology, pharmacology/toxicology, automation of clinical laboratories, and biomedical engineering) will receive program emphasis in accordance with their needs and opportunities for development.

Fundamental Sciences

Support of the fundamental sciences can be justified both in terms of the immediate value of the knowledge gained in improving the diagnosis, treatment, and prevention of disease, and, more importantly, in terms of its long-term value to mankind. In a very real sense, support of the basic medical sciences can be regarded as a capital "one-time" investment made by this generation not only for its own benefit but for all future generations. The immediate gain is great; the long-range value is beyond measure.

The pay-off of fundamental research can best be demonstrated by noting some of the major advances in knowledge that have emerged from the biomedical sciences at an accelerating rate during this past century. The past century has seen:

-- The first proof that disease can be caused by bacteria and viruses.
-- The development of antiseptics, vaccines, and antibiotics.
-- The abolition of the great plagues that previously afflicted mankind.

-- Major advances in our understanding of the nature of disease as it affects the various organs and tissues of the body.

The past half-century has seen:

-- The discovery that many proteins of the body are enzymes, each of which catalyzes a specific chemical reaction within the body.
-- The description of the thousands of different enzymes that carry on the complex metabolic activities of the living organism.
-- The first clear demonstration that disease can result from an alteration in protein structure (sickle-cell anemia, 1949).
-- Extensive studies on the structure of enzymes and other proteins, and how alterations in this structure can lead to disease.

The past score of years has witnessed:

-- The affirmation of the one-gene, one-enzyme hypotheses: that the detailed information determining the structure of each enzyme, or protein, is encoded within the deoxyribonucleic acid (DNA of the nucleus) and that each enzyme, or protein, is represented by a single gene.
-- The description of the structure of DNA as a double spiral or helix by Watson and Crick in 1953, and the first enzymatic synthesis of DNA by Kornberg and of ribonucleic acid (RNA) by Ochoa.
-- Demonstration of the fact that viruses contain nucleic acids which modify and regulate the metabolic processes of cells they infect.

The past decade has seen:

-- The cracking of the genetic code by Nirenberg in the early 1960's.
-- Discovery of the processes by which information encoded within the DNA is first translated to ribonucleic acid and then transcribed into protein.

As we look to the 70's and 80's it can be predicted that the biomedical sciences will explore:

-- The detailed structure of the 46 chromosomes within the nucleus of each cell to see how the information is encoded and stored within the DNA.
-- The way in which the activity of each gene is turned on and off and controlled to produce the array of different proteins and enzymes that are needed within each cell.
-- The means by which the identical genes in the differentiated cells of one type of tissue--such as muscle--are regulated and directed to synthesize one pattern of enzymes and proteins, whereas those in other tissues and organs--such as skin, liver, and nerve--produce markedly different patterns.
-- How alteration of the information encoded within each gene leads to hereditary disease, and possible methods for its correction.

The fundamental knowledge being uncovered is bound to have a profound impact on our broad understanding of the biology of human cells and how they operate to utilize the information stored within the DNA. The knowledge gained will also increase our understanding of genetic disease and how its often catastrophic effects might be minimized or corrected. There are over 1,000 different diseases which are believed to be genetically transmitted or in which genetic mechanisms appear to have a highly significant role. These diseases range from sickle-cell anemia and cystic fibrosis to mongolism and many forms of mental retardation. Diabetes and high blood pressure are examples of diseases in which genetics appears to have a very important role. Although the incidence of any single genetic disease is not great, these diseases as a group tend to affect the very young; and the toll of mortality, illness, extensive hospitalization, and medical care exacted by them is very high. Since these diseases are transmitted to future offspring, the total burden of genetic disease on mankind is great indeed.

62-645 O - 71 - pt. 3 - 57

The underlying cause of these diseases lies either in the genetic code or in the way the code is read out and translated within the cell. Because of the importance of understanding the fundamental processes which lead to these diseases, it has been proposed in previous testimony before the Congress that a major program on the genetics of disease be developed which emphasizes the further development of fundamental genetic knowledge and the extrapolation of this knowledge into new approaches to the diagnosis, treatment, and prevention of genetic disease. The focal point for this effort will lie within the NIGMS, but Institutes with program interests in genetics will collaborate. An inter-Institute coordinating committee has been appointed to see that these funds are wisely allocated.

The Institute already has a significant base of support in the area of genetics, and the success of this research is leading to the increased feasibility of a major advance in the alleviation of this large group of diseases. Much of this early success can be attributed directly to basic genetic research on biological systems less complex than man, including viruses and bacteria. With the armamentarium of genetic principles thus derived, it is possible now to study the inherited diseases of man more directly.

During the coming year an increasing proportion of available resources will be directed toward human genetic disease. Several areas of emphasis have been selected because they are particularly relevant to the extension of basic genetic knowledge to research on the genetic aspects of disease in man. These include (1) banks of human cell lines wherein strains of human cells representing diverse types of genetic disease can be preserved and used as needed by investigators requiring these cell lines for their research; (2) better methods for the detection of the carrier state of certain genetic diseases; (3) the detailed mapping of the genes on human chromosomes; (4) extensive research on the regulation and control of the expression of the genetic information encoded in the human chromosome.

Although genetics and genetic biochemistry are at the focal point of scientific interest at this time, other fundamental research areas also demand urgent attention. Progress in these areas will have profound implications for cancer research, neurobiology, and for an understanding of the processes of development and aging within the human body. Some of the important problems are listed below:

-- The development of new arrays of instruments and techniques that will help us to explore the detailed structure of proteins and nucleic acids.
-- Development of high-resolution electron microscopes that will enable scientists to visualize the individual atoms of proteins, nucleic acids, and other biological macromolecules.
-- Determination of the internal structure of enzymes to understand how complex chemical reactions, difficult to execute within the laboratory, are carried on with apparent ease within the enzyme molecule.
-- Research on how the structure and biological activity of enzymes and other proteins can be modified by drugs, heavy metals, and other toxic agents, leading to marked changes in the metabolic behavior of the human body.
-- The detailed study of the sequential steps which characterize the cell cycle and the process of cell division, in an attempt to discover the regulatory processes that lead cells into and out of the division process.
-- Studies on the relationship of changes in cell structure to the selective expression of the information encoded within the cell's genetic apparatus.
-- Research on the detailed structure of cell membranes and cytoplasmic organelles; how these structures are formed within the cell, and how they are modified during the cell's life span.
-- Studies on the phenomenon of contact inhibition, by which normal dividing cells stop dividing on contact with other cells--a phenomenon missing in cancer cells.
-- Studies of the biology of cell surfaces and cell junctions, and on the mechanisms by which cells recognize, identify, and communicate with other cells.

-- Detailed studies of the biology of cell movement, and how their movements are regulated and controlled.
-- Detailed studies on the differentiation of primitive cells into the highly specialized forms that make up the array of different tissues and organs of the body.

In accordance with its primary function to support fundamental research in sciences basic to medicine, it is the task of NIGMS to spearhead this drive for basic biological and medical knowledge that will improve understanding of biological processes that lead to disease. Although the immediate "pay-off" of this research is significant, its long-term implications to health are beyond measure. The immediate or short-range "pay-off" can be demonstrated by the fact that for a number of years biochemists have known that hemoglobin is a protein with four subunits consisting of two alpha and two beta globin chains. In thalassemia--a disease common among Mediterranean peoples and their offspring in this country--the beta chains of hemoglobin are made in insufficient amounts while the alpha chains are made in normal quantities. Because of the beta chain deficiency, the red cells are prematurely destroyed in the body, producing persistent and often severe anemia. During the past year, an Institute grantee found evidence of a substance in thalassemic red cells that inhibits beta globin synthesis. Efforts are now being made to isolate the inhibiting factor and determine its chemical nature. This may lead us to clues as to how to prevent the inhibitor from accumulating in thalassemic cells and thus hopefully to the eventual development of successful treatment for this disease. Similarly, during the past several years several NIGMS grantees have been carrying out extensive research on the "microtubules" of cells, which appear to have an important role in cell movement and in the process of cell division. Recently neuropathologists have become intensely interested, since the common senile changes of the aging brain and premature appearance of such abnormalities which constitute an important disease of the nervous system known as Alzheimer's presenile dementia, a disease resulting in premature atrophy of the brain leading progressively to a state of total helplessness and prolonged institutional care, appears to result from microtubular abnormalities. Understanding of the cause may lead ultimately to its correction.

Special Programs

Trauma

Trauma has become a disease of epidemic proportions. It is the leading killer in the 1-44 year age group. Trauma victims require 22 million hospital days each year, equivalent to 120 hospitals of 500 beds each. The cost of personal injuries in 1968 was $17 billion, and 5 million work days were lost.

The Institute now supports nine trauma research centers, sophisticated units designed for the study of man's reactions to injury and for the development of new approaches to patient care, and 30 individual trauma research projects. Many of the problems of trauma require exploration in depth at the biochemical and physiologic level, and involve both basic scientists and clinical investigators. Thus the need for sophisticated monitoring and diagnostic equipment has brought basic science oriented bioengineers into the study teams; while, at the other extreme, psychiatrists are studying behavioral responses to injury. Past investment in the area of burns is beginning to pay off. In severely burned patients, lives have been saved by total fluid replacement within 24 hours; the application of pigskin for human grafting has reduced infection, the leading cause of death from burns; and a new antibacterial agent shows great promise in controlling surface infection in burn patients.

A symposium on trauma sponsored by NIGMS in May 1970 clearly defined a number of critical areas for research, extending from improved resuscitation techniques to better rehabilitation procedures. The research challenges offered by the symposium have resulted in a greater interest in studies of injured patients and an influx of exciting new concepts in trauma care. This program will receive special

emphasis in fiscal year 1972.

Anesthesiology

The NIGMS program in anesthesiology supports research on the use of anesthetic agents, basic physiologic and metabolic changes resulting from anesthesia, relief of pain, management of respiratory failure, resuscitation, and intensive care. The present program includes regular research projects, three multidisciplinary program projects, and four anesthesiology research centers where investigations range from the development of basic information to clinical trial and application of research findings.

The anesthesiologist's responsibilities and expertise involve him in many phases of patient care, including the management of respiratory complications, inhalation therapy, and the use of analgesia in patients with chronic and severe pain. Anesthesia research is being expanded to include studies of the mode of action of inhalation anesthetics and muscle relaxants, the nature and control of pain, obstetrical and neonatal resuscitation, post-operative respiratory complications, and research on the pulmonary and systemic effects of drowning. The Institute plans to continue to develop the program because of its direct impact on the delivery of health services.

Diagnostic Radiology

The purpose of the Diagnostic Radiology Program is to support research on the use of various forms of radiation for the development of new approaches to the diagnosis of disease. The NIGMS program includes one radiology center, one program-project, and 19 individual research projects in a broad research effort utilizing ionizing radiation, radioactive isotopes, infrared radiation, thermography, and ultrasonic techniques for the investigation of structure and function in disease. The development and evaluation of new diagnostic equipment is an important objective of the program. Diagnostic nuclear medicine is an increasingly important area and offers unique opportunities for improved organ visualization studies of the dynamic function of organs and of regional blood flow. The application of new diagnostic techniques to the special problems of trauma patients is expected to make significant contributions to the trauma research program.

Automated Clinical Laboratories

This program has the goal of bridging the gap between new laboratory discoveries and the development of reliable and accurate diagnostic tests which are readily accessible to the physician and can speed the process of diagnosis and treatment. The NIGMS program focuses on the development and testing of new analytical procedures, the development of standard reference materials, and the design of automated equipment and of the computer hardware essential to reliable and successful automation. Presently available mechanization has already lessened the cost per test to the patient, and it is anticipated that further automation will reflect a substantial further reduction.

A new approach to laboratory analysis has been developed and incorporated into an instrument known as GeMSAEC, under an interagency agreement with the Oak Ridge National Laboratory. Work during the past year has markedly improved the capacity and reliability of this instrument. The first commercial model has now been installed in a clinical laboratory exclusively for service work.

Rapid progress is being made in the automation of bacterial culturing and identification of pathogenic bacteria. Present procedures delay this important identification by at least 24 hours. By means of the automated procedure, this time lag may be reduced to four hours, thus enabling the physician to institute therapy before the bacteria have had a chance to produce septicemia or other serious side effects. This saving in time will also contribute to significant reductions in the cost of hospitalization for patients with serious or life-

threatening infectious disease.

Pharmacology/Toxicology

The overall objective of the Pharmacology/Toxicology Program is to improve medical therapy through improved understanding of the action of drugs and how their action is influenced by other factors, such as genetic differences among patients, concomitant administration of other drugs, etc. These studies are providing a basis for the safer use of presently available drugs and are contributing to the design of more effective therapeutic agents.

The pharmacology/toxicology centers, which provide a wide spectrum of integrated scientific activities ranging from basic laboratory science through to clinical application, are becoming an increasingly important resource for the improvement of medical therapy. During 1972 particular attention will be given to the consolidation and continued development of the existing pharmacology/toxicology centers and to the further development of clinical pharmacology. Newly developing areas which will be emphasized are pharmaco-genetics and chemical mutagenesis.

A badly neglected and important problem has been the lack of adequate knowledge related to the action of drugs in children and infants. During the past two years, efforts to stimulate studies in pediatric pharmacology have been encouraging and will continue to receive emphasis during 1972.

Biomedical Engineering

The program in biomedical engineering combines the mathematical skills and the analytical ability of the engineer with the knowledge and understanding of biological systems by the life scientist, in order to focus upon the solution of engineering problems associated with research on living systems and with the delivery of health care. Engineering methodology is also applied to the processing of medical information.

Significant progress is being made on many research projects. Of particular interest has been the development of telemetry systems for application to medical problems. For instance, a miniature radio telemetry system for monitoring fetal electrocardiograms in obstetrical patients during labor has been developed. This highly reliable, easily operated system permits the attending medical staff to detect important danger signals which indicate the onset of fetal distress. The system has worked equally well in a special perinatal clinical research center and in a typical community hospital. In another NIGMS-supported project a portable telemetry pack to monitor signals from the brain, eye, heart, and muscles has been developed. Although this telemetry pack should have many uses, it is particularly valuable for the study of epilepsy. Patients with this disease are frequently kept in a hospital for a considerable period during which no seizures occur, but the attacks recur when they return home. This telemetry pack will enable physicians to study the brain waves and other physiological characteristics of the patient in his home environment in an attempt to find the precipitating factors leading to the seizures.

During the coming year emphasis will be placed on the application of engineering theory and practice to research on the clinical evaluation and management of critically ill patients through (1) the development of new systems for rapid data acquisition and display that involve new types of transducers and integrated electronic circuitry, and (2) the development and application of mathematical models of physiological control systems to predict more accurately and rapidly the clinical status of the acutely ill patient.

Research Grants Program Analysis

Fields	1971 Estimate	1972 Estimate	Increase or Decrease
Clinical Sciences	$8,911,000	$8,911,000	---
Pharmacology-Toxicology research	6,496,000	6,496,000	---
Bioengineering	9,757,000	9,757,000	---
Behavioral Sciences	867,000	867,000	---
Fundamemtal Sciences	48,853,000	49,378,000	+$525,000
Subtotal regular program	74,884,000	75,409,000	+525,000
General research support grants	6,978,000	6,218,000	-760,000
Scientific evaluation and planning	1,487,000	1,487,000	---
Pharmacology-Toxicology research centers	3,593,000	3,593,000	---
Anesthesiology and diagnostic radiology centers	950,000	950,000	---
Total research grants	87,892,000	87,657,000	-235,000

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting continuations	786	$53,871,000	705	$57,369,000	-81	+$3,498,000
2. Competing projects	284	21,013,000	243	18,040,000	-41	-2,973,000
3. Subtotal regular program	1,070	74,884,000	948	75,409,000	-122	+525,000
4. General research support grants.		6,978,000		6,218,000		-760,000
5. Scientific evaluation and planning		1,487,000		1,487,000		---
6. Pharmacology-Toxicology research centers		3,593,000		3,593,000		---
7. Anesthesiology and diagnostic radiology centers		950,000		950,000		---
8. Subtotal special grants		13,008,000		12,248,000		-760,000
9. Total research grants	1,070	87,892,000	948	87,657,000	-122	-235,000

Fellowships

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Total Fellowships.....	---	$18,454,000	---	$15,142,000	---	-$3,312,000

Introduction:

Through its various fellowship programs, the National Institute of General Medical Sciences fosters the training of highly qualified scholars for research and academic careers in the sciences related to health. To accomplish this objective support is provided for predoctoral, postdoctoral and special fellowships and also for research career program awards. Consistent with the interests and responsibilities of the Institute, fields of training include not only the broad spectrum of fundamental biomedical sciences, but also certain target areas such as biomedical engineering, pharmacology/toxicology, and selected clinical sciences exemplified by anesthesiology, diagnostic radiology and surgery. During fiscal year 1971, some 1,600 individuals will receive support under these several programs in leading institutions throughout the Nation. Many former fellows and awardees are now acknowledged leaders in their respective fields of science, and it can be predicted with confidence that from the pool of talented scholars for whom support is currently being provided will emerge many outstanding biomedical investigators and teachers of the future. Funds requested for 1972 will provide for an estimated total of 1,140 awards in the various programs, about 90% of which will represent continuations and the remainder, new awards.

Program Plans in 1971 and 1972:

Predoctoral Fellowships: Over the past decade, the Institute's program of predoctoral fellowships has provided support for some 5,600 young scholars for graduate training in a wide range of biomedical disciplines of concern to the entire NIH. Indicative of the scholastic success of these fellows in their graduate careers is the fact that, even by the most conservative estimate, no fewer than 4,500 (80 percent) have successfully attained the Ph. D. degree, which is the basic requirement for the pursuit of a career of research and teaching in nearly all institutions of higher learning. Relieved of the necessity of diverting time and energy to income-producing endeavors, these fellows have been able, according to a recent report of the National Research Council, 1/ to complete their doctoral-degree requirements in one to two years less time than would have been possible in the absence of financial support for full-time training.

Recognizing that training grants constitute a more effective and efficient mechanism for the support of predoctoral training than does a system utilizing central review of individually awarded fellowships, the decision was made to phase out the NIH predoctoral fellowships program. Thus, the awarding of new predoctoral fellowships was discontinued early in fiscal year 1971. The NIGMS will honor its commitments to all present predoctoral fellows, and for this purpose an amount of $2,450,000 is requested for the support of an estimated 440 continuation awards in 1972.

Postdoctoral Fellowships: These fellowships serve to enable talented young Ph. D.'s and M. D.'s to receive the additional year or two of advanced training, required with increased frequency because of the growing complexity of the biomedical sciences, to qualify them for responsible positions of research and teaching. That this program is serving as an important source of biomedical research and teaching manpower for our country's academic institutions is evidenced by a recent study of

1/ Effects of NIGMS Training Programs on Graduate Education in The Biomedical Sciences, March 1969

the positions currently occupied by 108 former NIGMS postdoctoral fellows who completed their training during the three-year period ending June 30, 1970. The results of this study indicate that a strikingly large proportion (85 percent) of these former fellows hold positions in academic institutions. Of the 92 so employed, 35 are in schools of medicine, six are in other health professional schools, and 51 are distributed among graduate schools and colleges of arts and science, agriculture, and engineering. Fifteen others are pursuing their careers in government or private research institutes and industrial laboratories, and only one was reported to be unemployed at the time of the survey.

Approximately 400 postdoctoral fellows will be supported by NIGMS in fiscal year 1971, with the $3,368,000 available. A total of $1,716,000 is requested for fiscal year 1972 in order to permit the continuation of this program at an estimated level of 207 awards.

Special Fellowships: The special fellowship program, which is characterized by a high degree of flexibility with regard to eligibility requirements, stipend levels, and duration of award, has proved to be a particularly effective mechanism for implementing the Institute's programmatic objectives. As originally designed, and as administered during the early 1960's, these awards were utilized primarily to support mature scientists in mid-career for appropriate periods of advanced or specialized training in the fundamental sciences for the purpose of updating or otherwise enhancing their research capabilities. In recent years, as the Institute's program goals have become less generalized and more clearly focused on meeting manpower needs in certain targeted areas, the special fellowship program has served as an important vehicle for accomplishing these objectives. It is being utilized to an increasing degree, for example, to support young physicians for research training in selected clinical sciences such as anesthesiology, diagnostic radiology and surgery for careers in academic medicine. In addition, particular emphasis during the last few years has been directed toward the support of qualified young engineers and biologists for training in the interdisciplinary field of biomedical engineering. The success of this latter endeavor is indicated by the fact that in fiscal year 1970, 57 special fellows were receiving training in biomedical engineering, compared to 11 in 1965.

During the current year, and in 1972, continued emphasis in this program will be devoted to the fostering of research training in the targeted areas indicated above. In addition, considerable effort will be directed to the development of more substantial representation in the fields of basic and clinical pharmacology, clinical chemistry, human genetics, and trauma, all of which are in need of well-trained investigators and teachers.

The important contribution of this program to the staffing of our Nation's academic institutions is indicated by the results of a recent survey of the positions currently held by 70 former special fellows whose awards terminated during the period from July 1, 1967, through June 30, 1970. The data reveal that 64 of these individuals (91 percent) are now employed in academic positions. Approximately two-thirds of these (43) are in schools of medicine and the remainder hold posts in other types of schools and colleges.

Thus, the special fellowship program, although relatively small in terms of awardees, is playing an important role in advancing the training missions of NIGMS. The $2,876,000 available for this program during the current year will provide support for approximately 190 individuals, and the $2,176,000 requested for 1972 will permit its maintenance at an estimated level of 148 awards during the forthcoming year.

Research Career Development Awards: This program, which is designed to foster the development of young scientists of outstanding potential for careers of independent research in the sciences related to health, has contributed, and continues to contribute, to an important degree to the provision of faculty members for our Nation's medical schools and other academic institutions. Illustrative of this

contribution are the results of a recent study of the positions currently held by the Institute's former development awardees. The data reveal that, of a total of 373 former awardees, 335 (90 percent) now hold positions in academic institutions. Of these 268 are in schools of medicine, 12 are in schools of dentistry, public health, pharmacy and veterinary medicine, and 55 are in other types of schools or colleges. In terms of rank, 311 (93 percent) of those in academic positions are at the level of associate professor or above. When it is further realized that virtually all of the Institute's current awardees are also contributing to some degree to the teaching and research training of future physicians and biomedical investigators, the significance of this program to academic medicine is eminently clear.

In this program, as in the special fellowship program, continued emphasis is being placed on the encouragement of research and academic careers in such areas of biomedical engineering, basic and clinical pharmacology, anesthesiology, diagnostic radiology and surgery. In addition, an effort will be made through appropriate programming activities to increase representation in the fields of human genetics and trauma research, which have recently been identified as warranting special attention by this Institute.

The $7,714,000 available to this program in fiscal year 1971 will suffice to support 315 development awards compared to 323 for the previous year. These are long-term awards, the costs of which escalate annually as institutional salaries increase. In order to meet ongoing commitments and to maintain this important program at an estimated level of 312 awards during the forthcoming year, a total of $7,800,000 is requested for 1972.

Research Career Awards: Although new career awards have not been granted since 1964, provision must be made for the support of 33 ongoing awards which constitute commitments for fiscal year 1972. For this purpose, an amount of $1,000,000 will be required.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting	1,012	$12,329,000	979	$11,944,000	-33	-$385,000
b. Competing	47	739,000	34	544,000	-13	-195,000
2. Supplementals	(200)	96,000	(125)	90,000	-(75)	-6,000
3. New Awards	541	5,290,000	127	2,564,000	-414	-2,726,000
4. Total fellowships	1,600	18,454,000	1,140	15,142,000	-460	-3,312,000

Fellowships (By type of award)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Predoctoral	656	$3,450,000	440	$2,450,000	-216	-$1,000,000
2. Postdoctoral	403	3,368,000	207	1,716,000	-196	-1,652,000
3. Special	191	2,876,000	148	2,176,000	-43	-700,000
4. Development Awards	315	7,714,000	312	7,800,000	-3	+86,000
5. Career Awards	35	1,046,000	33	1,000,000	-2	-46,000
6. Total Fellowships	1,600	18,454,000	1,140	15,142,000	-460	-3,312,000

Fellowships Program Analysis

Program Area	1971 Estimate	1972 Estimate	Increase or Decrease
1. Clinical Sciences	$1,025,000	$910,000	$-115,000
2. Pharmacology-Toxicology	1,200,000	1,060,000	-140,000
3. Bioengineering Sciences	1,660,000	1,450,000	-210,000
4. Behavioral Sciences	185,000	160,000	-25,000
5. Fundamental Sciences	14,384,000	11,562,000	-2,822,000
6. Total Fellowships	18,454,000	15,142,000	-3,312,000

Training Grants

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Total training grants...	---	$38,385,000	---	$38,385,000	---	---

Introduction

The major purpose of the graduate training grant program of the National Institute of General Medical Sciences is to provide highly skilled medical scientists and faculty for the health professional schools of the United States. Although much of the Nation's biomedical research is conducted within medical schools by their faculties and staff, nearly one-half of the PHS research grants support is awarded to university schools other than medicine, as well as hospitals, research institutes, and industrial laboratories. Consequently, projected needs for trained scientific manpower include these groups.

The development of a broadly based program of medical research and the improvement of the Nation's health care system depend more upon the existence of well-trained manpower than upon any other single factor. Through the collaboration of scientists and physicians the newer knowledge that is emerging from each of the scientific disciplines can make significant contributions to the improvement of the Nation's health care system. Within the biomedical sciences, today's research training is tomorrow's research; today's research is tomorrow's health care. As the citizen of 1970 would be totally dissatisfied with the quality of pre-antibiotic medical care available in 1940, so will the citizen of the year 2000 be dissatisfied with the 1970 level of medical care. Consequently, the NIGMS-trained scientists are an important resource for the research efforts of each of the categorical Institutes of the NIH.

Scientific disciplines encompassed within NIGMS training programs include biochemistry and molecular biology, biomedical engineering and systems physiology, biophysics, medical genetics, pharmacology and toxicology, clinical chemistry, automated clinical laboratory medicine, and trauma. The Institute also is almost the sole source of support for research and academic training in clinical areas such as anesthesiology, diagnostic radiology, and general surgery--disciplines which lie outside the primary missions of the categorical Institutes.

As new areas of science develop and become potentially important to clinical medicine, there must be an adequate supply of scientific manpower to translate research discoveries into meaningful applications. The training of these persons must begin many years in advance of the anticipated need, since a minimum of seven years of graduate training beyond the baccalaureate degree is necessary to produce a fully competent biomedical scientist.

Program Plans in 1971 and 1972

The Institute's policy in recent years has emphasized support of graduate training programs of high scientific merit and demonstrable productivity. To maintain these qualities as well as to be responsive to the dynamic, evolutionary characteristics essential to any scientific endeavor, a significant number of previously funded training grants of lesser merit have been discontinued. These have been replaced, in part, with new programs. Thus the Institute's training programs are continually being reoriented to reflect newly emerging manpower demands, and the development of newer scientific approaches.

The Institute's training programs are organized into four major areas of emphasis: (1) Basic Health Sciences; (2) Pharmacology-Toxicology; (3) Bioengineering

Sciences; (4) Clinical Sciences. Funds requested for 1972 to support these areas will permit approximately 487 awards, compared with 514 in 1971, a decrease of 27.

Basic Health Sciences

Training in six basic science disciplines (anatomical sciences, biochemistry, biophysical sciences, genetics, microbiology, physiology), plus the behavioral sciences and a special multidisciplinary program in biological sciences, constitutes the major category of training programs supported by the NIGMS. Scientists trained in these areas contribute to the development of basic knowledge upon which applications and advances in all clinical sciences are dependent.

The solution of many of the current medical problems often requires simultaneous application of highly specialized knowledge and expertise to several fundamental fields. Recognition of this trend is reflected in the Institute's training programs, which bring together the knowledge and approaches of several disciplines. Interactions are particularly notable among biochemistry, microbiology, and genetics; biophysics, physiology, and engineering; and anatomy and pathology. For example, the development of an effective, modern research and training program in basic and human genetics depends upon advances in research and training in biochemistry. Thus, graduate programs in basic science disciplines are mutually supportive and interdependent, as well as vitally important for research and training in the clinical specialties.

Although the Institute's basic science programs predominantly support predoctoral training in the fundamentals of the basic medical sciences, they also serve to attract and train postdoctoral students from the physical sciences who wish to utilize their unique knowledge and capabilities for medical research. In addition, the Institute's programs support extensive postdoctoral training for physicians who wish to enter careers in medical research.

The Institute plans to continue to strengthen all relevant basic science disciplines and to stimulate their increased involvement with medical problems--both clinical and social in scope. Thorough research training for future faculty of biomedically oriented departments continues to be one of the primary goals of the NIGMS. As new medical schools are established and the size of the classes in ongoing medical schools increases, demands for the graduates of these training programs continue to be great. Scientists trained in each of the basic science disciplines are being increasingly sought to fill positions in clinical departments of medicine, pediatrics, surgery, etc.

Pharmacology-Toxicology Training Program

The last quarter century has witnessed a medical revolution because of many important drugs which have eased the suffering and saved the lives of millions of patients. However, the best drugs are useless if not prescribed, dangerous if misused; and much research must be completed to provide precise and specific information regarding their use. The primary objective of the pharmacology and toxicology program is to eliminate the great shortage of investigators and teachers in this area.

The Institute's training program has had a marked impact on the number of graduate degrees awarded in pharmacology and toxicology. Since 1958 the number of pharmacology degrees awarded annually in the United States has doubled, and more than 50 percent of these individuals received support from NIGMS. More than half of these persons are currently employed in academic research careers in medical schools. This high proportion of trainees engaged in academic careers has helped to alleviate the shortage of faculty members needed in medical schools to maintain superior standards of medical education.

Many emerging areas of research remain neglected, and trained persons in pharmacogenetics, chemical or drug-induced mutagenesis, carcinogenesis or

teratogenesis, immunopharmacology, toxicology, and perinatal and developmental pharmacology are critically needed. To solve many of the health problems associated with drug interactions and toxicity, and to achieve rational therapeutic procedures, emphasis must be placed upon these areas of research training. With increasing interest and need to evaluate and prevent environmental pollution and drug-induced or chemical intoxication, the needs for such individuals will increase dramatically. Despite major efforts on the part of the Institute and its grantees, the areas of clinical pharmacology and toxicology continue to experience severe manpower shortages, and it is expected that these shortages will continue for at least five more years.

Biomedical Engineering Sciences

These programs encourage and enhance the development of the basic engineering sciences which are of obvious importance in solving health care problems. An urgent need exists to bring the knowledge and techniques of bioengineering and biomathematics into medical research. The clinical setting provides a particularly challenging opportunity for fruitful collaboration between physicians and engineers to develop important research programs and innovative new approaches to assure significantly improved patient care.

The program in biomedical engineering combines the engineer's mathematical skills and analytical ability with the life scientist's knowledge and understanding of biological systems. Particular emphasis is placed on the development of new instruments, devices, and systems needed for biomedical research and improved delivery of health services (patient monitoring, intensive care units, and modular segments of hospital information systems). Specialized manpower is urgently needed in specific areas such as the application of engineering concepts to the study of the control of biological systems; bioinstrumentation; biomaterials; use of computers in patient monitoring; prosthetic systems; and the automation of clinical laboratories.

Clinical Sciences

The Institute has research training programs in surgery, diagnostic radiology and nuclear medicine, anesthesiology, pathology. epidemiology, and the special Medical Scientist Training Program. In each program, the trainees gain the competence to conduct basic or applied research closely related to the clinical disciplines. The Medical Scientist Training Program, designed to integrate medical education with graduate-level training in medically relevant scientific fields, is available to a limited number of highly selected individuals. The graduates of these programs are expected to become major contributors to our understanding of human disease and its treatment, and thereby lay the foundation for better medical care. In addition, these special awards have motivated schools to improve and increase the flexibility of their medical curricula.

In response to specific congressional appropriations in 1966 to provide support in those areas where new knowledge and technology are urgently needed, NIGMS expanded and broadened its research and faculty training programs in anesthesiology, surgery, and diagnostic radiology. Anesthesiology and radiology present special problems because of the critical shortage of specialists in these areas. Few radiologists and anesthesiologists remain in medical schools to train additional clinicians urgently needed in these specialties.

Among the research training programs in pathology, there is an increasing emphasis on clinical laboratory science. Because there are only a handful of high-quality training centers in the clinical laboratory sciences, especially those competent in automated systems, progress in this important program has been relatively slow.

Because of mounting concern over the Nation's capability for treating trauma victims, selected surgery programs are directing their research training toward the

pathophysiology of injury and the improved treatment of trauma victims. It is anticipated that committed and planned increases in the medical scientist programs will be achieved through gradual decreases in the current levels of training support in some clinical research training areas, as well as in selected fundamental science programs.

In 1967, the NIGMS initiated a program of five-year training grants for the support of clinical residency programs to increase the number of practicing physicians in anesthesiology. In the interim five years, changed circumstances, such as the initiation of the Medicare and Medicaid programs, the rapid rise in residency salaries paid by hospitals, coupled with the inadequate stipend levels provided by training grants, and the necessity for the NIGMS to concentrate its resources on research and faculty training led to the decision to phase out the support of clinical training grants in anesthesiology at the termination of their present commitments.

Distribution of Training Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting	410	$31,035,000	389	$31,309,000	-21	+$274,000
b. Competing...	88	6,210,000	98	6,726,000	+10	+516,000
2. Supplemental.....	-	100,000	-	-	-	-100,000
3. New Programs.....	16	690,000	-	-	-16	-690,000
4. Scientific Evaluation and Planning.....	(2)	350,000	(2)	350,000	-	-
5. Total Training Grants.....	514	38,385,000	487	38,385,000	-27	-

Training Grants (By type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Graduate.....	486	$37,235,000	486	$38,008,000	-	+$773,000
2. Clinical Training Anesthesiology.	28	800,000	1	27,000	-27	-773,000
3. Scientific Evaluation and Planning.....	(2)	350,000	(2)	350,000	-	-
4. Total Training Grants.....	514	38,385,000	487	38,385,000	-27	-

Training Grants Program Analysis

Program Area	1971 Estimate	1972 Estimate	Increase or Decrease
1. Basic Health Sciences.....	$21,010,000	$21,010,000	-
2. Pharmacology-Toxicology.....	4,000,000	4,000,000	-
3. Bioengineering Sciences.....	2,631,000	2,631,000	-
4. Clinical Sciences	10,394,000	10,394,000	-
5. Scientific Evaluation and Planning.....	350,000	350,000	-
6. Total Training Grants.....	38,385,000	38,385,000	-

Collaborative Research and Development

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	---	---	3	$54,000	+3	+$54,000
Other expenses.....	---	$4,548,000	---	3,553,000	---	-995,000
Total.....	---	4,548,000	3	3,607,000	+3	-941,000

Introduction

The NIGMS research contract program provides a mechanism for the support of targeted research programs designed to achieve a specific objective or to advance a specific direction of research. Although limited in scope, the contract program--through its highly directed approach--provides a complementary research and development effort that enables the Institute to achieve goals that cannot readily be accomplished through regular grant procedures. Areas of needed contract effort are identified by the scientific staff in consultation with scientists from their respective research areas.

Program Plans in 1971 and 1972

Pharmacology-Toxicology

The last quarter-century has witnessed the discovery of many important drugs which have eased the suffering and saved the lives of millions of patients. Many of these drugs, although valuable in a large percentage of the patients to whom they are prescribed, have adverse reactions in a limited number of cases. In addition to the harm and hazard to the patients affected, the occurrence of these adverse reactions may make useless an otherwise valuable drug. It is therefore important to discover these adverse reactions early and to undertake the research needed to discover the possible relationship of these reactions to the particular characteristics of the groups of patients involved, particularly with regard to age, sex, blood grouping, and other genetic characteristics, and to find dosages and approaches to administration that will limit the hazards involved. In some instances redesign of the drug to a less toxic form may be feasible.

In an effort to meet this major health problem head-on, NIGMS for several years has supported a contract effort with Tufts University School of Medicine, in collaboration with six Boston hospitals, aimed at the detection, treatment, and prevention of adverse drug reactions in man. They have computerized their program and now have 8,500 patients under study. Progress to date has been significant. Last year this group reported that among women taking birth control pills those with blood type A have three times as many blood clots in their legs and lungs as those with blood type O. They are now working with other clinical investigators at Tufts and in other research centers to find out why those with type A have the greater clotting tendency. This year this same group of scientists has shown that a new but widely used diuretic substance known as ethacrynic acid, used to stimulate the kidneys to remove excessive fluid from the body, causes serious gastrointestinal bleeding in certain patients when given intravenously. Additionally, the Tufts group has shown that the second most widely used semi-synthetic penicillin, ampicillin, causes an increased incidence of adverse drug reaction as compared with other available and less expensive forms of penicillin of equal effectiveness. The adverse reaction caused by this one particular penicillin not only causes discomfort and prolongation of illness but frequently causes a

prolongation of stay in the hospital.

Scientists at the Research Triangle Institute of North Carolina have elegantly refined existing methodology and instrumentation and developed new techniques and methods for isolating infinitesimally small amounts of drugs and drug metabolites (break-down products) of significance to the health of man. During the past year these scientists have found that a metabolite of a very widely used oral contraceptive steroid may result in birth defects of a severe nature in mice. The metabolism of this drug in the human female is currently under study, and the Food and Drug Administration is being kept informed as to their findings. Research on similar steroids, barbiturates, and common pain-relieving preparations is continuing by this group. It has been found, for example, that common forms of barbiturates consist of two similar chemical structures, one of which has greater activity than the other. Techniques for the separation of these isomers are being investigated, and studies on their relative activities will be conducted during the coming year. An amount of $2,000,000 will be used in 1971 and 1972 for pharmacology-toxicology contracts.

Biomedical Engineering and Automated Clinical Laboratories

This Institute, through a variety of mechanisms, continues to provide broad support for the introduction of the principles and practices of engineering science into biomedical research and development. Using these engineering principles, new knowledge arising from the biological and medical sciences is being applied to the development of prototype instruments and devices that will aid in the more precise and accurate diagnosis and treatment of disease. The collaborative research and development program for the automation of clinical laboratories is such an effort.

An overview of the work load of clinical laboratories in the United States has revealed that in 1969 it was approximately one-half billion tests. It is estimated that this number will double within five years or less. Thus, by 1975, these laboratories will be faced with the performance of approximately a billion tests per year, and with a simultaneous requirement that the quality be increased and the cost decreased. The solution of this critical problem is to find ways to mechanize and automate the clinical laboratory.

To help resolve this situation the Institute has directed a large portion of its collaborative research and development effort toward this area. The goal is to develop a totally automated modular laboratory system that can be adapted to benefit all sizes of hospitals from the small community hospital to the large university hospital complex.

The major areas being concentrated on at this time are: clinical chemistry, hematology, microbiology, and urine analysis. Contract support is directed towards the more critical problems found in these areas. Included are accurate methods for the determination of chemicals in blood; easier, rapid and more accurate methods for the assay of enzymes and hormones; and automatic accessioning of biological samples as they appear in the laboratory receiving office. Support in this area will be decreased by $1,000,000 in 1972, providing a total support of $548,000.

Other Contracts

Continued contract support will be provided in the Fundamental Sciences at the same level as in 1971 of $1,000,000.

An increase of three positions and $59,000 will be required to effectively administer the contracts program. This increase is offset by a decrease of $1,000,000 reflecting a total decrease for this activity of $941,000. Special emphasis will be placed in the developing and awarding of contracts in the field of genetics.

62-645 O - 71 - pt. 3 - 58

Training Activities

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	15	$249,000	15	$266,000	---	+$17,000
Other expenses.....	---	105,000	---	107,000	---	+2,000
Total.....	15	354,000	15	373,000	---	+19,000

This intramural program was established in this Institute in 1966 for the purpose of training outstanding young scientists in pharmacology-toxicology and related areas. The original implementation of the program was at a level of 10 Research Associate appointments with an authorized growth to a level of 30. Personnel and expenditure restrictions have limited this planned growth. Fifteen Research Associates will be supported in 1971 and 1972.

This program will continue at the same level of support as in 1971 with a mandatory increase of $17,000 in personal services and communication costs and $2,000 for payment to the "National Institutes of Health Management Fund" for centrally furnished services.

Review and Approval

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel Compensation and benefits.....	120	$1,724,000	123	$1,895,000	+3	+$171,000
Other expenses.....	---	1,853,000	---	1,951,000	---	+98,000
Total.....	120	3,577,000	123	3,846,000	+3	+269,000

This activity provides the supporting professional and clerical personnel required for the planning, review, analysis, and management of the extramural programs of the Institute and supports the National Advisory General Medical Sciences Council.

The increase of $269,000 includes three new positions and $60,000 to provide the additional staff required in the field of genetics, $126,000 for annualization of pay increase, other increased costs and benefits and $83,000 for payment to the "National Institutes of Health Management Fund" for centrally furnished services.

Program Direction

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	56	$887,000	56	$933,000	---	+$46,000
Other expenses.....	---	430,000	---	457,000	---	+27,000
Total.....	56	1,317,000	56	1,390,000	---	+73,000

This activity includes the Office of the Director and supporting professional and administrative staff required to provide the overall leadership necessary for the administration and management of the research effort of the Institute.

The mandatory increase of $73,000 includes $46,000 for personal services, $15,000 for increased communication costs and $12,000 for payment to the "National Institutes of Health Management Fund" for centrally furnished services.

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Research Grants (Public Health Service Act, Title IV, Part E)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$87,392,000	Indefinite	---	$87,657,000

Purpose: To provide support of research in the fundamental and clinical sciences which relate directly to human health and disease.

Explanation: Regular research grants and large-scaled program projects are made to non-profit institutions and individuals to establish, expand and improve research activities which are germane to the mission of this Institute.

Accomplishments in 1971: In 1971, 1,070 research grants and program projects were supported. Increased emphasis was given to studies of the genetics of desease. We have continued our support and development of pharmacology, automated clinical laboratories and the study of trauma.

Objectives for 1972: It is anticipated that further support will be provided to programs in the fundamental sciences; such as, genetics of disease, cell structure and function, and bioorganic chemistry which are critical to the practical solution of medical problems. The special programs in trauma, pharmacology and toxicology, clinical instrumentation, and biomedical engineering will continue to be supported in areas considered most likely to find application at the clinical level.

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Fellowships (Public Health Service, Title IV, Part E)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$18,454,000	Indefinite	---	$15,142,000

Purpose: Funds are provided annually for postdoctoral and special fellowships, as well as for research career program awards to encourage training not only in the broad spectrum of fundamental sciences but also targeted areas such as biomedical engineering, pharmacology-toxicology and in selected clinical sciences such as anesthesiology, diagnostic radiology and surgery.

Explanation: The Institute's fellowships program provides training to young scientists for careers of teaching and research in the health sciences.

Accomplishments in 1971: In 1971, approximately 1,600 fellows will receive support in leading institutions throughout the Nation. Many former fellows and awardees are now acknowledged leaders in their respective fields and it can be predicted with confidence that from the pool of talented scholars for whom support is currently being provided will emerge many outstanding biomedical investigators and teachers of the future.

Objectives for 1972: In 1972 approximately 1,140 fellows will be supported in the various programs. Continued emphasis will be directed to development in the fields of basic and clinical pharmacology, clinical chemistry, human genetics and trauma.

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Training Grants (Public Health Service Act, Title IV, Part E)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$38,385,000	Indefinite	---	$38,385,000

Purpose: The major purpose of the graduate training grant program of NIGMS is to provide highly skilled medical scientists as well as faculty for the health professional schools of the United States. The development of a broadly based program of medical research and the improvement of the Nation's health care system depend more upon the existence of well-trained manpower than upon any other single factor.

Explanation: The NIGMS research training program is the Nation's most significant Federal program for the training of medical scientists in a diverse array of fields to meet the current and future manpower needs of medical schools, universities, hospitals, and research institutes.

Accomplishments in 1971: In 1971 the program will support 514 grants in the following areas: basic health sciences, pharmacology-toxicology, bioengineering sciences, and clinical sciences.

Objectives for 1972: The Institute will continue to emphasize support of graduate training programs of high scientific merit and demonstrable productivity. The training programs are continually being reoriented to reflect newly emerging manpower demands as well as the development of newer scientific approaches. It is anticipated that committed and planned increases in the medical scientist program will be achieved through gradual decreases in current levels of support in some clinical research training areas. It is estimated that approximately 487 grants will be supported in 1972.

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Collaborative Research and Development (Public Health Service Act, Title IV, Part E)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$4,548,000	Indefinite	3	$3,607,000

Purpose: The NIGMS research contract program provides the mechanism for the support of the total research effort for targeted programs and is utilized to achieve a specific objective or to advance a specific direction of research.

Explanation: Collaborative research and development in the biomedical sciences and supportive areas are conducted by contract with institutions.

Accomplishments in 1971: The NIGMS is engaged in the support of collaborative research and development in the biomedical sciences and supportive areas by contracts. In this program every attempt is being made to get tangible results of research into use in the patient care area. Progress has been made in the identification of previously unreported metabolites of several drugs, including steroids and barbiturates, which appear to cause physiological effects.

Objectives for 1972: This Institute, through contracts, will continue to provide broad support for research and development of the pharmacology-toxicology program, biomedical engineering, and automated clinical laboratories as well as the fundamental sciences with special emphasis on genetics.

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Training Activity (Public Health Service Act, Title IV, Part E)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
15	$354,000	Indefinite	15	$373,000

Purpose: This intramural program was established in this Institute in 1966 for the purpose of training outstanding young scientists in pharmacology-toxicology and related areas.

Explanation: The original implementation of the program was at a level of 10 research associate appointments with an authorized growth to a level of 30. Personnel and expenditure restrictions have limited this planned growth. Fifteen research associates will be supported in 1971 and 1972.

Accomplishments in 1971: In 1971, this activity will support the training of 15 young scientists in pharmacology and toxicology, thus reinforcing strongly the total National Institutes of Health research effort.

Objectives for 1972: In 1972, this Institute will continue to support and train the same number of research associates as in 1971.

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Review and Approval (Public Health Service Act, Title IV, Part E)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
120	$3,577,000	Indefinite	123	$3,846,000

Purpose: This activity provides the staff for the planning, review, analysis, and management of the extramural programs of the Institute and supports the National Advisory General Medical Sciences Council.

Explanation: The extramural program supports a broad base of fundamental and applied biomedical research and training activities aimed at the solution of certain major health problems.

Accomplishments in 1971: A total of 1,584 research and training grants and 1,600 fellowships were funded in 1971. The professional and supporting staff effectively maintained surveillance of these 3,184 grants.

Objectives for 1972: In 1972, it is planned to apply a more stringent evaluation of the Institute's programs to insure initiation of research and training grants to new programs of high promise plus full support to programs of productivity and quality.

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Program Direction (Public Health Service Act, Title IV, Part E)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
56	$1,317,000	Indefinite	56	$1,390,000

Purpose: This activity supports the Office of the Director and provides for the overall leadership necessary for the administration and management of the research effort of the Institute as well as staff support for program analysis, finance and information.

Explanation: The National Institute of General Medical Sciences supports a broad base of fundamental and applied biomedical research programs aimed at the solution of certain major health problems. The Institute Director and his staff are responsible for the overall direction, planning, and evaluation of these programs.

Accomplishments in 1971: The Director and his staff provided continuing guidance and surveillance over the research training and grants program.

Objectives for 1972: This staff will continue to assure that the basic and applied programs are closely interrelated to more rapidly carry basic discoveries to full fruition in health care.

New Positions Requested
Fiscal Year 1972

	Grade	Number	Annual Salary
Collaborative Research and Development			
Contract Administrator	GS-15	1	$22,885
Contract Specialist	GS-13	1	16,760
Clerical Assistant	GS-5	1	6,548
		3	46,193
Review and Approval			
Health Science Administrator	GS-15	1	22,885
Scientist Administrator	GS-13	1	16,760
Clerical Assistant	GS-5	1	6,548
		3	46,193
Total new positions, all activities		6	92,386

FRIDAY, MAY 7, 1971.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

WITNESSES

DR. GERALD D. LaVECK, DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. PHILIP A. CORFMAN, DIRECTOR, CENTER FOR POPULATION RESEARCH, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
GEORGE F. RUSSELL, JR., EXECUTIVE OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
EARL M. HUBSCHER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
B. FRANK GARDNER, JR., ACTING ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

National Institute of Child Health and Human Development

Object Classification (in thousands of dollars)

Identification code 09-30-0844-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	5,122	5,604	6,163
11.3	Positions other than permanent	310	281	274
11.5	Other personnel compensation	42	50	56
11.8	Special personal service payments	17	20	22
	Total personnel compensation	5,491	5,955	6,515
12.1	Personnel benefits: Civilian employees	529	642	680
21.0	Travel and transportation of persons	216	227	265
22.0	Transportation of things	33	56	61
23.0	Rent, communications, and utilities	158	188	200
24.0	Printing and reproduction	138	140	160
25.0	Other services	11,401	21,290	25,066
26.0	Supplies and materials	371	456	645
31.0	Equipment	260	1,366	1,973
41.0	Grants, subsidies, and contributions	57,365	64,165	66,967
99.0	Total obligations	75,962	94,485	102,532

Personnel Summary

	1970 actual	1971 est.	1972 est.
Total number of permanent positions	431	473	494
Full-time equivalent of other positions	43	39	38
Average number of all employees	442	474	503
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0844-0-1-651	1970 actual	1971 est.	1972 est.
Program by activities:			
1. Grants:			
(a) Research	43,210	50,237	54,229
(b) Fellowships	3,960	3,786	3,653
(c) Training	12,283	10,142	9,085
Total grants	59,453	64,165	66,967
2. Direct operations:			
(a) Laboratory and clinical research	7,032	9,104	11,171
(b) Collaborative research and development	5,097	15,455	18,484
(c) Biometry, epidemiology, and field studies	2,032	2,187	2,200
(d) Training activities	75	83	85
(e) Review and approval	2,099	2,490	2,591
(f) Program direction	776	1,001	1,034
Total direct operations	17,111	30,320	35,565

Program and Financing (in thousands of dollars)—**Continued**

Identification code 09-30-0844-0-1-651		1970 actual	1971 est.	1972 est.
	Total program costs, funded [1]	76,564	94,485	102,532
	Change in selected resources [2]	−602	.....	.....
10	Total obligations	75,962	94,485	102,532
	Financing:			
25	Unobligated balance lapsing	96	550	.....
	Budget authority	**76,058**	**95,035**	**102,532**
	Budget authority:			
40	Appropriation	76,949	94,436	102,532
40	Portion withdrawn (Public Law 91-204, sec. 410)	−1,097	.....	.....
40	Pay increase (Public Law 91-305)	243	.....	.....
41	Transferred to other accounts	−37	−13	.....
43	**Appropriation (adjusted)**	**76,058**	**94,423**	**102,532**
46.10	**Proposed transfer for wage-board pay increases**	.....	32	.....
46.20	**Proposed transfer for civilian pay act increases**	.....	486	.....
46.30	**Proposed transfer for military pay act increases**	.....	94	.....
	Relation of obligations to outlays:			
71	Obligations incurred, net	75,962	94,485	102,532
72	Obligated balance, start of year	45,419	50,430	65,326
74	Obligated balance, end of year	−50,430	−65,326	−75,808
77	Adjustments in expired accounts	−1,335	.....	.....
90	Outlays, excluding pay increase supplemental	69,616	79,007	92,020
91.10	Outlays from wage-board supplemental	.....	30	2
91.20	Outlays from civilian pay act supplemental	.....	463	23
91.30	Outlays from military pay act supplemental	.....	89	5

[1] Includes capital outlay as follows: 1970, $486 thousand; 1971, $1,366 thousand; 1972, $1,973 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $24,917 thousand; 1970, $24,315 thousand; 1971, $24,315 thousand; 1972, $24,315 thousand.

NOTES

Includes $411 thousand in 1971 and $411 thousand in 1972 for activities previously financed from: Research resources, 1970, $411 thousand.

Includes $36 thousand in 1972 for activities previously financed from (in thousands of dollars):

	1970	1971
National Heart and Lung Institute	51	36
National Institute of Arthritis and Metabolic Diseases	107	--
National Institute of Allergy and Infectious Diseases	10	--

Excludes $50 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	1971
Office of the Secretary	3	3
Office of the Director	49	47

Excludes $1,057 in 1972 for activities transferred to: Health manpower, 1970, $1,057 thousand; 1971, $1,057 thousand.

INTRODUCTION OF DR. LA VECK AND ASSOCIATES

Mr. FLOOD. We will continue with the National Institutes of Health. The next item is the National Institute of Child Health and Human Development.

The presentation will be made by Dr. Gerald D. LaVeck, the Director. Doctor, do you have any people with you you want to introduce?

Dr. LAVECK. I would like to introduce Dr. Philip Corfman, Director of our Center for Population Research and Mr. George Russell, our Executive Officer.

Mr. FLOOD. We have a biographical sketch of you, Doctor. In case these other witnesses are called upon, will you have biographical sketches of them put in the record too?

Dr. LAVECK. Yes, sir.

(The information follows:)

BIOGRAPHICAL SKETCH OF GERALD D. LAVECK, M.D.

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: University of Washington, B.S., 1948; University of Washington, M.D., 1951.

EXPERIENCE

1966–present: Director, National Institute of Child Health and Human Development.

1967–present: Clinical Professor of Pediatrics, Georgetown University School of Medicine.

1966–1967: Acting Scientific Director, National Institute of Child Health and Human Development.

1965–1967: Clinical Associate Professor in Pediatrics, Georgetown University School of Medicine, 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 Director, Rainier School, Buckley, Washington.

1963: Clinical Associate Professor of Pediatrics, University of Washington School of Medicine.

1960–1963: Clinical Assistant Professor of Pediatrics, University of Washington School of Medicine.

1958–1960: Instructor in Pediatrics, University of Washington School of Medicine.

1958–1961: Medical Director, Rainier School, Buckley, Wash.

1957–1958: Instructor in Pediatrics and Fellow in Mental Retardation, University of Washington School of Medicine, Department of Pediatrics, Neurology, and Neuropathology.

1956–1957: Resident, Pediatrics, Children's Orthopedic Hospital, Seattle, Wash.

1955–1956: Assistant Resident, Pediatrics, Child Health Center and King County (Wash.) Hospital.

1953–1955: Senior Assistant Surgeon, U.S. Public Health Service, Epidemic Intelligence Service, Communicable Disease Center, Atlanta, Ga.

1952–1953: Resident, Public Health, Seattle King County Department of Public Health.

1951–1952: Intern, Rotating, Vancouver General Hospital, Vancouver, B.C.

Association memberships: Diplomate, American Board of Pediatrics; Fellow, American Academy of Pediatrics; and Fellow, American Public Health Association.

Awards, honors: Department of Health, Education, and Welfare Superior Service Award, April 11, 1966.

Publications: Numerous papers and book contributions relating to mental retardation, pediatric neurology, developmental disorders, and infectious diseases.

BIOGRAPHICAL SKETCH OF PHILIP A. CORFMAN, M.D.

Name: Philip A. Corfman, M.D.

Position: Director, Center for Population Research; National Institute of Child Health and Human Development.

Birthplace and date: Berea, Ohio, July 19, 1926.

Education: Oberlin College, 1950, Bachelor of Arts; Harvard Medical School, 1954, Doctor of Medicine.

Experience: Present, Director, Center for Population Research, NICHD; 1967–68, Chairman, Public Health Service Population Committee; 1967–68, Assistant to Director for Population Research, NICHD; 1966–67, Acting Program Director, Reproduction Program, NICHD; 1965–66, Program Associate for Population Research, Reproduction Program, NICHD; 1964–66, guest scientist, Navy Medical Research Institute, Bethesda, Md.; 1964–65, consultant in obstetrics and gynecology, Reproductive Biology Program, NICHD; 1963–64, Assistant visiting obstetrician and gynecologist, Harlem Hospital; 1963–64, visiting fellow, Vanderbilt Clinic, Columbia-Presbyterian Hospital; 1962–63, member, medical executive committee, Rip Van Winkle Foundation; 1960–63, attending obstetrician, Columbia Memorial Hospital, Hudson, N.Y.; 1959–63, obstetrician and gynecologist, Rip Van Winkle Clinic, Hudson, N.Y.; 1956–59, Obstetrical and gynecological residency, Boston Lying-In Hospital and the Free Hospital for Women; 1956–59, teaching fellow in obstetrics and gynecology, Harvard Medical School; 1954–56, surgical internship and first year residency, Boston City Hospital, Fifth Surgical Service (Harvard).

PROFESSIONAL SOCIETIES

American Board of Obstetrics and Gynecology.

American College of Obstetricians and Gynecologists.

Fellow of the American Public Health Association; consultant to Program Area Committee on Population and Public Health.

Food and Drug Administration Advisory Committee on Obstetrics and Gynecology.

International Society for Research in the Biology of Reproduction.

Society for the Study of Fertility.

Publications: Various publications on the development in evolution of contraceptives, cancer etiology, and cytogenetics.

GENERAL STATEMENT

Mr. FLOOD. I see you have a prepared statement. How do you wish to proceed?

Dr. LAVECK. I would like to read it.

Mr. FLOOD. Suppose you do that.

Dr. LAVECK. Mr. Chairman, and members of the committee, we need to know more about why the body changes with age; why some children are born with a defective brain or a crippled body; and how man's own living habits and the conditions surrounding him affect his development. What prompts populations to reproduce at certain rates? How do ever-increasing numbers of people affect the quality of life? All of these critical issues are under intensive investigation.

To aid in this search for discovery, the National Institute of Child Health and Human Development conducts and sponsors research on human biology encompassing the entire life span. While this research portfolio includes broadly-based biomedical and behavioral studies, it also indicates particular attention to studies of the special needs of the pregnant woman, the developing embryo, the newborn, the growing

child, the mentally retarded, and the mature and aging adult. Excessive population growth is a problem of special research concern.

The material you have before you explains in detail the scientific issues with which our Institute program deals, and the research being done by our own scientists and those supported by us. The 1972 budget includes a net program increase of $8,865,000 over the 1971 level.

Program emphasis for 1972 will be in population research and in child health. Most of my remarks will be concentrated on these two areas.

AREAS OF POPULATION RESEARCH

Congress indicated its support for population research with the passage of the Family Planning Services and Population Research Act of 1970. In this act, the Deputy Assistant Secretary for Population Affairs is given responsibility for the coordination of all population research supported or conducted by the Department. We work very closely with the Deputy Assistant Secretary for Population Affairs, Dr. Louis Hellman, and his staff.

Our country's population has increased 50 percent in the last 30 years and is likely to increase another 50 percent before the year 2000. One cannot assess the impact of population growth without considering its effects on the health of children, families, and society as a whole. For example, avoiding unwanted births can significantly reduce infant mortality, prematurity, and mental retardation.

The Institute's Center for Population Research supports research and research training in three areas: The development of new methods of fertility regulation; the study of the medical effects of current contraceptive methods; and population research in the social sciences.

NEW CONTRACEPTIVE METHODS

No currently available contraceptive method is fully satisfactory and the Institute is directing research efforts to develop new ones.

To date, the contraceptive development program at the Institute has consisted primarily of directed fundamental research relevant to the eventual production of new agents useful as contraceptives. During 1971 this program became more product oriented, and by the end of 1972 it will include many phases of drug development from synthesis through clinical testing. Our goal is to develop several new methods of fertility regulation before the end of this decade.

For example, Institute-supported research to disrupt the function of a structure of the ovary, the corpus luteum, shows promise. Its primary function is to produce progesterone, a hormone necessary for the establishment and maintenance of pregnancy. Specific inhibitors have been found which can block the production of progesterone and could eventually be used therapeutically as a once-a-month pill.

Scientists within the Institute's laboratories are exploring the mechanism of action of a placental hormone (HCG), a substance necessary to maintain pregnancy. This work is an example of our interest in the important problem of infertility. However, it is also relevant to the closely related field of contraceptive development since a thorough understanding of basic biologic processes can lead to the development of new methods.

MEDICAL EFFECTS OF CURRENT BIRTH CONTROL METHODS

Evidence exists that the current hormonal contraceptives have adverse medical effects in significant numbers of women; thus the Institute supports research in this area. The importance of this work is highlighted by the surprising finding of west coast investigators that women who decide to use oral contraceptives are somehow different from women who choose other methods of fertility control. They found a higher rate of uterine cervical dysplasia, a precursor of cervical cancer, in women who chose oral contraceptives. The suspected higher incidence of cervical cancer in oral contraceptive users may be due to preexisting differences in the women.

Mr. FLOOD. You mean physical differences?

Dr. LAVECK. We don't really know what the differences are. Before a woman selects the type of contraceptive she wants to use, she already may be different from other women, choosing other methods.

Mr. FLOOD. What is extraordinary about women being different?

Dr. LAVECK. The extraordinary point is that when one wants to study the relationship between the use of the pill and cancer, one must consider the events that may in some way predispose to cancer.

If one were only to compare women who were using intrauterine devices with women using the pill to see who has the most cancer, this would not be adequate. Many variables must be controlled.

Mr. FLOOD. The difference is why do certain types take the oral and other types use other things. That is your first question I suppose.

Dr. LAVECK. That is correct; that is a legitimate question to ask. The investigators were unable in this particular study to find differences in women with respect to age, number of pregnancies, or other factors that clarify why pill users have more dysplasia of the cervix even before they start to use the pill.

Mr. FLOOD. Any income factors involved?

Dr. LAVECK. There were income differences in that the pill users had a slightly greater income and also weighed less than those that chose the IUD. Other than these, there were no apparent differences.

Mr. MICHEL. On the last point, was there any significant reluctance on the part of women to use the pill because of that weight factor?

Dr. LAVECK. Not that I am aware of in this study.

Within the Institute's laboratories, investigators are exploring whether the estrogens used in oral contraceptives may be responsible for certain forms of hypertension found among users. Other fields of investigation include case-controlled retrospective studies to determine if cancer of the breast and strokes occur more commonly in pill users. In 1972, special attention will be given to expansion of drug metabolism studies. Of particular urgency is the identification of optimal formulations and dosages of oral contraceptives.

POPULATION RESEARCH IN SOCIAL SCIENCES

To modify population trends for the benefit of society and its individual members, we must first understand what determines these trends. Why, for example, do some groups maintain high fertility and others low? How do children in large families differ from those in small families? Population growth cannot continue indefinitely.

Without further research on the relationship of social and economic factors and the decisionmaking of couples regarding family size, we have neither a rational basis for deciding when we should try to attain a stationary population nor insight into measures necessary to achieve this.

Institute-supported investigators have reported that at least one-fifth of all births in the United States between 1960 and 1965 were unwanted. Thus prevention of only unwanted births during those years would have reduced the U.S. population growth by 4.7 million.

The general picture of fertility control in this country is one of wide-spread failure to time conception successfully, and of failure to limit family size to the number of children wanted.

For 1972, the President's budget includes $37,718,000 for the support of population research and training, an increase of $9,600,000 over the 1971 level.

IDENTIFICATION OF FETAL GENETIC DEFECTS

The importance of children to our society is self-evident when we remember that over 70 million of our citizens are children and youth under age 18. We need to insure that mothers are helped to produce healthy babies; that infants receive optimal care and nutrition; and that abnormalities of development leading to handicapping conditions and mental retardation are prevented or ameliorated.

Fear of having a defective child is experienced by most women during pregnancy. Prenatal diagnosis may alleviate this fear and also offers hope for the prevention of mental retardation and other handicapping abnormalities arising from genetic defects. Using aminocentesis, a technique which involves drawing off a small amount of fluid surrounding the fetus, offers this opportunity. More research is needed in order to identify disorders that can be diagnosed prenatally, to develop techniques to permit earlier detection, and finally to devise methods of treating the fetus. Currently over 40 abnormalities can be diagnosed before birth using aminocentesis. In collaboration with seven medical centers, the Institute is developing an aminocentesis registry to monitor the safety of this procedure and to ensure that the procedure is used only in the best interests of parents and society.

MATERNAL HEALTH AND CHILD DEVELOPMENT

Scientific information concerning dietary needs during pregnancy is meager. Furthermore, the extent to which maternal nutrition influences the development of the fetus is controversial. In experimental animals, maternal malnutrition has been shown to reduce body growth, brain size, and learning ability in offspring. In humans, few studies have been directed specifically at the effects of nutritional improvements; all are confounded by the presence of many other adverse medical, social, and ecological factors which accompany malnutrition. Several studies are being initiated in humans and subhuman primates to determine whether normal nutritional status correlates with birth weight and the incidence of mental retardation and other neurological defects.

GROWTH AND NUTRITION

The study of the long formative period betwen early infancy and adulthood involves research leading to an understanding of the complex interplay of factors that determine the physical maturation and health of the child and young person. Adequate nutrition has long been known to be essential to good physical growth. Yet it is only recently that the social cost of malnutrition has begun to be widely appreciated.

Children who suffer from severe malnutrition requiring hospitalization in the first year of life are shorter, weigh less, have a smaller head circumference and a lower developmental quotient 3 to 4 years later than children of the same age who are not malnourished.

If malnutrition continues beyond the first 4 months of infancy, the child is more likely to display defective intellectual development later in childhood. Several studies are underway to determine how severe malnutrition must be to produce intellectual deficits and at what stage it is the most devastating.

MENTAL RETARDATION

From its beginnings, NICHD has had a commitment to study the development of man's special faculty—his extraordinary intellect—and to find new ways to overcome the factors that bar some from fulfilling their richest intellectual potential. As with a child's physical development, the growth of his mental capabilities begins with the genetic factors he inherited from generations before him. These are molded, sometimes irrevocably, by the forces of his prenatal environment; are profoundly affected by the events surrounding birth and adjustment to postnatal existence; and thereafter depend upon how the sum of all these experiences interacts with a lifetime of contacts with the nutritional and environmental conditions, diseases, experiences, and people that make up his world. All of these developmental variables are being studied by scientists supported by the Institute.

Of the 6 million Americans who are mentally retarded, approximately 250,000 are in institutions at any one time and almost 700,000 are attending special classes. The cost of mental retardation to the country comes to about $8 billion a year. Not included in these financial costs are the pain, frustration, and other intangible social costs that seriously reduce the quality of life for the retarded and their families.

The complexity of the problem of mental retardation has been highlighted in a detailed study of mental subnormality in a selected community where almost 3 percent of the children studied were found to be mentally subnormal. Of the children identified as subnormal, one-half showed positive signs of neurologic damage. The study is important because it demonstrates that children born to parents who themselves have been inadequately housed, nourished and educated are at risk to a variety of hazards—prenatal, perinatal, and postnatal. The combined interaction of these produce mental retardation in a substantial portion of those who survive.

The Institute's future work in mental retardation will place strong reliance on the work to be done in the 12 mental retardation research

centers authorized by Congress in 1964. Eleven of these will be active by the end of the current fiscal year.

The budget provides for $46,903,000 in 1972 for research and training activities in child health, an increase of $460,000 over the 1971 level of support. Included in this total is a budget request of $13,310,000 for all mental retardation activities. Of this, $5,375,000 is for the support of mental retardation research centers.

ADULT DEVELOPMENT AND AGING

Over 20 million persons in the United States are over 65. Many of these are in poor health. One million are maintained in institutions, and 65 percent of Federal health funds are spent on persons over 65. The Institute's adult development and aging program is geared to improving the health of the mature and aging citizen, and thereby reducing the cost of care.

Operant conditioning techniques have been used for many years to change and control actions involving voluntary skeletal muscles. During the last decade further research has shown that some involuntary body responses can be operantly controlled. Investigators at the Institute's Gerontology Research Center have found that some patients with abnormal heart rhythms can learn to control these abnormalities and even maintain such control after leaving the hospital thereby improving health and activity.

Research in 1972 will continue to seek new knowledge about cellular aging and about the changes in mental functioning with age.

The 1972 budget request is $7,180,000 for aging, a decrease of $1,353,000 from the 1971 level.

SUMMARY

Mr. Chairman, the Institute's work on population research, child health, and aging will contribute knowledge on some of the critical health and social problems of our time.

For 1972, the budget request is for $103,232,000, a net increase of $9,556,000 over the 1971 level of $93,676,000.

I will be happy to answer any questions.

Mr. FLOOD. You do have a real increase of almost $8½ million?

Dr. LAVECK. Yes, sir.

Mr. FLOOD. If you take out of that the increase for population and reproduction research programs, there is a net decrease for the rest of your activities?

Dr. LAVECK. That is correct.

POPULATION AND REPRODUCTION RESEARCH

Mr. FLOOD. For the population and reproduction program, you have increases of $6,100,000 under research grants, $1 million under the laboratory and clinical research, and $2,500,000 under collaborative research and development. Is that right?

Dr. LAVECK. Correct.

Mr. FLOOD. In total how much do you have budgeted for population and reproduction research in 1971 and how much for 1972?

Dr. LaVeck. In 1971 we have $28.1 million for all population research. For 1972 it is $37.7 million, an increase of $9.6 million.

Mr. Flood. That includes reproduction research?

Dr. LaVeck. Yes, sir; it does.

FUNDS REQUESTED UNDER FAMILY PLANNING ACT

Mr. Flood. How much of the increase is to carry out the new family planning legislation that passed Congress late in the last session?

Dr. LaVeck. Mr. Chairman, in our justification document we cite the existing Public Health Service Act as well as section 1004 of the Family Planning Services and Population Research Act of 1970. We have not stated how much of the funds would come from one act and how much from the other since the two authorities overlap.

Mr. Flood. That is why I asked you.

Dr. LaVeck. Our preference, of course, is to fund research under section 301, the old authorizing legislation because this is an indefinite authorization.

Mr. Flood. How much of the increase is due to the Family Planning Act passed late in the last session?

Dr. Marston. We have the situation here in which we have two authorities under which we can carry out everything we propose to do. I hope we don't have to have the confusion of separating the programs because the continuity of the program——

Mr. Flood. I simply want to know how much.

Dr. Marston. We have not made such a determination.

Mr. Miller. We do a similar thing in the National Center for Health Service Research and Development. We have section 304 and 301. We want to be able to cite either authority, no matter what projects we support. We don't identify a specific amount of money in either one.

Mr. Flood. Family planning is one of the "in" things now. As we have said many times, 5 years ago you wouldn't dare mention the term. Now everybody but the Bureau of Mines is doing it. So we want to know how much of this money you are requesting is the result of that action taken by Congress late in the last session?

Dr. Marston. I think we can answer that question. As you know, that legislation did give new authorities. As far as the amount of funds are concerned, the population research was a priority item before the legislation was passed.

The specific answer to your question is that I would expect that there would have been an increase of this order in this particular part of the budget whether the legislation had passed or not.

NEED FOR POPULATION RESEARCH INCREASE

Mr. Flood. Aside from the fact that Congress passed a new law, why is the increase necessary?

Dr. LaVeck. Only in the last 4 or 5 years has this area received much in the way of funding and emphasis.

We are particularly concerned about the need for developing an array of new contraceptive agents. We need to know more about the oral contraceptives and their adverse effects. Information is needed on

the social sciences and how economic and social factors relate to population dynamics and how families make decisions regarding the number of children they would like to have.

ADVANCES IN POPULATION AND REPRODUCTION KNOWLEDGE

Mr. FLOOD. Now you have such an extremely popular program and have been spending those millions of dollars, what more do you know about population and reproduction than you did last year?

Dr. LAVECK. I think there are many examples. I cited in my opening statement knowledge that has been obtained from the national fertility studies the Institute supported in 1965 and 1970 which shows how many unwanted children there are.

In 1965 the study also for the first time demonstrated how many women were using oral contraceptives.

Mr. FLOOD. How much more do you know about population and reproduction than you did a year ago?

Dr. LAVECK. One of our major efforts is to develop new contraceptive methods and we do know a good deal more about some very promising compounds that we didn't know about or talk about last year at this hearing.

For example, we are supporting research on an interesting group of compounds called prostaglandins. There has been a good deal of excitement in the scientific community about these compounds. They might provide a method of family planning if some of the initial studies that are now being carried out prove to be as promising as some of us think they will.

MALE CONTRACEPTIVE METHODS

We are also working on male methods.

Mr. FLOOD. Male pills?

Dr. LAVECK. It is uncertain at this stage to define the male methods as pills or injections. There are new compounds such as the chlorohydrin series. All of the studies up to now have been done in animals and have been successful in inducing temporary sterility in the male. We feel this is a promising new lead.

We have found out in the last year or two for the first time how the sperm actually penetrates the egg. It sounds like a very simple procedure and something that everyone should know about, but fertilization is not fully understood.

Recently one of our grantees described some of the enzymes that are secreted by the head of the sperm which dissolves the coating of the egg and permits the sperm to fertilize the egg.

At the same time we have investigators who are looking for ways to inhibit those enzymes so that fertilization can't occur. This would be a method of family planning.

POPULATION RESEARCH CENTER GRANT PROGRAM

Mr. FLOOD. Tell us about this new population research center grant program. For instance, how many centers? We would like to know where they will be. What would you do at these centers and how much will they cost? Who are they, where are they, what will they do and so on?

Dr. LaVeck. As you know we have mental retardation research centers and in many respects these population research centers are modeled after the mental retardation centers.

Mr. Flood. Go on and tell us about how many there are. Are there 11?

Dr. LaVeck. The population research centers?

Mr. Flood. Yes.

Dr. LaVeck. This program has just started. We have made one award. That was about a month ago to Vanderbilt University.

Mr. Flood. How many are you going to have?

Dr. LaVeck. We anticipate having between 10 and 12 centers by 1975. Hopefully we would like to have two to three new centers each year.

Mr. Flood. Any ideas, this morning, of where they are going to be?

Dr. LaVeck. No, sir.

Mr. Flood. What do the people do, apply for them?

Dr. LaVeck. That is correct. We have notified universities of the availability of these funds and the program objectives. We have made many announcements through various scientific channels. We have had a tremendous response from universities. Many have expressed an interest in developing an interdisciplinary center to study population problems.

Mr. Flood. What will they do at the one they have? And how much will it cost?

Dr. LaVeck. That center at Vanderbilt costs about a quarter of a million dollars a year for core support. That may be one of our smallest centers. We anticipate a cost of a half million dollars per year per center for core support.

The center at Vanderbilt is in the medical school and includes the departments of obstetrics, internal medicine, biochemistry, physiology, and anatomy. There is a close relationship with other departments. Their main focus is to study cell genetics, fertilization, hormones, infertility, and new contraceptive methods.

COORDINATING THE MENTAL RETARDATION RESEARCH CENTERS

Mr. Flood. You have the 11 centers going now. Do they go off in 11 directions? How do they decide what phase of this broad spectrum of the subject they are going to be engaged in?

Dr. LaVeck. I think we have learned a good deal from our Mental Retardation Research Centers and we have found each university differs considerably in regard to the strengths in specific areas. All of our Mental Retardation Research Centers are quite different. We anticipate this will be the case with the population research centers.

Mr. Flood. After you make the grant, here's $500,000 to university "X". Do they have carte blanche to do what they want to do, or do you have a finger in the pie or any sort of programs to be distributed among the 11? Do they all come in Monday morning at 9 and knock on your door with the same program?

Dr. LaVeck. They make application and state what they are going to do in the centers. This research is then approved by our advisory committees.

Mr. Flood. You are in a position to stop anything?

Dr. LaVeck. If they deviate from the intended purpose we can exert an influence on the center.

Mr. Flood. Here comes seven and all say we are going to do the same thing. What do you do in a case like that?

Dr. LaVeck. We would certainly discourage that.

Mr. Flood. They are now discouraged, now what happens?

Dr. LaVeck. I should say, Mr. Chairman, the chances for seven centers all wanting to do the same thing would be very, very slight. But if by chance that happened, we might very well suggest that there be a regional center where one could pool the resources from two or three centers that want to do similar activities.

Mr. Flood. But you are aware of the potential at least?

Dr. LaVeck. Yes, sir.

MENTAL RETARDATION CENTERS OF NICHD AND MATERNAL AND CHILD HEALTH

Mr. Flood. How do the mental retardation centers in this appropriation differ from the ones under the maternal and child health appropriation? Is this duplication? Why do you want these?

Dr. LaVeck. No, sir; there is no duplication. The Mental Retardation Research Centers' construction grants were approved by Congress in 1963. There were actually three parts to that legislation. One was to construct mental retardation centers.

Mr. Flood. I am talking about the program, not bricks and mortar.

Dr. LaVeck. I think the construction grants explains the program differences. We are concerned with the Mental Retardation Research Centers. Then there are the university-affiliated facilities for the mentally retarded.

These are not constructed for research purposes. These facilities are to train personnel and to demonstrate services for the mentally retarded. These are administered by the Social and Rehabilitation Service but receive support principally from the Health Services and Mental Health Administration.

The third type of construction—and again this means program—are the community facilities for the mentally retarded. This is a program to provide direct services to mentally retarded persons.

So the HEW supports research centers, training centers, and service centers.

Mr. Flood. So does the Maternal and Child Health appropriation, doesn't it?

Dr. LaVeck. That supports the university-affiliated facilities or training centers. They also support diagnostic clinics. Maybe that is what you are referring to. They sponsor many diagnostic clinics located primarily in university settings.

Mr. Flood. One of our pet hates is duplication. We have had the Maternal and Child Health people come in and say they are doing this and that and need so much to fund their centers. They are doing a good job.

In you come now and you want funds for your centers for mental retardation.

Dr. LaVeck. I can assure you there is no duplication in this particular program. I am very familiar with the Maternal and Child Health Services program.

Mr. Flood. Are you familiar with both programs?

Dr. LaVeck. I am familiar with the mental retardation programs, yes.

Mr. Flood. Are you familiar with the maternal and child health program?

Dr. LaVeck. Yes, I am. There is no duplication. We are concerned with research and the supply of researchers only, although we work closely with those centers that provide training.

Mr. Flood. What progress has been made in this problem of mental retardation in these centers of yours?

Dr. LaVeck. One of our real successes in the Institute is the development of the Mental Retardation Research Centers. In 1963 we were spending about $2 million for mental retardation research and very little interdisciplinary research was being conducted.

Congress, in providing funds for these centers, has initiated a major advance as far as this field is concerned. In the 12 centers there are now 1,600 people working on retardation problems. Still I am told there are 1,000 vacancies in the centers. They are moving very quickly into some exciting research efforts.

Mr. Flood. A thousand vacancies—jobs?

Dr. LaVeck. Job vacancies for scientists and support personnel, yes. The centers are still in the expansion phase.

Mr. Flood. It is not hard to get people to take jobs in the Government.

Dr. LaVeck. These are not Government jobs.

Mr. Flood. In effect they are; aren't they?

Dr. LaVeck. I did not make myself clear, Mr. Chairman. There are 1,600 people, non-Federal employees, working in universities where they have mental retardation research centers. They are working specifically on mental retardation, a problem that previously was of limited interest to investigators.

RETARDATION RESEARCH PROGRESS

Mr. Flood. What research progress are they making with this problem of mental retardation in your centers?

Dr. LaVeck. I mentioned in my opening remarks some of the epidemiologic studies that one of the centers carried out to determine the prevalence of mental retardation.

Mr. Flood. What did it show?

Dr. LaVeck. This study showed about 3 percent.

Mr. Flood. How many centers do you have in operation?

Dr. LaVeck. Twelve centers.

Mr. Flood. What are they doing at the ninth and the 11th?

Dr. LaVeck. As I mentioned before, all of these centers are quite different, and at the Boston Children's Medical Center, for example, they are oriented more toward the neurological problems of the mentally retarded. They have been studying convulsions in the young baby.

A convulsion in a baby 2 or 3 weeks of age is considered to be serious. Whereas if this occurs in a 2- or 3-year-old child, it doesn't have the

same potential for serious damage. They have studied 137 young infants under 3 weeks of age who had convulsions and found that about half of them 4 years later turned out to be normal children. But 30 percent turned out to be abnormal in the sense of having mental retardation or other neurologic abnormalities. About 20 percent died.

This longitudinal study provided new data on what happens to babies with convulsions.

They have also pointed out the importance of brain wave studies on these young babies and have demonstrated that this test predicts very accurately whether a child 4 years later will be normal or abnormal. This is an example of work being done at one of the centers.

Mr. FLOOD. Normal or not normal vis-a-vis mental retardation?

Dr. LAVECK. Yes; and also other handicapping problems such as cerebral palsy, continued seizures, and severe behavioral problems.

THE LOCATION AND WORK OF THE CENTERS

Mr. FLOOD. Suppose you have the record show for a half a dozen at least, maybe all of them if you want to, what they are doing, and what progress they are making with reference to mental retardation.

Dr. LAVECK. We will be pleased to submit that.

(The information follows:)

EXAMPLES OF PROGRESS AND ACCOMPLISHMENTS OF MENTAL RETARDATION CENTERS SUPPORTED BY THE NICHD

GEORGE PEABODY COLLEGE FOR TEACHERS, NASHVILLE, TENN.

This center has undertaken a broadly based program of applied research in language development, reading, personality, and motivational factors in performance and early intervention with disadvantaged minority group children. Through these efforts, diagnostic techniques for specifying reading skills have been accelerated in retarded children through innovative procedures and incentive methods. Research with severely behaviorally disordered children has demonstrated that they can be identified under 3 years of age and helped through special education services, parents can learn and apply behavior management skills in a short time to improve the total family's adjustment; these skills can be successfully transmitted from parents to other parents. The majority of these children are now in regular preschool placements.

UNIVERSITY OF CHICAGO, CHICAGO, ILL.

Research teams at this center have extended and further developed the method of fibroblast tissue culture for the study of storage diseases. This work has greatly enhanced the study of human genetics, particularly the diseases which lead to mental retardation. Practical aspects of this research include improved diagnoses, identification of carriers, prenatal diagnosis, genetic counseling, and search for therapeutic agents. Investigators here were the first to develop chemical methods for antenatal diagnoses, permitting accurate, inexpensive, and rapid assessments of mucopolysaccharides and potentially to other heritable diseases.

WALTER E. FERNALD STATE SCHOOL, WALTHAM, MASS.

Investigators at this center are among the foremost in the development of behavior modification techniques for changing the behavior of severely and profoundly retarded individuals, including the development of language skills. Many children, previously destined to the back wards of institutions, have been rehabilitated to markedly higher levels of function. Other researchers have also participated in the development of new chromatographic screening techniques which have proven of value in detecting metabolic disorders in newborn infants.

UNIVERSITY OF WISCONSIN, MADISON, WIS.

The impact of psychosocial deprivation on the intellectual development of infants and very young children is being actively studied by center investigators at the University of Wisconsin. A group of infants whose mothers and older siblings are characterized by subnormal levels of intellectual performance, minority group status, and socioeconomic definition have been enrolled in an enriched program of mental stimulation and socialization. The mothers have also received guidance in child rearing and training for vocational placement. At the age of 3 years, these children are significantly ahead of a matched control group in mental, social, and personality development. They will continue to be tested to determine whether these gains will be sustained through school age.

UNIVERSITY OF COLORADO MEDICAL CENTER, DENVER, COLO.

An investigator at the University of Colorado has learned more about the relationship between malnutrition and impaired biochemical maturation of cerebral tissue both in man and animals. He has demonstrated a deficiency in vitamin A and folic acid in the chi'dren of migrant farmworkers who function at subnormal levels of intelligence.

UNIVERSITY OF KANSAS, LAWRENCE, KANS.

Prospective studies designed to diagnose all forms of abnormal fetal growth in newborn infants have been in progress at the Kansas Medical Center unit of the University of Kansas Center since 1967. A new classification of abnormal somatic growth during fetal life has been developed from the results of these studies. Clinical correlates in the mothers and infants are being examined to determine etiology, immediate postnatal course, and long-term prognosis in the five classification groups. Results to date indicate that infants who have small body size for dates rarely have respiratory distress syndrome (RDS). On the other hand, the incidence of severe RDS and deaths from RDS are significantly higher in extremely malnourished newborn infants than in normally grown infants, regardless of their fetal age.

FUNDING OF THE RETARDATION RESEARCH CENTERS

Mr. FLOOD. How much do you have budgeted for them—1971 and 1972, for each one?

Dr. LAVECK. We will supply that.

(The information follows:)

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT—MENTAL RETARDATION CENTER SUPPORT, FISCAL YEAR 1971-72 ESTIMATES

Mental retardation research centers	1971 estimate	1972 estimate [1]
1. University of Chicago, Chicago, Ill.	$300,000	
2. Children's Hospital, Cincinnati, Ohio	500,000	
3. George Peabody College for Teachers, Nashville, Tenn.	1,000,000	
4. University of Colorado Medical Center, Devner, Colo.	300,000	
5. University of Washington, Seattle, Wash.	1,000,000	
6. University of Claifornia at Los Angeles, Los Angeles, Calif.	1,600,000	
7. Albert Einstein College of Medicine, Yeshiva University, New York, N.Y.	1,200,000	
8. University of Kansas, Lawrence, Kans.	1,200,000	
9. Walther E. Fernald State School, Waltham, Mass.	800,000	
10. Children's Hospital Medical Center, Boston, Mass.	500,000	
11. University of North Carolina, Chapel Hill, N.C.	300,000	
12. University of Wisconsin, Madison, Wis.	800,000	
Total	9,500,000	[1] 10,700,000

[1] Distribution to individual centers will be determined at the time of apportionment, and will be based on priority scores assigned in the grant review process.

GERONTOLOGY RESEARCH CENTER

Mr. FLOOD. About your gerontology research at Baltimore. We have heard a lot about that. Are they going full blast over there? Are they in full operation?

Dr. LAVECK. We are not in full operation at the Gerontology Research Center.

Mr. FLOOD. How long has it been there?

Dr. LAVECK. It opened in June 1968.

Mr. FLOOD. How much money have they had?

Dr. LAVECK. They spend approximately $2 million per year.

Mr. FLOOD. Why are they dragging their feet for the last 3 or 4 years?

Dr. LAVECK. One of our problems, Mr. Chairman, is in employment positions for the investigators working in that Center.

You recall that in 1969 this Institute had 578 budgeted positions, and then the Revenue and Expenditure Control Act resulted in a loss of 159 positions for us. Many of the positions that were lost at that time were intended for the Gerontology Research Center.

In fact the majority were intended for the Gerontology Research Center. We have not been able to provide the number of positions to fully staff the facility.

Mr. FLOOD. You mean the reason they are not going full blast is because they can't get people, the right kind of people?

Dr. LAVECK. We have not been able to devote the number of positions and the resources to that program because of our more recent commitments to population research. This is not a question of finding good people, it is that the resources won't go around.

Mr. FLOOD. So you have realined your priorities. That is going on all over town.

Dr. LAVECK. Yes, we have realined our priorities. It is unfortunate that the Gerontology Research Center was not staffed completely in earlier years as was planned.

Mr. FLOOD. In view of the other things that are now gung ho, they have gone down a few pegs on the totem pole; right?

Dr. LAVECK. I still thing we are accomplishing a great deal at the Gerontology Research Center.

Mr. FLOOD. But they have been reassigned in your priorities?

Dr. LAVECK They have not been No. 1 on the priority list; that is correct.

TRENDS IN LONGEVITY

Mr. FLOOD. A person 40 years old has very little more life expectancy today than a person of that age 50 years ago; is that right?

Dr. LAVECK. That is correct.

Mr. FLOOD. Is that one of the problems? Are you interested in telling the people 40 years old they can expect more longevity?

Dr. LAVECK. We are certainly interested in prolongation of life, but we are primarily concerned with increasing the quality of life for older people.

Mr. FLOOD. This would startle the average person. We hear all the talk and read the articles about increased life expectancy and then we find out 40 or 50 years ago a 50-year-old person had about the same life expectancy as a 50-year-old person has today.

Dr. LAVECK. The reduction in death rates has occurred primarily in the young groups. There has been little change in longevity for those over age 50.

Mr. FLOOD. A lot of people will be surprised.

Mr. MICHEL. How has life expectancy increased?

Dr. LAVECK. It has increased because of reduction in infant mortality, for example.

Mr. MICHEL. What is it for men and women?

Dr. LAVECK. The life expectancy in this country is approximately 74 for females and 67 for males.

Mr. MICHEL. There is a 7-year spread now. That wasn't true 10 years ago?

Dr. LAVECK. I don't know, sir; although the gap has widened over the years.

Dr. MARSTON. These overall figures can be deceptive. You can, for example, have major changes in chances of survival after myocardial infarction, as pointed out in the Heart Institute's testimony, but this can be offset by such things as higher death rates from lung cancer and accidents.

So it is difficult to draw too many conclusions from a single overall figure of this type without recognizing it is a composite of shifts, some of them up and some of them down.

RESEARCH PROGRESS ON AGING

Mr. FLOOD. Do you have anything to report to us showing any real progress in the last few years, not just the last year, in the field of research on aging?

Dr. LAVECK. I think a possible breakthrough is the one that I mentioned in my opening remarks. At our Gerontology Research Center we have succeeded in training individuals who have extra beats of their heart to control their heart rate. I think this is a fascinating beginning showing that involuntary body functions can be controlled at will.

Mr. FLOOD. The Yogi people have been doing that for 1,000 years. What is so new about that?

Dr. LAVECK. This is a new finding. Some eight patients have been studied and taught to either speed up or slow their heart rate, thereby reducing extra beats that occur as a result of heart damage.

There are two research groups that are studying the effects on old people with senile behavior of breathing pure oxygen under greater than normal pressure. Preliminary studies, and I emphasize "preliminary," indicate that there is improvement in memory and cognition in the older people. We are eager to pursue this.

Mr. FLOOD. That is a dangerous thing to fool around with, isn't it?

Dr. LAVECK. It is carefully supervised at teaching hospitals.

Mr. FLOOD. I can see where that would make sense, yes.

Mrs. REID. Most people don't breathe correctly, Mr. Chairman.

Mr. FLOOD. I am sure of that.

PROGRESS IN NUTRITION RESEARCH

Your research program on nutrition—what progress are you making in that?

Dr. LaVeck. Good nutrition is essential for normal growth. The controversial questions we wish to answer, however, deal with the relation between maternal or infant malnutrition and subsequent intellectual development of the child.

Recently we have started several new studies. One is in Harlem where 1,200 women in the lower socioeconomic group will be studied during their pregnancy. Some will receive protein supplementation to see if those women who get extra protein have larger, healthier babies.

Mr. Flood. You say Harlem. We always wind up in the ghetto. What about the other economic areas? We have come to find out, during the past few years, many of these things that are bad or that people should know about more and more, we are beginning to learn, surprisingly, the so-called middle-class people and so-called upper-class people, whoever they are, show a surprising ignorance of these very important things for obviously different reasons. Are you aware of these things?

Dr. LaVeck. Yes, sir.

Mr. Flood. The reasons wouldn't be the same why they don't know. What about that? You are poor and can't buy the food, this we can understand. But what about the people who can but are malnourished?

THE ECOLOGY OF MALNUTRITION

Dr. LaVeck. Right now we are negotiating a contract on the ecology of malnutrition in which we are exploring the questions you raised.

Mr. Flood. Ecology of nutrition?

Dr. LaVeck. Yes.

Mr. Flood. Another popular word these days, "ecology."

Dr. LaVeck. The purpose of the study is to determine why malnutrition exists in some families and not in others although income is the same.

How do they use their money? How do they select their food? What do they know about nutrition? I think these are terribly important questions that need to be answered.

Mr. Flood. That is why I raised it.

Dr. LaVeck. We will have such a study underway very shortly.

COORDINATION OF NUTRITION RESEARCH

Mr. Flood. Again this question of duplication. How do the things you are doing in this area differ from the Institute of Arthritis and Metabolic Diseases?

Dr. LaVeck. The National Institute of Arthritis and Metabolic Diseases is the focal point for nutritional research at NIH.

Mr. Flood. Yes, I know.

Dr. LaVeck. Our interest is really in one area; namely, how does nutrition affect child development? Their interests are much broader. The Arthritis Institute is concerned with the physiology and biochemistry of various nutrients, deficiency diseases, a wide array of inborn errors in metabolism, and many other topics. Just as the Heart Insti-

tute is interested in diet and its effect on the heart, we are interested in nutrition and its relation to growth and development.

Mr. FLOOD. Aren't they?

Dr. LAVECK. The Arthritis Institute is not involved as we are with the investigation of nutrition and its impact on growth and intellectual development in children.

Mr. FLOOD. Mr. Michel?

WORLD AND U.S. POPULATION GROWTH TRENDS

Mr. MICHEL. Doctor, in this whole area of population control, is your shop more concerned about what has happened throughout the world or what has happened in our own country? I recall the figures you related to the effect that in 30 years our country's population has increased 50 percent and we're likely to have another 50-percent increase by the year 2000 to 300-some-odd million people. In the rest of the world it is now 3½ billion and it will be 7 billion in 30 years.

Correct me if I am wrong, but I think immediately after the war women in this country were having on an average 3.2 children.

Dr. LAVECK. That is right.

Mr. MICHEL. We have that back down to about 2.6 now?

Dr. LAVECK. Yes, sir.

Mr. MICHEL. Which is kind of a remarkable decline in our own country, right?

Dr. LAVECK. That is right.

Mr. MICHEL. But, except for Japan and a few other places, everything is going the other way around us.

Dr. LAVECK. Particularly in the developing countries, yes, sir.

Mrs. REID. Will the gentleman yield?

Mr. MICHEL. Yes.

AID FUNDS FOR NICHD RESEARCH

Mrs. REID. We had a discussion last year about your receiving money from AID. Have you received any in the last year?

Dr. LAVECK. I recall the discussion. We did receive money in 1969 from AID, $1.5 million to help support research on a once-a-month pill. However, in view of the concern expressed by this committee, we decided not to accept additional funds from that Agency. We did not accept funds for contracts in 1970 or 1971 and we do not plan to do so in the future.

Mrs. REID. I serve on the Subcommittee on Foreign Operations and I am pleased to hear that.

Dr. MARSTON. This has been canceled out absolutely and completely.

U.S. POPULATION GROWTH TRENDS

Mr. MICHEL. Going back to the original question, in view of what is taking place both here and abroad, is your shop more concerned with what goes on in our own country?

Dr. LAVECK. We are concerned with the problem throughout the world, but our primary interest is what is going on in our country.

Mr. MICHEL. One further point. Is it right that we need 2.2 children to just keep ourselves current populationwise?

Dr. LaVeck. 2.1 is correct for replacement, yes, sir.

Mr. Michel. We are surely not going to get that—I can't foresee it at least—in the immediate future in this country.

Dr. LaVeck. It would be some time before we would be able to reach 2.1 children per family.

Mr. Michel. In view of the remarkable progress we have made in the last few years, is it in the realm of possibility within a reasonably short time?

Dr. LaVeck. There is a problem. The birthrate dropped steadily until it reached its lowest level in 1968. In 1969 and again in 1970 it went up. The reason is that we have more young women in the reproductive age groups now. So we are going to see more babies born for the next few years even though more families may be getting closer to 2.1 children per family. It takes a long time before this levels out and we attain a stationary population.

NUMBER OF UNWANTED CHILDREN

Mr. Michel. When you mentioned one-fifth of the children being unwanted, did those studies show in what economic areas those were?

Dr. LaVeck. Yes.

Mr. Michel. What did it show?

Dr. LaVeck. Unwanted children were twice as common in the lower socioeconomic group.

Mr. Michel. And, of course, you said had it not been for that there would be 4.7 million fewer people throughout the country. What the study shows is that they were in that particular area and the chances are a good many of them end up being problems which we have to deal with across this table with sums of money required for welfare programs.

Dr. LaVeck. Yes.

EXTENT OF USE OF CONTRACEPTIVES

Mr. Michel. What percentage of the women are using the pill today, would you say, in our country?

Dr. LaVeck. The latest figure I have is about 8½ million women are on the pill, which would make about 20 percent of women in the reproductive age.

Dr. Corfman. That is about right. We are completing the 1970 survey. We expect the percentage may have changed.

Mr. Michel. How about those using the loop?

Dr. Corfman. We figure there are about 2 million loops in use in the United States, but again that is a conservative figure. The only way we can get data now is by asking manufacturers how many they are manufacturing and how many they have distributed, but we have no way of knowing how many are in use without actually asking people.

SIDE EFFECTS OF BIRTH CONTROL PILLS

Mr. Michel. I asked you earlier whether or not women were reluctant to use the pill because of what has been published with respect to the possible gain of weight, and you responded that it really wasn't very significant, is that right?

Dr. LaVeck. Some women report weight gain, some women report weight loss. Changes in weight are commonly seen in pill users, and I am sure there are some women who reject the pill for this reason, but I don't think this is a major reason.

Dr. Corfman. Data from the 1970 National Fertility Survey are very important to answer that question. It has been suggested that pill use has leveled off in this country. Manufacturers say this. They are complaining about it actually. We are very anxious to find out whether use has decreased or leveled off.

Mrs. Reid. What about blood clotting in the legs?

Dr. LaVeck. This has been well investigated now and, from studies carried out at Johns Hopkins, women who use the pill have a risk of about four to four and a half times greater than nonpill users of having blood clots in the legs, and elsewhere. Studies in Great Britain have also revealed that the death rate is greater from blood clots in women on oral contraceptives. However, the overall risk is small. Approximately three out of every 100,000 women on oral contraceptives will die from a blood clot. Thus the risk is not great, but it is measurable.

Mrs. Reid. Is there any way of discovering this condition before a woman takes the pill?

Dr. LaVeck. This is one of our research efforts.

Dr. Corfman. I remember you asked the same question last year. Last time all I could say was there seems to be a difference in blood type; those who are A, or AB, are more apt to have this problem. We recently awarded two new contracts designed to develop a simple method of detecting women who are susceptible to this problem.

Mr. Flood. It is hard to hear you.

Dr. Corfman. I said we have recently awarded two new contracts designed to develop a simple method of detecting who are susceptible to this problem.

Dr. Marston. When one talks about the risk of taking the pill, one must also keep in mind the risk of having unwanted pregnancies, and the complications of pregnancies. I believe that the situation is still that the risk from complications of pregnancy is higher than the risk from taking the pill. So one must balance these two, rather than just arriving at a conclusion that one prevents death by decreasing the use of the pill, because decreasing the use of the pill would, in fact, increase the probability of death from complications of pregnancy.

Priority of Population Research Versus Control With Present Knowledge

Mr. Michel. Doctor, you are concerned primarily with research and I don't really need much of a sales pitch when it comes to research funds for mental retardation and many other areas, but I must share some of the concern of the chairman when you say research for population control.

What causes us to reproduce is no secret. It is not clear to me exactly what more we need to find out about population control as such. Wouldn't it be much wiser to take that money, which we are going to be putting into research on control, and disseminate the material and information to the people who really are the cause of it all in the first place? Aren't there just some very elementary things that have to be

done to control population, period, without any fancy research on what makes it all possible?

Dr. LaVeck. Are you referring mainly to our efforts in the social sciences?

Dr. Marston. There is a more general question. I think this does become a policy question for NIH and for the Government. I think we have a special situation as far as population information and information on reproduction is concerned.

Many people feel this is the most urgent single problem facing the world at present, and that everything else that we try to do on this earth eventually is dependent on having some way to avoid the continued growth of the population at the current rates.

Second, there is inadequate knowledge about reproductive physiology and about the ways in which one can modify the growth rate—the population rate—that is acceptable to most of the people. The best example is this discussion that we just had a few minutes ago concerning the pill. Clearly we still need more information, more research, on the side effects and the alternatives that might be found, to decrease the risk and to get improved, acceptable methods of contraceptive control.

INADEQUACY OF POPULATION CONTROL KNOWLEDGE

Mr. Flood. If the gentleman will yield; Mr. Michel, as usual, asked a very practical question. You know what he means. He has asked a very simple question, so what about it? Here he is and there she is. Now what are you going to do about it?

Dr. Marston. For some women who will take the pill, it will be satisfactory. There are some who run a risk.

Mr. Flood. He is not talking about the pill.

Dr. Marston. Am I misunderstanding your question about why we need more information?

Mr. Michel. You know it is a popular thing, there is no question about it, and we are inclined to relate these things with dollar expenditures. You are going to justify it all, and you say, "Yes, we put so many hundreds of thousands or millions of dollars into this population center, this one and this one." The issue is just how do we keep from having more unwanted babies, period. Why does there have to be very much research? Don't we already know how to prevent unwanted babies? Shouldn't this be primarily a practical, service job?

Dr. Marston. I thought it was your question, whether we had adequate knowledge or not. I think the case is overwhelmingly that we do not have adequate knowledge to be used by the population to have effective fertility control. The reason for the need for more research is that we do not have enough information. If we had more information, then it would be possible to do the practical job that you talk about.

I would agree completely that the question of motivation, the question of social customs, the questions of being convinced is very important, and may eventually be more important than the knowledge base. But we do have an inadequate knowledge base at present.

Mr. Miller. Could I make this point too, Mr. Michel? The budget before you has about two and a half times as much in it for family planning services as it does for research, so there is a very heavy emphasis in that area, and also in reference to a previous question

of yours, family planning services are devoted to the United States. That money is spent in this country, so that to the degree it is international, and, of course, national boundaries aren't truly important in research, but it seems to me whatever concern you have about international aspects of family planning program, why it is the service program, and that is not international. It is solely national.

DETECTION OF FETAL ABNORMALITIES

Mr. MICHEL. If I might now turn to—I can't find it in your testimony here—where you were speaking of the number of things we may be able to determine now from the fetus. You didn't say at what age or at what time frame.

Dr. LAVECK. The usual time is between the 13th and 18th week of gestation. This is the latest time that one can do this procedure, and still have the information back early enough to do something about the pregnancy.

Mr. MICHEL. What was that figure again—40?

Dr. LAVECK. At least 40. Since this was written it probably has gone up to 50 or more.

Mr. MICHEL. What are those? Give me a few of them.

Dr. LAVECK. The chromosomal defects such as mongolism or Downs syndrome are excellent examples. Commonly in some of these research centers doctors will examine a pregnant woman, especially a pregnant woman over age 40, for example, using this technique to see if she is carrying a mongoloid child. Such a woman has about one chance in 60 of having a mongoloid child just because of her age. This is one of the common reasons, but there are other chromosome and metabolic abnormalities that can be detected by amniocentesis.

Mr. MICHEL. My followup question is a hypothetical case. If my wife were to find that out at that point in her pregnancy, with what degree of certainty would the doctor be able to say, "From what we are able to find you are going to have a mongoloid child"? Are we getting to that point?

Dr. LAVECK. I would say with that particular disorder we are close to 100 percent certain.

Mr. MICHEL. Then I guess the decision would be you either want to go through with your pregnancy, or you do not.

Dr. LAVECK. This would be the parents choice, depending on whether abortion was legal in that particular state.

Mr. FLOOD. Do you get the woman's consent before this test is made?

Dr. LAVECK. Oh, yes; consent would certainly be required.

Mr. FLOOD. Is this a safe procedure?

Dr. LAVECK. The most recent surveys indicated no fetal death at all from the procedure.

Mr. FLOOD. I wasn't speaking of the mother, I was speaking of the fetus.

Dr. LAVECK. No deaths had been reported in the latest survey, but one of the reasons we are conducting an amniocentesis registry is to make absolutely certain that this is true. Although it appears to be a perfectly safe procedure perhaps miscarriages or premature deliveries are being missed.

There are also a host of other diseases that we call inborn errors in metabolism. Dr. Stetten mentioned some of these.

Mr. MICHEL. In this group of 50, when you find there might be some malady occuring in the child, are there any that could be corrected before the child is born?

Dr. LAVECK. Only one that I am aware of before the birth of the child, and that is the RH problem; however, if one knew at the time of delivery that a child had a particular disease, early treatment could be started and mental retardation might be prevented.

Mr. MICHEL. It is a very interesting subject and it ought to be developed more in the record here, so would you please send some additional examples of these 50, if you would—the more significant ones.

(The information follows:)

AMNIOCENTESIS IN PRENATAL DIAGNOSES

Milunsky, et al. (New Eng. J. Med. 283:1370; 1441; 1498, 1970) have recently tabulated the disorders that, with our present knowledge, can possibly and usefully be diagnosed before birth. Chromosomal defects, although omitted from the list can also be diagnosed prenatally.

PRENATAL DIAGNOSIS OF HEREDITARY METABOLIC DISORDERS BY AMNIOCENTESIS

Disorders of lipid metabolism

Fabry's disease*
Gaucher's disease
G_{m1} gangliosidosis (generalized gangliosidosis)
Metachromatic leukodystrophy
Niemann-Pick disease
Refsum's disease

Mucopolysaccharidoses

Hurler's syndrome
Hunter's syndrome
Maroteaux-Lamy syndrome
Morquio's syndrome
Sanfilippo syndrome
Scheie's syndrome

Amino acid and related disorders

Argininosuccinic aciduria
Citrullinemia
Cystinosis
Homocystinuria
Hyperammonemia, type II
Hyperlysinemia
Hypervalinemia
Ketotic hyperglycinemia

Maple-syrup-urine disease

Severe infantile
Intermittent
Methylmalonic aciduria
Ornithine-alpha-ketoacid transaminase deficiency
Disorders of carbohydrate metabolism
Fucosidosis
Glycogen-storage disease (type II)
Glycogen-storage disease (type III)
Glycogen-storage disease (type IV)
Galactosemia
Mannosidosis
Pyruvate decarboxylase deficiency
Glucose-6-Po_4 dehydrogenase deficiency
Miscellaneous disorders
Acatalasemia
Adrenogenital syndrome
Chediak-Higashi syndrome
Congenital erythropoietic porphyria
Cystic fibrosis
I-cell disease
Lesch-Nyhan syndrome*
Lysosomal acid phosphatase deficiency
Marfan's syndrome‡
Orotic aciduria
Xeroderma pigmentosum

All disorders listed are autosomal recessive, except for those marked *(X-linked recessive) or ‡(autosomal dominant).

PRIORITIES IN RESEARCH AND TRAINING GRANT PROGRAMS

Mr. MICHEL. I notice the number of research grants is up.

Dr. LAVECK. Yes, sir.

Mr. MICHEL. From 732 to 760, and those would be what primarily?

Dr. LAVECK. The increased number of grants will be all in population research.

Mr. MICHEL. As the chairman brought out in his line of questioning, aging is at the bottom of the priority list.

Dr. LAVECK. That is correct.

Mr. MICHEL. But your training grants go down from 116 to 100, and they went down in 1971 from 131 to 116. Did any of this get picked up in the manpower program?

Dr. MARSTON. No. The salary component of these training grants in this Institute was transferred to the Manpower Bureau, so the actual amount of money is essentially level between 1971 and 1972.

USE OF MEDICAL SERVICES BY THE AGED

Mr. MICHEL. You said too, I think, in your testimony that we have 20 million people, give or take a few, over the age of 65. That is one-tenth of the population—less than one-tenth. But you also said that two-thirds of our medical expenditures were for those persons over the age of 65; is that right?

Dr. LAVECK. That is correct.

Mr. MICHEL. Doctor, you are raising a finger.

Dr. BERLINER. Two-thirds of the Federal expenditures; is that correct?

Mr. MICHEL. That is quite a difference. I had never seen that particular statistic. It was so striking to me that I got to putting the things together, and I thought if that is actually the case, then we really do have to have some reordering of priorities here, putting more into this problem of aging, if that group over 65 is the cause of that much of our medical expense problem. It would seem to me we ought to be doing more in that field.

Dr. MARSTON. I suspect this is one of the inevitabilities of human life, that there will be more problems of a medical nature as one approaches the end of a normal lifespan. The focus has to be on premature death and on increased comfort in the aging, but I suspect it would be an unrealistic goal to expect that there would not be, for all time, more need for medical help in the aged than in the young and vigorous person.

OTHER INSTITUTES WORK ON THE PROBLEMS OF AGE

Mr. MICHEL. Dr. Marston, since the budget request shows a reduction in the aging category, what can be shown at any place out at NIH to make up for that decline in the field of aging?

Dr. MARSTON. There are a number of things one can say. For instance, there is a very significant increase in work on arteriosclerosis, which is one of the major problems of aging. There is work that is being done on stroke, which is a major problem in aging. There is the large and dramatic increase in the support of research on cancer, which does have a higher incidence of problems in the aged. So I think

it would be unfair to focus on just the aging program of this Institute, and to conclude that we are putting less emphasis on the problems of older people. In fact, I would say very strongly, and I think the Department would back this, that we do continue to have a major emphasis in 1972 on the problem of the whole spectrum from birth to death.

Mr. MICHEL. I think it is good to have that for a balanced record. Sometimes we tend to get some of the things submerged in these dollar figures, and someone looking at this record says, "Gad, they must not have any concern for the aging population," which, of course, is not true. That is all, Mr. Chairman.

Mr. FLOOD. Mr. Natcher?

EFFICACY OF TRANQUILIZERS FOR CHILDREN

Mr. NATCHER. I know a little boy, Doctor, who is perfectly normal and healthy in every respect. He is full of life and he is a real cowboy. As far as I know, Doctor, every gland in his body works perfectly. Why should he take tranquilizers just because his teacher is a little tired or is having extremely long weekends? Do you run into this, Doctor?

Dr. LAVECK. Yes.

Mr. NATCHER. What do you do about it? What are you saying about it?

Dr. LAVECK. Our position on this, of course, is that children and adults should not be taking medication unless there is a clear indication for taking medication. There is a particular condition in children that is amenable to amphetamines, and occasionally to tranquilizers. It is referred to as the brain damage behavior syndrome or minimal brain dysfunction. These children are usually of normal intelligence, but hyperactive, aggressive, into everything, unable to sit still in the classroom, and one finds minor deviations from normal on the neurologic examination. They may have abnormal brain waves.

These children, when put on amphetamines, for example, tend to calm down and profit from their educational opportunities. However, to take every hyperactive child who is hard to manage in school, and recommend this type of medication, would be a grave error.

Mr. NATCHER. Doctor, have you made any studies concerning the number of children ages from 6 to 10 who are taking tranquilizers now, in any of the adjoining counties of Virginia and Maryland? Do you know anything about it?

Dr. LAVECK. No, sir, I do not. The reports are that as high as 5 to 10 percent in some localities are being treated for this hyperactive syndrome.

Mr. NATCHER. That is right low for some localities, isn't it, Doctor?

Dr. LAVECK. It could be. Our Institute is really not involved in drug abuse. Mental Health has been more deeply concerned. In fact, we have not been investigating this problem, although perhaps we should know more about it. We have not been supporting research on drug abuse or on the efficacy of psychotropic drugs.

Mr. NATCHER. Doctor, do you hear of cases where some little boy or girl is given tranquilizers just by virtue of the fact that he is overly active at home? His mother decides that he needs to take them because

she is a little tired. Who does the prescribing? Do they talk to doctors about it?

Dr. LaVeck. I think there are examples of what you have just said. I know in institutions, particularly institutions for the mentally retarded, where children are overly active and into things, that there is a strong tendency to try to calm the children down a little bit to make it easier on the staff. This has to be watched at all times.

Mr. Natcher. Doctor, this child is perfectly healthy. The child is examined and the child is discovered to be a normal, perfectly healthy child, but full of life and very active. Is that a child who should have tranquilizers?

Dr. LaVeck. Not in my opinion.

Mr. Natcher. Doctor, you have heard of cases where they are given them, haven't you?

Dr. LaVeck. Yes, sir.

Mr. Natcher. We have it before another subcommittee. You would be surprised at the percentage that we hear who are receiving tranquilizers. Normal, healthy children.

ADOLESCENT HEALTH CARE

Are we going to have a period here, in about 10 or 15 years, where three-fourths of our boys and girls will have a life expectancy of 35 or 40 years?

Dr. LaVeck. You raise a very important question that I can't answer.

Mr. Natcher. You should be dealing with it a little bit, Doctor.

Dr. LaVeck. We do some research of this type, but the Mental Health Institute has concern for delinquency and drug abuse, if that is what you're referring to.

Mr. Natcher. Mental Health?

Dr. LaVeck. The National Institute of Mental Health.

Mr. Natcher. These children are not unsound mentally.

Dr. Marston. The Mental Health Institute has the responsibility for the whole drug abuse program.

Mr. Natcher. Let's not bring drugs into it, Doctor. Let's just say it is the way they are living without drugs. Where would that fall?

Dr. LaVeck. This would fall within our Institute.

Mr. Natcher. In other words, let's claim a little of it now, Doctor.

Dr. LaVeck. Yes, sir.

Mr. Natcher. Is it a very serious matter?

Dr. LaVeck. If the question you ask is: Do children between the ages of 14 and 16, who do not take drugs, pose a particular problem? The answer is yes; but not to the same degree as the life-and-death situations of the newborn.

Mr. Natcher. They are not eating right or living right.

Dr. LaVeck. Nutrition is a major problem area. This was pointed out in a recent publication by the National Academy of Sciences. Teenagers do not eat appropriately. There is no question about this. This is well established and needs to be rectified. I think more pediatricians are seeing adolescents now. In the past, adolescents had no one to go to for health supervision. They were too old to go to the pediatrician and too young to go to the internist. It was a neglected period of life. In fact, adolescent clinics are emerging in many of our major medical

centers, where they are exploring such problems as learning difficulties, obesity, and other nutritional difficulties, and some of the psychological problems that are commonly seen in that age group. Acne, for example, is commonly seen in this age group. It creates a crisis for these young people, and yet no one really pays much attention to it. A minor physical problem can cause a major psychological difficulty.

Mr. NATCHER. Thank you, Mr. Chairman.

Mr. MILLER. Mr. Natcher, I don't want to leave the impression on the record that Mental Health's only role in the kind of problem you cite solely is drug abuse. They have a broad spectrum of responsibility for these kinds of problems you are describing—for research into the way man lives, into his whole social environment and behavior as well as the delivery of assistance to communities. They are not just concerned with things like alcoholism or drug addiction, but they are much more active in the area than any other part of HEW.

Mr. NATCHER. Dr. Marston, you know a lot more about this than I do. This is a very serious problem with a lot of people in this country, and they are talking about it, Doctor. Somebody ought to be looking at it.

Mr. CASEY. Will you yield?

Mr. NATCHER. Yes, I yield.

ADVERTISEMENT OF NONPRESCRIPTION TRANQUILIZERS

Mr. CASEY. You were talking about youngsters taking tranquilizers. One thing that disgusts me is you will see ads on TV for some of these over-the-counter tranquilizers, for school kids. They have an ad showing the children having an exam, they are all nervous and the ad says, "Stop, try Compoz," encouraging them to take this. I don't know what is in that particular over-the-counter drug, but it is certainly trying to encourage, the harried housewife, and students to take this type of medication. I just think we have enough of that going on without advertising, too, on the TV. I agree with the gentleman that it is getting to be a problem.

Mr. SMITH. Will the gentleman yield?

Mr. NATCHER. I yield.

Mr. SMITH. I ran into this. I wanted to take my dog on an airplane and since a dog tranquilizer would require a prescription from a veterinarian I would have to go to a vet to get a tranquilizer, so I went down to the drugstore and got some for people because no prescription was required for tranquilizers for humans.

Mr. FLOOD. Mrs. Reid?

LONG-TERM EFFECTS OF ORAL CONTRACEPTIVES

Mrs. REID. Thank you, Mr. Chairman.

I have just a couple of additional questions. We did discuss some of the effects in some women, such as weight change and blood clotting due to the use of oral contraceptives. What about studies concerning the effects that prolonged usage of oral contraceptives will have on later life? Are such studies going on?

Dr. CORFMAN. I am not so sure I understand the question.

Mrs. REID. Would there be any ill effects other than the immediate effects? Could there be ill effects from the prolonged usage of oral contraceptives?

Dr. CORFMAN. There are studies on the possible relationship between pill users and cancer which would come into that category. The same would apply to studies we have underway on the possible relationship between pill use and various metabolic diseases, particularly diabetes. We have a variety of epidemiological studies on this particular problem.

Mrs. REID. But I suppose this has not been used long enough to really know.

Dr. CORFMAN. That is exactly it. Take cancer as an example. This year was the first time that we could start studies on cancer, because most carcinogens in humans take on the average 10 years to take effect. Pills have been in general use about that long.

COORDINATION OF NUTRITION RESEARCH

Mrs. REID. How do you correlate your studies on nutrition with those done by other agencies within the National Institutes of Health and the Department of Agriculture, for instance?

Dr. LAVECK. I am not aware that we have much in the way of overlap with other agencies, but the coordinating responsibility—Dr. Marston can correct me if I am wrong—rests with the Arthritis Institute; is that not correct?

Dr. MARSTON. That is right in terms of general programs. Coordination within NIH has several aspects. All requests for support through grants come into a central office at NIH, and are controlled as they go through the review system. In some instances, a request for a grant in nutrition might go to two or three Institutes to see where it fits best, but it will be supported by only one, rarely by joint support from two Institutes.

In my office I have an individual who has responsibility for all of the contract work that we support. Therefore he sees to the coordination across Institutes as far as contracts are concerned.

Then as far as the intramural work is concerned, Dr. Berliner, wearing another one of his hats, presides over that and sees to it that there is not unnecessary duplication.

For most problems, one Institute clearly has the major responsibility. In the case of nutrition, it is the Institute of Arthritis and Metabolic Diseases. Most things in nutrition that are done anywhere else, in addition to these formal checks, would have informal checks with the group working on nutrition in the Arthritis and Metabolic Diseases Institute.

Mrs. REID. Do you know, for instance, what is going on in the Department of Agriculture in this area?

Dr. MARSTON. In the nutrition area? I either know or I can find out through one of these various mechanisms quite quickly.

Mrs. REID. And you do look into this before you go into any new program?

Dr. MARSTON. Yes. In most of the work, experts in these fields maintain close contact with each other. We also have for all of science publications, with full reports and in abstract form, on all of the research that is done anywhere. This is available to make cross checks.

Mrs. REID. Is this something which really concerns you?

Dr. MARSTON. The coordination part?

Mrs. REID. Yes.

Dr. MARSTON. It has been in nutrition. As you know, there have been a number of task forces, and much discussion at the departmental level, on nutrition. These activities, in the last couple of years particularly, have been built up. The need for coordination in growing programs of that type has been recognized and followed. In general, I find that our mechanisms also allow for the type of duplication that one wants. In most of science, when you have a finding you want some other group, if it is an important finding, to confirm it because so often the initial finding, looked at by one investigator, may not tell the whole story. Therefore you usually want at least one other group to essentially duplicate that work, and often to expand it into other areas.

I think we have pretty good controls, as well as one can, through these various mechanisms that I have spoken about, to avoid useless duplication. Sometimes, you know, there may be similar studies, with one focused on particular problems of youth, that Dr. LaVeck would want to have because of his interest, while another study might focus a different aspect of interest to the Arthritis and Metabolic Diseases Institute.

Mrs. REID. Thank you, Doctor. Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Smith?

MALNUTRITION AND MENTAL DEFICIENCY RESEARCH

Mr. SMITH. Doctor, it says here "several studies are underway to determine how severe malnutrition must be to produce intellectual deficits, and at what stage it is the most devastating."

How do you set up a study like that? You can't have a control group. How do you do that?

Dr. LAVECK. We have one study with primates where we have a supplemental group and a control group. The study is to determine how important maternal nutrition is to the brain development of the offspring.

Mr. SMITH. Can you measure intellectual deficits in primates?

Dr. LAVECK. No, sir. This is to measure the number of brain cells and the size of the brain, which indirectly correlates with intelligence. It is a study that we can't do in humans. We do have some studies in humans. Our major one is in Guatemala.

Mr. SMITH. I wondered if you were keyed into that one?

Dr. LAVECK. Yes, sir. We are studying people in four villages in the lowlands of Guatemala, where we are providing a dietary supplementation.

Mr. SMITH. That has been underway about 4 years, has it?

Dr. LAVECK. We have been funding it since 1965, but for several years we were involved in planning. The actual supplementation started in January of 1969, so there has been a little over 2 years of supplementation. That is the principal human study that we have underway. It should define the relationship between the amount of protein intake and intellectual development, and the critical time period involved.

Mr. SMITH. How long will it be before we begin to get some answers?

Dr. LAVECK. I have been assured that within 1 year we ought to have some preliminary data. I certainly hope so.

Mr. SMITH. Are you still using soybean protein?

Dr. LAVECK. Incaparina is the supplement.

Mr. SMITH. With primates, is that what you are referring to in a sense in your testimony?

Dr. LAVECK. I was referring primarily to the Guatemala study. We have a study in Bogotá, which is in the pilot phase. It differs from the Guatemala study in that it compares siblings in a family, one sibling who is malnourished and one who is not. The reason the design differs is to permit control for genetic factors as best one can. These too may be a cause of mental retardation. In that study the pilot phase will end next year, and then they will go into the large study.

Mr. SMITH. Will any of these studies indicate to what extent food in some instances could be prescribed instead of drugs?

Dr. LAVECK. I would hope so, yes, sir.

Mr. SMITH. That is all I have, Mr. Chairman.

Mr. FLOOD. Mr. Casey?

Mr. CASEY. Thank you, Mr. Chairman.

THE NATIONAL FERTILITY SURVEY

Doctor, when was this survey with Institute support made with reference to unwanted births; between 1960 and 1965?

Dr. LAVECK. This was the National Fertility Survey carried out in 1965 by Princeton University. Similar studies were done in 1960 and 1955, but not supported by our Institute since we were not established at that time.

Mr. CASEY. So did they make this inquiry at the time of the birth, during the pregnancy, or after the child is a year old, or when?

Dr. LAVECK. They made it at the time of the interview. The child might be 1 year old or 10 years old. The accuracy, of course, can be questioned as in any interview survey, but it would appear that if there is going to be an error it would be an underestimation. The parents would tend not to admit that a child was unwanted.

Mr. CASEY. You might have made a survey of the parents of some of those we had down here the other day, and maybe you would find all of them unwanted.

Dr. LAVECK. That is right. The situation might change at different times.

CONTENTS OF ORAL CONTRACEPTIVES

Mr. CASEY. Is there only one pill, Doctor?

Dr. LAVECK. The pill is based on a compound with two hormones in it, an estrogen and a progestin. There are many variations of the exact progestin or estrogen. The dosage may differ and the synthetic derivative may differ. When we speak of the pill, we are referring to a medication with two hormones in it, but there are variations as to amount and type of hormone derivative.

Mr. CASEY. But basically that is the only oral contraceptive you have?

Dr. LAVECK. That is the only type that is licensed; that is correct.

EXPERIMENTAL ORAL CONTRACEPTIVES

Mr. CASEY. Are others in an experimental stage?

Dr. LAVECK. Yes, sir.

Mr. CASEY. Have any of them been licensed for experimental use?

Dr. LAVECK. Yes. One such compound is referred to as the mini pill. It's made up of a progestin, chlormadinone, and has been studied extensively in other countries and to some extent in this country. Recently this compound has been found to cause breast tumors in beagles and has not been studied in humans in this country in the last year.

Dr. CORFMAN. There are about 20 different formulations on the market now, Mr. Casey. They are all based on the two classes of compounds that Dr. LaVeck mentioned. There is now in testing the so-called mini pill which uses just one compound at a very low dose. What is different about it is that the woman takes the pill every day. She doesn't have to remember whether it is a pill day or not. This is a very effective means of contraception. There has been a problem that some of the chemicals that have been used have caused breast tumors in beagles and have been withdrawn from use, but other formulations don't cause these problems, and so the mini pill is still a likely development in the next few years.

Mr. CASEY. It is a likely development, you say?

Dr. CORFMAN. Yes.

TYPES AND SIDE EFFECTS OF IUD'S

Mr. CASEY. Is there more than one IUD?

Dr. LAVECK. Yes, there are a number of IUD's based on their shape, but there is a new IUD that may soon be licensed, which is called the copper-T or the copper-7. It differs in that there is a copper filament around the IUD, which has an antifertility effect in itself. It has been shown in studies to be very effective as a method of birth control, approaching 100 percent in preliminary studies, and differing from other IUD's in that more women can tolerate it without having adverse effects.

Mr. CASEY. Do the IUD's have any effect such as the pill? Do they cause any cancer? Do they have any side effects?

Dr. LAVECK. There is no evidence that they cause cancer although some changes have been described in the cervix. Their main problem is that they may cause infection, excessive bleeding, and pain.

VANDERBILT POPULATION RESEARCH CENTER

Mr. CASEY. So far you have only established one population control center, is that right?

Dr. LAVECK. That is correct. It is not a population control center, but a population research center.

Mr. CASEY. What are you going to do at that center besides your research on contraception and learning more about fertility? Are you going to render any services at this center?

Dr. LAVECK. This center is at Vanderbilt, and is under the control of the medical school there.

Mr. CASEY. You are going to fund it but you don't know what they are going to do?

Dr. LAVECK. We are going to fund it and we know what is planned. Of course they do render services at the hospital, but we do not fund that particular part of their work. We are supporting only the research and the necessary resources so that a multidisciplinary team can carry out research in this field.

FEDERAL FAMILY PLANNING SERVICE EFFORTS

Mr. CASEY. This is, as the chairman said, a hot subject. Who is distributing the services as far as the Federal Government is concerned?

Dr. LAVECK. The National Center for Family Planning Services and the Office of Economic Opportunity are the principal sources of support for services in family planning.

Dr. MARSTON. The National Center for Family Planning Services is in the Health Services and Mental Health Administration.

POPULATION RESEARCH AT CATHOLIC UNIVERSITIES

Mr. CASEY. All the research you are funding is in the field of medicine, finding new types of pills, IUD's, and so forth. Are you considering any research centers which might be oriented toward some of our particular religious groups who have religious convictions against these devices and medicines?

Dr. LAVECK. Mr. Casey, religious affiliation would not be a deterrent to having a center at a university. I would think that the Catholic universities might very well want to have population research centers, and we would encourage this.

Mr. CASEY. I would also think so. I would think somebody would, because there is a very large segment of our population, and of course they have their own little arguments going on pro and con now trying to reconcile the tenets of their faith along with this clamor now for population control. I am just wondering if that is being taken into consideration?

Dr. LAVECK. We would be very pleased to receive applications.

Mr. CASEY. Are you going to wait until somebody comes up with a proposal? I would certainly think that should be taken into consideration.

Dr. CORFMAN. Our announcement on the centers, Mr. Casey, went to all universities, and we have received replies from a number, including Catholic schools. We do support research at a number of Catholic institutions, particularly on the social science side. Also we worked very closely with the Human Life Foundation in the establishment of their new program here in Washington. This agency supports reproduction research funded by the Catholic bishops.

Mr. CASEY. When parents find fetus defects, and we have had one witness here prior to your appearance who said they could then decide whether they wanted an abortion or not, do we finance that sort of an operation?

Dr. LAVECK. The abortion itself? No, sir.

Mr. CASEY. You say that defects can be determined in 13 to 18 weeks. Eighteen weeks is approximately 4½ months. Children have been born at 4½ to 5 months and lived, haven't they? Some of them have been fairly normal.

Dr. CORFMAN. There may be some that have lived at that age, yes.

Mr. CASEY. Of course I know you are not advocating it here, but couldn't we get to the point, if you are going to make a decision at 18 weeks, couldn't you just say wait until after it is born to make sure we are right, and if we are right then you can just put it away like a sick horse, couldn't you?

Dr. LAVECK. I have worked with mentally retarded children all my professional life, and such an idea is completely unacceptable to me personally, and I am sure to everyone in the room here.

Mr. CASEY. With the breakthroughs we are making on some of these things, I can see the reverse. Somebody says we don't want a child who has this defect, whatever it might be, and 3 years later, if a brilliant scientist makes a breakthrough it is cleared up.

Dr. LAVECK. That is always a possibility.

Mr. CASEY. That is all, Mr. Chairman.

Mr. FLOOD. I might say before you leave, Doctor, I am very much impressed by this matter that Mr. Natcher has raised. The only thing the matter with it today is that I didn't think of it. We have been talking about this for some time. This is really an important matter. And then the statement given by Mr. Casey that these TV shows are pushing and urging it, trying to sell these things, would it concern you enough to bring to the attention of the FCC this kind of problem, and indicate to the FCC that you do not believe at NIH that the FCC should permit this kind of thing to continue? Everybody has been upset about tobacco for several years.

Mr. CASEY. They can go to the drug store and buy it right over the counter.

Mr. FLOOD. This is a very alarming, shocking, dramatic point that Mr. Natcher has raised here. I would like to think, Doctor, that you and your advisers would examine this with some attention. There has been little said here this week from your shop that has struck me more than this.

Dr. MARSTON. Mr. Chairman, this is a very important subject. I know that the FDA is very much involved in the whole question of over-the-counter drugs, and how best to handle them. The Mental Health Institute and we also have responsibility. I would be glad to put a brief statement, in response to this, in the record and, in the longer range, to take under advisement what you have suggested.

Mr. FLOOD. You have special commissions and special advisory groups appointed and created to advise you on a number of matters, which is good. I wonder why you don't have such an advisory group named to examine this very, very striking thing.

Dr. MARSTON. May we then proceed in this way and put some information on this in the record?

Mr. FLOOD. This strikes me, as you develop the subject and with this nationwide concern about drug abuse and narcotics, that this kind of

thing is being done to the degree that it is almost an invitation to the children to acquaint themselves with these tranquilizers.

Mr. CONTE?

AGING RESEARCH

Mr. CONTE. I am most disturbed about the Institute's proposed cutbacks in research on aging and find it almost increbile that, in the year of the White House Conference on Aging, this is being done. By what amount is this activity being cut and what is the rationale for this decision?

Dr. LAVECK. Our Institute will provide $7,180,000 for aging research in 1972, a decrease of $1.35 million from 1971. We would very much like to be able to increase all of our important programs. However, the first priority for this coming year has been assigned to contraceptive development and the medical effects of contraceptives, while aging research has been forced to take a lower priority.

Mr. CONTE. Considering the very important responsibilities that the Institute has for research and training in pediatrics, reproductive physiology, population planning, the problems of adolescence, and mental retardation, do you believe that you can adequately handle a program of research on aging which has such different staff requirements?

Dr. LAVECK. Because of the continuity of human development across the lifespan there is scientific logic in placing the support of aging research within a structure concerned with human development. This was reflected in the decision of Congress to place research on aging within NICHD. The institute has no unusual difficulty in securing appropriate staff to develop the needed programs in research on aging.

Mr. CONTE. What is your estimate of the effects intensified research on aging might have in serving to decrease the number of patients in nursing homes?

Dr. LAVECK. There is no doubt that research on aging will permit a reduction in the percentage of his lifespan the average person has to spend dependent on society and thus in a nursing home or similar environment.

This is true because biologic aging processes are important in a great many of the diseases that afflict older persons—atherosclerosis, cancer, arthritis, and a host of other diseases. Research on aging processes may be expected to make possible procedures that will affect the incidence and management of many of these chronic diseases favorably. For example, the decay with age in the ability of the body to utilize carbohydrates and to maintain serum fats at a low level is probably important in the develoment of atherosclerosis. The loss of immunological competence with age is probably important in the development of cancer. It seems clear that as we learn more about aging processes we will be able to modify these and many other diseases favorably.

In addition much research is needed on the medical, psychological, and social opportunities that society makes available to older persons. Such research will not only make possible a great improvement in the quality of life of older persons, it will also increase their contributions to society. It will at the same time reduce the need for the institutionalization of the elderly.

RESEARCH ON EFFICACY OF DRUGS FOR THE AGING

Mr. CONTE. We see many articles in the press about the supposed effects vitamin E, other vitamins, and drugs have on the health of the aging. Is any significant research being conducted to find out what health claims are true and when the public is being misled?

Dr. LAVECK. An insufficient amount of research is being conducted on the differences between the nutritional and other needs of young adults and those of older persons. NICHD supports a small amount of such research, but a great deal more needs to be done. The differences to be found may prove to be substantial and translatable into medical procedures of value to the middle-aged and elderly. Thus NICHD looks forward to supporting more research in this area. For example, despite much publicity to the contrary, it is not clear whether treatment of the postmenopausal state with hormones is generally useful and harmless. NICHD is starting a program on this type of treatment. It is also interested in the hormonal changes that occur with age in men. The changes, from a quantitative standpoint, are large. Nevertheless, we do not know how much is to be gained or lost by their modification. Many other examples could be given ranging from a decreased output of insulin in the latter half of life to inadequate calcium metabolism in that period.

On the other hand, many claims are put forward that on investigation prove to have no foundation. Investigations supported by many different agencies may indicate that the claims are without foundation. The final common pathway through which the public is protected against such unsubstantiated claims is the Food and Drug Administration.

LACK OF FEDERAL FOCAL POINT FOR AGED HEALTH CARE

Mr. CONTE. Where in the Federal Government is responsibility for health care for the aged centered? Who is looking at this problem from a medical point of view, as opposed to an insurance point of view?

Dr. LAVECK. Many different Federal programs are concerned with the health care of the aged. These programs are within the DHEW. In most cases they are concerned with a particular function that affects all citizens rather than the elderly per se.

The Community Health Service of HSMHA has several programs particularly concerned with the elderly—the home health services program, the nursing home program, and the program by which it establishes professional standards for care under the medicare program.

The National Institute of Mental Health, also within HSMHA, has a discrete program of research concerned with the mental health of the elderly.

Finally, NICHD, as it has examined the field, has inevitably come to feel a responsibility for research in health care. It supports a small amount of such research.

It is far from clear what should be the Federal focal point for the health care of the aged.

Mr. CONTE. Thank you.

Mr. FLOOD. Thank you, Doctor.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Amounts Available for Obligation

	1971	1972
Appropriation	$94,436,000	$103,232,000
Real transfer to:		
"Departmental Management"	-13,000	---
Real transfer from:		
"National Institute of Neurological Diseases and Stroke (Proposed transfer for increased pay costs)"	+62,000	
"National Institute of General Medical Sciences (Proposed transfer for increased pay costs)"	+262,000	---
Comparative transfers to:		
"Office of the Director"	-47,000	---
"Departmental Management"	-3,000	---
"Health Manpower"	-1,057,000	---
Comparative transfer from:		
"National Heart and Lung Institute"	+36,000	---
Total, obligations	93,676,000	103,232,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
95	Research.....	--	$50,223,000	--	$54,229,000	--	$4,006,000
	General research support grants...	--	(3,909,000)	--	(3,475,000)	--	(-434,000)
	Scientific evalutaion.....	--	(100,000)	--	(100,000)	--	(-)
	Mental retardation research centers.....	--	(3,875,000)	--	(5,375,000)	--	(+1,500,000)
101	Fellowships.....	--	3,786,000	--	3,653,000	--	-133,000
103	Training.....	--	9,085,000	--	9,085,000	--	--
	Direct Operations:						
105	Laboratory and clinical research.	265	9,254,000	281	11,517,000	+16	+2,263,000
107	Collaborative research and development.....	40	15,469,000	45	18,521,000	+5	+3,052,000
112	Biometry, epidemiology and field studies.....	24	2,200,000	24	2,227,000	--	+27,000
113	Training activities.....	4	86,000	4	93,000	--	+7,000
114	Review and approval.....	92	2,544,000	92	2,808,000	--	+264,000
115	Program direction..	48	1,029,000	48	1,099,000	--	+70,000
	Total obligation..	473	93,676,000	494	103,232,000	+21	+9,556,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions..	473	494	+21
Full-time equivalent of all other positions.....	39	38	-1
Average number of all employees.....	474	503	+29
Personnel compensation:			
Permanent positions.....	$5,762,000	$ 6,619,000	+$857,000
Positions other than permanent.....	289,000	294,000	+5,000
Other personnel compensation.....	73,000	84,000	+11,000
Subtotal, personnel compensation	6,124,000	6,997,000	+873,000
Personnel benefits.....	654,000	704,000	+50,000
Travel and transportation of persons.	227,000	270,000	+43,000
Transportation of things.....	56,000	63,000	+7,000
Rent, communications, and utilities..	188,000	204,000	+16,000
Printing and reproduction.....	140,000	166,000	+26,000
Other services:			
Project contracts.....	16,649,000	19,545,000	+2,896,000
Payment of NIH Management Fund.....	3,518,000	4,150,000	+632,000
Other.....	1,204,000	1,466,000	+262,000
Supplies and materials.....	456,000	651,000	+195,000
Equipment.....	1,366,000	2,049,000	+683,000
Grants, subsidies, & contributions...	63,094,000	66,967,000	+3,873,000
Total obligations by object.....	93,676,000	103,232,000	+9,556,000

Summary of Changes

1971 estimated obligations	$ 93,676,000
1972 estimated obligations	103,232,000
Net change	+9,556,000

	Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Increases:				
A. Built in:				
1. Annualization of 1971 pay increase costs	---		---	342,000
2. Annualization of positions new in 1971	---		---	139,000
3. Within-grade pay increases	---		---	161,000
4. FTS rate increase	---		---	21,000
5. One additional day of pay	---		---	28,000
B. Program:				
1. Research grants		42,339,000	---	+7,600,000
2. Laboratory and clinical research		6,813,000	+16	+1,400,000
3. Collaborative research and development		15,352,000	+5	+3,000,000
C. Payment to "National Institutes of Health Management Fund" for centrally furnished services		3,518,000	---	+632,000
Total increases.	---		+21	+13,323,000
Decreases:				
A. Program:				
1. Research grants		42,339,000	---	-3,594,000
2. Fellowships		3,786,000		-133,000
3. Laboratory and clinical research		6,813,000		-40,000
Total decreases.	---		---	-3,767,000
Net change	---		+21	+9,556,000

62-645 O - 71 - pt. 3 - 61

Explanation of Changes

Built-in Increases -- These increases provide $342,000 for annualization of 1971 pay increase costs; $139,000 for annualization of positions new in 1971; $161,000 for within-grade increases; $28,000 for one additional day of pay in 1972; and, $21,000 for FTS rate increases.

Research Grants -- The increase of $7,600,000 will be used to expand the population and reproduction program by $6,100,000 and mental retardation research centers support by $1,500,000. Decreases of $3,594,000 will be made in the following programs: aging $1,341,000, child health $1,819,000, and General Research Support Grants $434,000.

Fellowships -- The decrease of $133,000 will fund 12 fewer fellowships in 1972.

Laboratory and clinical research -- The increase of 16 positions and $1,400,000 will be used to expand the reproduction and population program by $1,000,000 and the child health program by $400,000. This increase is offset by a $40,000 decrease.

Collaborative research and development -- An increase of 5 positions and $3,000,000 will be used to expand the Institute's research contract program. The population and reproduction contract program will be increased $2,500,000 and the child health program $500,000.

Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1971 House Report	
Mental retardation research	
1. Committee suggestion that mental retardation research be vigorously pursued.	1. The Institute increased the special line item in the appropriation for Mental Retardation Research Centers from $1,875,000 in 1970 to $3,875,000 in 1971 and has again increased its request to $5,375,000 in 1972.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation Requested
Public Health Service Act Section 301--Research and Investigation, in general.....	Indefinite	$103,232,000
Title IV, Part E---National Institute of Child Health and Human Development.....	Indefinite	
Family Planning Services and Population Research Act of 1970, Section 1004-- Research Grants and Contracts.....	$50,000,000	

The legislative authority which provides for the award of grants for research, research training, and fellowships is included in section 301 of the Public Health Service Act.

The Public Health Service Act, Title IV, National Research Institutes, Part E, Institutes of Child Health and Human Development and of General Medical Sciences--

"Sec.441. The Surgeon General is authorized, with the approval of the Secretary, to establish in the Public Health Service an institute for the conduct and support of research and training relating to maternal health, child health, and human development, including research and training in the special health problems and requirements of mothers and children and in the basic sciences relating to the processes of human growth and development, including prenatal development."

Sec.444. The Surgeon General shall, through an institute established under this part, carry out the purposes of section 301 with respect to the conduct and support of research which is the function of such institute... The Surgeon General is also authorized to provide training and instruction and establish and maintain traineeships and fellowships, in the institute established under section 441 and elsewhere in matters relating to diagnosis, prevention, and treatment of a disease or diseases or in other aspects of maternal health, child health, and human development, with such stipends and allowances (including travel and subsistence expenses) for trainees and fellows as he deems necessary, and, in addition, provide for such training, instructions, and traineeships and for such fellowships through grants to public or other nonprofit institutions."

The Family Planning Services and Population Research Act of 1970--

"Sec.1004. (a) In order to promote research in the biomedical, contraceptive development, behavioral, and program implementation fields related to family planning and population, the Secretary is authorized to make grants to public or nonprofit private entities and to enter into contracts with public or private entities and individuals for projects for research and research training in such fields."

"(b) For the purpose of making payments pursuant to grants and contracts under this section, there are authorized to be appropriated $30,000,000 for the fiscal year ending June 30, 1971; $50,000,000 for the fiscal year ending June 30, 1972; and $65,000,000 for the fiscal year ending June 30, 1973."

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer to:		
Departmental Management	-$ 13,000	To establish the Federal Engineering Construction Agency
Real transfer from:		
National Institute of Neurological Diseases and Stroke	+ 62,000	Proposed transfer for increased pay costs
National Institute of General Medical Sciences	+ 262,000	Proposed transfer for increased pay costs
Comparative transfers to:		
Office of the Director	- 14,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director
Departmental Management	- 3,000	Transfer of Mental Retardation functions to Office of the Secretary
Health Manpower	-1,057,000	Transfer of institutional support funds to Health Manpower
Comparative transfers from:		
National Heart and Lung Institute	+ 36,000	To provide an equitable distribution of the Management Fund in 1972.

National Institute of Child Health and Human Development

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1964	($34,000,000)	($34,000,000)	($34,000,000)	($34,000,000)
1965	43,169,000	43,696,000	42,696,000	42,696,000
1966	53,524,000	53,524,000	55,024,000	55,024,000
1967	61,448,000	61,422,000	64,922,000	64,922,000
1968	68,621,000	68,621,000	74,621,000	68,621,000
1969	75,394,000	70,859,000	76,359,000	73,126,500
1970	75,852,000	73,098,000	80,800,000	77,192,000
1971	93,303,000	94,436,000	94,436,000	94,436,000
1972	103,232,000			

Justification

National Institute of Child Health and Human Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	473	$6,778,000	494	$7,701,000	+21	+$923,000
Other expenses	--	86,898,000	--	95,531,000	--	+8,633,000
Total.....	473	93,676,000	494	103,232,000	+21	9,556,000

General Statement

The National Institute of Child Health and Human Development conducts and supports research and training dealing with human development from conception through old age. This approach, which cuts across disciplinary lines and spands both normal and abnormal development, provides the sound scientific basis for improvements in the health and well-being of the American people of all ages.

To achieve this mission, the Institute has identified primary areas for programmatic development, each corresponding to clusters of problems of both scientific and social importance and urgency. These include family planning and the attendant consequences of over-population, the healthy development of the unborn and newborn, the intellectual and physical development of the young, the prevention and amelioration of mental retardation, and the understanding of the aging process.

The request of $103,232,000 for 1972 represents a net increase of $9,556,000 over 1971. The net increase is comprised of a program increase of $12,037,000; built-in increases of $691,000; a management fund net increase of $632,000; offset by program decreases of $3,370,000; and a decrease of $434,000 in general research support grants. The program increase will be used in two areas: $9,600,000 in population and reproduction and $2,400,000 in child health which includes an increase of $1,500,000 for the mental retardation research centers.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Regular project.....	$42,339,000	$45,279,000	+$2,940,000
Special program.....	7,884,000	8,950,000	+ 1,066,000
Total research grants	$50,223,000	$54,229,000	+$4,006,000

Introduction:

This activity supports regular research grant projects in population and reproduction, perinatal biology and infant mortality, growth and development, adult development and aging, and mental retardation. In addition, funds are provided for general research support grants, scientific evaluation grants, and mental retardation research center grants.

The $4,006,000 net increase in 1972 will be used to expand research in population and reproduction and mental retardation. This net increase provides a $6,100,000 increase in the population and reproduction program, a $1,500,000 increase in the Mental Retardation Research Centers, which are offset by a $1,341,000 decrease in the adult development and aging program, a $1,819,000 decrease in child health programs and a $434,000 decrease in general research support grants.

Research Grants: The mission of the National Institute of Child Health and Human Development is to solve the mysteries of human development from conception to the end of life. To attain this goal, the Institute expends the greatest portion of its funds in the research grant activity. These funds are distributed nationwide to scientists doing research in the fields of population and reproduction, perinatal biology and infant mortality, growth and development, adult development and aging, and mental retardation. The regular research grants program is the primary means of achieving these research objectives. Additionally, the activity funds special research programs--Mental Retardation Research Center Grants, Scientific Evaluation Grants and General Research Support Grants.

Program Plans for 1971 and 1972:

The increase of $4,006,000 will be used to expand the Institute's programs of population and reproduction and child health with particular emphasis on the first five years of life. Coupled with these program increases will be reductions for the support of General Research Support Grants and the Adult Development and Aging Research Grant Program.

Population and Reproduction. Research grants in population research are used to complement the total programs of the Center for Population Research. The grants support investigations of biological, behavioral, and social processes of reproduction and its regulation in humans and animals. These investigations range from studies of reproductive control in human and experimental animals to the increase of knowledge of the sociology of population growth.

The biomedical research program includes investigations of the wide range of reproductive phenomena. The acquisition of deeper insights into these basic biological processes of reproduction will permit the development of new contra-

ceptives which are compatible with health, are effective, and are generally acceptable. Reports of the adverse side effects of available oral contraceptives, and the unknown mechanism of action of intrauterine devices (IUD's) are evidence of the need for new contraceptives.

A number of priority areas have been identified for special emphasis: ovulation and gamete transport, luminal fluids of the reproductive systems, immunological aspects of the fertilization process, biology of the corpus luteum, releasing factors and gonadotropic hormones, population genetics, implantation, problems of infertility, and the biology of the male reproductive system. These are areas of investigation in biomedical research which are insufficiently supported and/or where the state of the art lacks sophistication.

Although primary stress is placed on biological problems in population research, behavioral research is also important to the understanding of reproduction, population dynamics, and family planning. Studies are needed on factors involved in beginning or discontinuing the use of contraceptives, and on the development of attitudes and decisions concerning child bearing and family spacing.

The nature and measurement of population change is receiving increased attention. The effects of population growth and increased social stress on animals are being studied by Institute grantees. The relationship of reproductive behavior to hormonal activity is also under investigation.

A portion of the increase in population research grants will be allotted to the Institute's new population research center grants which will provide core support to program initially direction in two to four institutions engaged in population research. This Population Research Centers Program provides an efficient means for consolidating the multidisciplinary effort necessary to understand and cope with the problems of population growth.

Child Health. Research on child health is carried out under the direction of three of the Institute's program areas: Perinatal Biology and Infant Mortality, Growth and Development, and Mental Retardation.

A major responsibility of this Institute is the stimulation and support of fundamental and clinical research aimed at the reduction of infant mortality, in particular, and at improving the health status of mothers and infants, in general. Such efforts will result in a vast improvement in the products of conception and thereby improve the quality of human life. To carry out its mission in this area, the Institute has developed a research program around the broad areas of 1) pregnancy and maternal health, 2) developmental biology, 3) fetal health and development, and 4) infant survival and well being.

The number of deaths occurring among infants before their first birthday is a major source of concern in the United States. During the first year of life, the risk, of dying is greater than at any other time until after the age of 65. The infant mortality rate in this country, which ranks thirteenth among the developed countries of the world, was 21.7 per 1,000 live births for 1968, and 20.7 per 1,000 live births in 1969. The latest firm figures for Sweden, the nation with the lowest incidence of infant mortality, show a mortality rate of 12.9 per 1,000 live births in 1967.

Growth and development research is concerned with the period of development extending from birth to adulthood. Special emphasis will be given in 1972 to studies of health and development of children under age 6, including the effects of nutrition on physical and mental development. In addition, more knowledge will be sought bearing on developmental changes at puberty and in the adolescent

period. Research on the behavioral aspects of human development will seek a more complete understanding of the processes involved in learning and cognitive development...to learn how to describe and measure them. Support will be given to studies of various aspects of human growth and development, on the interactions of individuals and their environments, and on the theoretical foundations of behavioral measurement.

Special attention will continue to be devoted to studies of the mechanisms by which malnutrition causes irreversible damage to cells, tissues, and organs, thereby limiting the achievement of inherited potential. Such information will facilitate development of improved methods of early diagnosis and more successful therapy for patients.

Greater efforts will be exerted to distinguish the periods in life most sensitive to nutritional deprivation and the extent to which malnutrition interacts with psychosocial deprivation to impede optimal growth and development. Fundamental to this aim is the need to define minimal nutritional requirements necessary to maintain normal growth and resistance to disease. Special attention will be given to the neuroendocrine control of growth and its relation to varying levels of nutrition.

Increased support will be given to studies designed to determine the critical periods in biological and behavioral development, when basic structure or patterns are established and after which rehabilitation may be impossible or less effective. The focus throughout the program will be upon identification of those periods when maximal impact from intervention programs might be obtained.

Too little is known about how the infant develops mechanisms for resisting disease and recurrent infections. It is necessary to study the individual components of these defense systems, as well as the interdependent immunologic mechanisms taken together as a single working entity. Support will be provided for studies in developmental immunology (both prenatal and postnatal) dealing with early detection of subclinical disease in neonates, as well as methods of properly treating and preventing such diseases.

In studying the complexity of human development from the behavioral standpoint, research on maximizing the capacity of the individual to learn will receive primary emphasis. Activities will be directed toward a variety of studies on infant behavior, including research on attention, discrimination, and perception in children under one year of age. This research will lead to a better understanding of learning and development throughout childhood. Much of the anticipated work bearing on learning will examine the ways the young child interacts with his environment, particularly in the crucial preschool years.

The Institute is the focal point within the NIH for research in Mental Retardation. One of its major areas of emphasis is directed to the research activities in the 12 mental retardation research centers.

Implementation of this authority resulted in construction grant awards for 12 research centers to institutions for research and training in 11 different states. Four of the centers are completed and became operational in 1968; two began operations in 1969, three in 1970, and two will begin operations in 1971, with the twelfth to open early in FY 1973.

Mental Retardation Research Centers	Fiscal Year Completed
1) University of Chicago Chicago, Illinois	1967
2) Children's Hospital Cincinnati, Ohio	1968
3) George Peabody College for Teachers Nashville, Tennessee	1968
4) University of Colorado Medical Center Denver, Colorado	1968
5) University of Washington Seattle, Washington	1969
6) University of California at Los Angeles Los Angeles, California	1969
7) Albert Einstein College of Medicine Yeshiva University, New York, New York	1970
8) University of Kansas Lawrence, Kansas	1970
9) Walter E. Fernald State School Waltham, Massachusetts	1970
10) Children's Hospital Medical Center Boston, Massachusetts	1971
11) University of North Carolina Chapel Hill, North Carolina	1971
12) University of Wisconsin Madison, Wisconsin	1973

Through the support of these mental retardation research centers and also the support of individual investigators through the project grant mechanism the Institute is seeking ways to prevent, manage, diagnose, and ameliorate the ravages of mental retardation. In this regard the Mental Retardation Program has identified a number of areas of special interest.

Longitudinal studies will be supported to determine the long-range consequences of aberrations of pregnancy, delivery, and the neonatal period on intellectual and physical development of the child. Additional research is vitally needed to explore early care and training of these infants for the purpose of overcoming adverse conditions which, in large measure, shape the child's early development.

Prenatal diagnosis offers new hope for the prevention of mental retardation. Significant steps have been made in this direction through development of the technique of amniocentesis which provides diagnostic access to the fetus. A sample of the fluid surrounding the fetus is withdrawn from the amniotic sac and analyzed for abnormalities. By conducting chromosomal and biochemical studies on cells obtained by this procedure, it is now possible to predict whether a fetus as young as 12 weeks will be born with a variety of disorders. The availability of such information can provide a means for determining possible courses of

action. More research is needed in order to identify other disorders that can be diagnosed prenatally, to develop techniques to permit earlier detection, and finally to devise methods of treating the fetus.

In low birth weight babies, the relationships between the socio-environmental stress, malnutrition and mental retardation need elucidation. In order more effectively to prevent mental retardation resulting from social and environmental stress, further specification is needed regarding the factors constituting stress, genetic components of learning, child-parent interaction patterns, and the inter-relationship of biological preocesses and social forces in development.

Adult Development and Aging

Ten percent of the U.S. population is older than 65 years, and 80 percent of those over 65 have one or more serious diseases. Two-thirds of the Federal money spent on health care in this country is spent on persons over 65. One million persons over 65 live in institutions. The health problems of the older person in this country are of major importance and contribute greatly to the drain on available health resources. The human suffering involved is immeasurable.

Environmental and genetic factors are important in the disease of older persons, but major factors in the origin of those diseases are aging processes themselves.

The Institute will continue to support research on aging by scientists at universities, hospitals, and research institutions and in such areas as the biological, medical, behavioral and social-psychological aspects of aging including the study of progressive changes in cells, tissues, organ systems and the individual.

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting projects	530	$30,864,000	550	$30,864,000	+20	(-)
2. Competing projects	202	11,475,000	210	14,415,000	+8	+$2,940,000
3. Subtotal regular program	732	42,339,000	760	45,279,000	+28	+2,940,000
4. General research support		3,909,000		3,475,000		-434,000
5. Scientific evaluation		100,000		100,000		(-)
6. Mental retardation research centers.		3,875,000		5,375,000		+1,500,000
7. Total res. grants.	732	50,223,000	760	54,229,000	+28	+4,006,000

Research Grants Program Analysis

1. Population & Reproduction Research	$10,364,000	$16,464,000	+6,100,000
2. Perinatal Biology & Infant Mortality	10,059,000	9,413,000	-646,000
3. Growth and Development	12,642,000	11,834,000	-808,000
4. Adult Development & Aging	3,592,000	2,251,000	-1,341,000
5. Mental Retardation	5,682,000	5,317,000	-365,000
6. Subtotal regular program	42,339,000	45,279,000	+2,940,000
7. General research support	3,909,000	3,475,000	-434,000
8. Scientific evaluation	100,000	100,000	(-)
9. Mental retardation research centers.	3,875,000	5,375,000	+1,500,000
10. Total research grants	50,223,000	54,229,000	+4,006,000

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Total Fellowships	$3,786,000	$3,653,000	-$133,000

The primary objective of the Institute's fellowship program is to increase the number of needed scientists qualified to carry on independent research in child health and human development.

This objective is carried out through four means: (1) postdoctoral fellowships are awarded to encourage and attract young investigators into obtaining research training and experience so that the country's research potential in a wide variety of disciplines can be maintained; (2) special fellowships are awarded to more advanced investigators, often faculty members on sabbatical leave, who find it highly productive to spend a year or two in research laboratories other than their own in which they can improve current skills or acquire new ones; (3) the highly successful research career development program provides support for younger investigators of demonstrated ability and provides the means whereby the grantee institutions can expand their potential; (4) the research career award provides stable support for the senior investigator.

Funds requested for 1972 will provide for 173 awards, compared to 185 in 1971, a decrease of 12.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting.....	125	$2,680,000	120	$2,600,000	-5	-$80,000
b. Competing.....	8	190,000	12	300,000	+4	+110,000
2. Supplementals.....	(2)	4,000	(2)	4,000	(-)	(-)
3. New.....	58	912,000	41	749,000	-17	-163,000
4. Total fellowships..	191	3,786,000	173	3,653,000	-18	-133,000

Fellowships (By type of program)

1. Postdoctoral.....	42	$379,000	35	$320,000	-7	-$59,000
2. Special.....	33	372,000	30	350,000	-3	-22,000
3. Research Career:						
a. Career.....	7	215,000	7	215,000	(-)	(-)
b. Development awards.....	109	2,820,000	101	2,768,000	-8	-52,000
4. Total fellowships..	191	3,786,000	173	3,653,000	-18	-133,000

Fellowships Program Analysis

1. Population & Reproduction.....	764,000	764,000	(-)
2. Perinatal Biology & Infant Mortality....	1,021,000	977,000	-$44,000
3. Growth & Development...	1,390,000	1,329,000	-61,000
4. Adult Development & Aging.....	263,000	251,000	-12,000
5. Mental Retardation.....	348,000	332,000	-16,000
6. Total fellowships.....	3,786,000	3,653,000	-133,000

Training Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Total Training Grants....	$9,085,000	$9,085,000	---

The training grant programs of the Institute are designed to (1) attract individuals to careers of interest to child health and human development; and (2) produce investigators who will contribute significantly to the mission of the Institute. In order to achieve these goals, the Institute supports training programs in population and reproduction, perinatal biology and infant mortality, growth and development, aging, and mental retardation. The goal of this training support is to produce research investigators capable of increasing knowledge of human development, not only in terms of physical form and function, but also in terms of mental, emotional, intellectual, and social development.

Training grants are available to institutions which can provide excellent programs for both predoctoral and postdoctoral trainees. These programs prepare both laboratory and clinical scientists for careers in areas of interest to child health and human development. Some of the grants provide clinical research training which prepares physicians who are not only skilled clinicians, but also scientists, able to evaluate research data critically, translate the results of research for patient care and keep abreast of their field.

Funds requested for 1972 will provide for 100 awards, compared to 116 in 1971, a decrease of 16.

Distribution of Training Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting	92	$6,610,000	85	$7,614,000	-7	+$1,004,000
b. Competing	14	1,453,000	9	801,000	-5	-652,000
2. Supplementals	(2)	16,000	(4)	40,000	(+2)	+24,000
3. New.....	10	906,000	6	530,000	-4	-376,000
4. Scientific evaluation.....	(1)	100,000	(1)	100,000	(-)	(-)
5. Total training grants.....	116	9,085,000	100	9,085,000	-16	(-)

Training Grants (By type of program)

1. Graduate	116	8,985,000	100	8,985,000	-6	(-)
2. Scientific evaluation.....	(1)	100,000	(1)	100,000	(-)	(-)
3. Total training .... grants.....	116	9,085,000	100	9,085,000	-6	(-)

Training Grants (Program Analysis)

1. Population & Reproduction.....	1,871,000	1,871,000	(-)
2. Perinatal Biology & Infant Mortality..	1,681,000	1,681,000	(-)
3. Growth & Development.	2,426,000	2,426,000	(-)
4. Adult Development & Aging.....	2,008,000	2,008,000	(-)
5. Mental Retardation...	1,099,000	1,099,000	(-)
6. Total training grants	9,085,000	9,085,000	(-)

Direct Operations

Laboratory and Clinical Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	265	$3,644,000	281	$4,165,000	+16	+$521,000
Other expenses.....	--	5,610,000	--	7,352,000	--	+1,742,000
Total.....	265	9,254,000	281	11,517,000	+16	+2,263,000

Introduction: Ten laboratories and branches conduct the Intramural Research operations in the program areas of the Institute. These include Developmental Biology Branch, Social and Behavioral Sciences Branch, Reproduction Research Branch, Laboratory of Biomedical Sciences, Behavioral Biology Branch, Children's Diagnostic and Study Branch, and the Gerontology Research Center (Baltimore), composed of the Laboratory of Molecular Aging, Laboratory of Behavioral Sciences, Laboratory of Cellular and Comparative Physiology, and Clinical Physiology Branch.

The net increase of $2,263,000 is made up of a program increase of $1,400,000, mandatory increases of $347,000, NIH Management Fund increase of $556,000 and a program decrease of $40,000.

Program Plans for 1971 and 1972: The Intramural Research Program has a program increase of $1,400,000. The Institute's Population and Reproduction program will use 12 positions and $1,000,000 and the Child Health program 4 positions and $400,000.

Population and Reproduction: The Institute is committed to a rapid expansion of and increased support for programs in reproductive biology. In its own laboratories, NICHD has assembled an intramural staff of scientists expert in many fields, to collaborate on research in reproductive biology. Staff, space, and breadth of studies have increased substantially during the past year which has facilitated the fundamental scientific work on which practical solutions to population problems will be based.

The Reproduction Research Branch of NICHD is involved in six major areas of study: the mechanism of action of hormones; the physiology of the menstrual cycle and female infertility; male reproductive biology, including fertility problems; the endocrinology of pregnancy; protein hormone isolation and characterization; and metabolism of the sex steroids.

These studies have various applications. An infertility clinic has been established in conjunction with some of these studies, and a new cause of female infertility has been identified. During 1972 additional patients will be accepted for treatment. Research on early pregnancy will continue to add to our knowledge about the causes of early abortion (miscarriage). Work on male and female reproductive biology and on protein hormones may aid in one development of new contraceptive methods and improvement in present methods, including rhythm.

The Pregnancy Research Branch will conduct research in the physiology of pregnancy, the effects of disease states on pregnancy, and identification of those factors which increase perinatal and maternal morbidity and mortality, using animal and clinical resources. Research will be focused on the development of methods for evaluating fetal growth, amniokenetics, placental function

and uterine competence in both qualitative and quantitative terms. It will also identify and define diagnostic and therapeutic aids that will enhance the health of the mother, her fetus and the newborn infant, and to advance the scientific knowledge of the process involved in gestation and delivery.

Studies on the sex steroids have led to data on hypertension in oral contraceptive users; a planned cooperative study with the NICHD's Center for Population Research will look for characteristics of women who can be expected to develop hypertension while using the oral contraceptives. This study could lead to more effective screening of prospective users.

Child Health: This program is concerned with the early development of the child. A program evaluating the effectiveness of pre-school stimulation in various environments so as to develop the most effective way of preparing children from deprived environments for adaptation to school situations will be continued in FY 1972.

The biology and molecular elements of learning and memory will receive increased emphasis. The present program which uses animal models will be expanded in an attempt to identify the biochemical, electrochemical and physiological consequences of social deprivation.

The developmental immunology activity will conduct basic and clinical research into the nature of inducing molecules and biologic mechanisms of development of immunity during intrauterine, neonatal periods, and infancy utilizing the disciplines of immunochemistry, cellular physiology and biochemistry.

Adult Development and Aging: It is increasingly clear that lifetime nutritional experience influences aging biochemical events during the declining years of life. Animal models indicate that longevity can be favorably modified in a variety of animal species through dietary manipulations. In experimental animals, dietary changes can modify longevity and the period of reproductivity both adversely and favorable.

Attempts to relate gene structure to cell function is a most promising area of scientific investigation and will open new avenues for the study of mental retardation. Gene expression is obviously related to intellectual performance; the majority of patients with genic abnormalities suffer significant demonstrable intellectual deficiencies.

Collaborative Research and Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	40	$ 633,000	45	$ 759,000	+5	+$ 126,000
Other expenses.....	--	14,836,000	--	17,762,000	--	+ 2,926,000
Total.....	40	15,469,000	45	18,521,000	+5	+3,052,000

Introduction:

This activity provides the Institute an effective instrument for the direction of research which has been designated as high priority.

The majority of funds administered through this activity are assigned to the Center for Population Research. This Center was officially designated by the Department in August 1968 to carry our the population research objectives directed by the President's Health Message to the Congress on March 4, 1968. On December 24, 1970 the President signed into Law the Family Planning Services and Population Research Act of 1970 which called for increased Federal effort in both research and services aimed at this problem.

A program increase of $2,500,000 will support the Institute's contract program in population research. These funds will be used to stimulate research on contraceptive development, the evaluation of the medical effects of contraceptives in use, and social and demographic studies. The five new positions requested will provide additional technical and clerical support to administer the Center programs.

The collaborative contract program for childhood development will increase by $500,000 for new projects in nutrition and early childhood development.

Program Plans for 1971 and 1972:

Center for Population Research

There are a variety of reasons for giving special and urgent attention to research to help modify population changes in our own country and throughout the world. The effects of these changes are pervasive and threaten levels of health and nutrition, the prevalence of poverty, the rate of economic development and many other related social problems.

Every year the world's population increases by 70 million people. Every three years, the world accommodates an additional 200 million persons--the current Unites States population. The food supply, natural resources, and social and economic institutions cannot be strained to limitless bounds: eventually our growth rate must approach zero. How and when this should occur are vital research issues.

Institute supported studies have shown that in the U.S. an estimated one out of five million women have neither adequate information about nor access to family planning. The Federal Government's policy is that every child should be a wanted child and that every couple has the right to information and services necessary for planning their families. Achieving this policy requires that information, services, and more nearly perfect means of contraception

than presently exist be available to all.

We must know more about the consequences of population growth and distribution, more about the determinants of family size, and more about reproductive processes--so that the technology to limit family size will be available to every individual.

Contraceptive Development

The ideal contraceptive would be effective, safe, inexpensive, reversible, self-administered, and acceptable to various population groups. No existing method fits all these criteria. Probably no single method will be universally satisfactory; the goal of contraceptive development is to develop many contraceptives, suitable to many kinds of people.

To rapidly develop a variety of new contraceptives, new approaches are underway in the following areas:

....development of new chemical compounds to achieve contraception in both sexes having safe dose formulations and without serious side effects

....development of methods which will allow for uninterrupted administration and constant release of potential contraceptive drugs

....development of chemical agents for control of the menstrual cycle

....development of new techniques for reversible female and male sterilization using mechanical devices

Until FY 1971, the contraceptive development program consisted primarily of directed fundamental research on topics considered relevant to the eventual development of new contraceptives. In fiscal year 1971, the Center will negotiate approximately 120 contracts for such research.

During FY 1971 and 1972 the contraceptive development program will begin concentrating on new or approved practical approaches and by 1973 it will include many phases of drug development, from synthesis through clinical testing, necessarily involving close cooperation with the pharmaceutical industry. The Institute's goal is the development of several new methods of fertility regulation before the end of this decade.

Medical Effects of Existing Contraceptives

This program involves research on the noncontraceptive effects of existing contraceptives and in 1972 it will also include research on the effects of other fertility regulating methods. A new Branch, the Fertility Regulating Methods Evaluation Branch was recently established in the Center for Population Research to direct this activity.

Evaluation of the oral contraceptives began in 1965 and remains the major area of interest. Beginning in 1972 and into the following four years, studies of the metabolism of steroid contraceptives--a remarkably neglected area--will be undertaken. The evaluation program will also emphasize investigations of the pharmacological properties of various estrogen-progestogen combinations in varying doses, with the aim of improving the clinical safety and efficacy of these widely used drugs. Research will explore doses, unique properties , and effects of oral contraceptive components, to determine whether equally effective or safer formulations can ben proposed. A secondary goal is to study the side effects of presently available formulations with as much precision as possible.

62-645 O - 71 - pt. 3 - 62

Methodology for doing this has improved greatly since the oral contraceptives were introduced 10 years ago.

Specific problem areas to be investigated include thromboembolism; cancer, carbohydrate and lipid metabolism; hypertension; general metabolic effects; behavioral effects; and fertility and outcome of pregnancy in former oral contraceptive users. Some effects are better understood than others, as a result of earlier studies.

Social Science Research

Population size, structure, distribution, and rate of growth are components of many current social problems. The knowledge necessary to assess how population is related to these problems, however, is incomplete. Problems of the individual also need clarification; for individuals to plan their families rationally, they need information based on research. For example, what effect does spacing children have on their growth and development? How effective has contraception been for its users? Finally, research attention must be focused on another major area; determination of the many diverse factors that influence popuation trends.

The Center's formal social science program began in fiscal year 1969 by concentrating on the continued measurement and analysis of fertility trends and differentials in the United States, the most important single contract being the support of another National Fertility Study in 1970. Other projects are design designed to study the determinants of fertility in a variety of cultural and sub-cultural settings, including ethnic sub-groups in the Unites States and certain foreign countries. Specific examples of social science studies include the incidence of induced abortion; the relationships between family planning and the status of women; social and economic determinants of age at marriage and family size; trends in marital disruption, remarriage, and fertility in remarriage; attitudinal factors affecting family size; analysis of social-economic factors associated with the decline in the birth rate in western Europe and in some of the less developed countries; methods of measuring unwanted child-bearing; the effects on fertilty of the transition from subsistence agriculture to a market-oriented agriculture; the social and psychological correlates and consequences of illegitimacy; the relationship between birth spacing and social mobility; the relationship between kin network and size of family; and the relationship of family size to social alienation in urban areas.

Research in the social sciences is being expanded as rapidly as possible to include studies of the ecological, economic and psychological consequences of population growth and distribution.

Child Health Programs

The interest of this Institue in child health begins at the moment of fertilization and continues through the developing years. This interest include the health of the mother and how her health effects fetus and infant. Special research opportunities and needs include studies on the early detection of abnormalities in utero, respiratory distress in the newborn, permaturity and the sudden infant death syndrome. Once the child has survived the hazards of intrauterine life the birth process, and adjustment to the new environment, the Institute's areas of interest shift toward study of factors affecting the kind of person the infant will become. These studies include research on both animals and humans and include nutritional, social, psychological and other environmental events. The Collaborative contract program is especially suited to research in the areas of nutrition and early childhood development.

Nutrition

Although evidence continues to accumulate concerning the possible effect of severe malnutrition (protein-calorie malnutrition) on the development of the

central nervous system and intellectual ability, little information is available concerning the possible effects of the types of under-nutrition more frequently reported in the U.S. (as indicated by anemia, retarded growth, or low levels of nutrients in the blood). Limited studies in this area were initiated in FY 1971, and additional work is needed to determine the consequences of the latter types of malnutrition on intellectual development. The specific goal is to ascertain whether the effects can be reversed by appropriate rehabilitation, by special food programs, or by special educational procedures.

Greater effort will be directed to determining whether periodic under-nutrition influences the receptivity of the preschool and school age child learning experiences. Of special importance here will be studies of emotionality, motivation, and ability to pay attention or to concentrate in preschool or school situations.

The psychological and attitudinal factors bearing on food selection and use are poorly understood and need investigation. Studies also will be supported seeking to determine the extent to which recurrent infection or illness precipitates malnutrition under marginal food intake levels.

Studies will continue to focus on the effect of malnutrition on fetal development and on the problem of prematurity. These studies will include the effect of nutritional supplements on both tne mother and child.

Currently utilized techniques for the assessment of nutritional status have a variety of shortcomings. Support will be given to studies and discussion workshops to explore and develop new methods for nutritional assessment.

Early Childhood Development

With expanding insight into cognitive development of the infant, the need for cross-cultural test procedures, and the strong interest in the effect of early environment on later development, improved standardized tests are needed. The Institute will support the collaborative research needed to improve tests and testing procedures for clinical diagnosis and child development research.

Many aspects of child development cannot be adequately pursued in human populations. Subhuman primates offer a variety of models for such studies. A specially designed primate breeding facility will be established to provide developmental researchers with high quality animals not currently available for specific studies.

Methods are not presently available for measuring the impact of social factors such as urbanization on the acquisition of social behavior patterns in children. We will support the development of suitable methodologies for such studies.

The physical and social environment also affects physiological development. Animal studies will be initiated to determine the impact of crowding, noise, and other environmental factors on physiological, physical and neurological development.

Past efforts have been directed toward coordinating data storage and analysis systems for the several major longitudinal studies of growth which we currently support. Efforts now underway support collaborative analyses of these data which we currently support. Efforts now underway support collaborative analyses of these data which we expect will yield new insights into factors affecting optimal child development. Close coordination of these studies with several concurrent efforts on minority populations in the U.S. and other populations in Latin American countries will be undertaken to determine variations in growth and development between ethnic groups.

Mental Retardation

Mental retardation today afflicts the lives of an estimated 6,000,000 persons in the Unites States. Its impact is directly felt by the some 20,000,000 family members who share the burden and problems of care of the retarded whose inadequate intellectual development impairs their ability to learn and to adapt to the demands of society. The causes of mental retardation are multiple and involve both physical and environmental factors operating singly or in subtle interactions.

Contracts for work on a cytogenetic registry, a study of variations in human chromosome preparation and the preparation of an animal model for mental retardation studies will be supported in 1971.

New studies in 1972 will explore how handling practices influence the course of intellectual and physical development in infants who suffered damage in utero, during birth, and in early postnatal life.

Biometry, Epidemiology and Field Studies

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	24	$331,000	34	$355,000	--	+24,000
Other expenses.....	--	1,869,000	--	1,872,000	--	+3,000
Total.....	24	2,200,000	24	2,227,000	--	+27,000

The Institute's scientific staff plans investigations and conducts research in epidemiologic and biometric theory, techniques and methods. They also collect and analyze program statistics for Institute programs and execute statistical studies for use in program planning, development and evaluation.

Program Plans for 1971 and 1972:

This activity will be supported at the same level in 1972 as in 1971. The increase of $27,000 is for mandatory increases only.

Training Activites

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	4	$62,000	4	$67,000	--	+$5,000
Other expenses.....	--	24,000	--	26,000	--	+2,000
Total.....	4	86,000	4	93,000	--	+7,000

This direct training program is designed to meet the needs of the Institute by providing supplementary or cross-disciplinary training for the scientific staff.

Program Plans for 1971 and 1972:

This activity will be supported at the same level in 1972 as in 1971. The increase of $7,000 is for mandatory increases only.

Review and Approval

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	92	$1,317,000	92	$1,529,000	--	+$212,000
Other expenses.....	--	1,227,000	--	1,279,000	--	52,000
Total.....	92	2,544,000	92	2,808,000	--	+264,000

This activity supports the personnel responsible for the administration of the Institute's several grant and contract programs. The services they provide include planning and developing programs for research grants, training grants, fellowships, and contracts which will best achieve the goals of the Institute; securing review and evaluation of all contract proposals prior to Institute funding, and also preparing grant applications for presentation to the National Institute of Child Health and Human Development Advisory Council; staff assistance to the Council; liaison with applicants, grantees, contractors, other components of the National Institutes of Health, advisory bodies, and interested organizations; continued evaluation of scientific activities and progress of the research and training grant programs and the contract programs; and the recording and reporting of fiscal and scientific information relevant to all grant and contract transactions.

Program Planns for 1971 and 1972:

This activity will be supported at the same level in 1972 as in 1971. The increase of $264,000 is for mandatory increases only.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	48	$791,000	48	$851,000	--	+$60,000
Other expenses.....	--	238,000	--	248,000	--	+10,000
Total.....	48	1,029,000	48	1,099,000	--	+70,000

The personnel supported by this activity are responsible for the general administration, direction, and coordination of Institute programs. They also review the programs and propose and plan new operations for the Institute.

Program Plans for 1971 and 1972:

This activity will be supported at the same level in 1972 as in 1971. The increase of $70,000 is for mandatory increases only.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Research Grants (Public Health Service Act, Title IV, Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$50,223,000	Indefinite	--	$54,229,000

Purpose: Provide support of research relating to maternal health, child health, and human development, including research 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.

Explanation: Research grants supported under this activity range from single objective projects to broadly-based, multidisciplinary projects involving the collaboration of a number of scientists. In addition to the regular research grants and program project awards, support is furnished for special mental retardation research centers, and general research support grants.

Accomplishments in 1971: In 1971, 732 projects will be supported in the regular program and 9 projects will be supported in the Mental Retardation Research Centers. Three Mental Retardation Research Centers will be funded from the regular research grants program.

Objectives for 1972: In 1972, 760 projects will be supported in the regular program in addition to continuing support for the special research grant programs. Basic core support at the 12 Mental Retardation Research Centers will be expanded. The basic research program will be maintained close to its 1971 level while increasing support in the selected areas of population and reproduction, and portions of the child health program including research on aspects of nutrition and mental retardation.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Fellowships (Public Health Service Act, Title IV, Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$3,786,000	Indefinite	--	$3,653,000

Purpose: The primary objective of the fellowships program is to increase the number of scientists qualified to carry on independent research in child health and human development.

Explanation: The above objective is carried out through four means: 1) post-doctoral fellowships are awarded in a wide variety of disciplines to encourage young scientists to obtain research training; 2) special fellowships are awarded to more mature individuals, often faculty members on sabbatical leave, who find it hightly productive to spend a year or two in research laboratories other than their own in which they can improve current skills or acquire new ones; 3) the highly successful research career development program supports the younger investigator of demonstrated ability and provides the means whereby the grantee institutions can expand their potential; 4) the research career award provides stable support for the senior investigator.

Accomplishments in 1971: In 1971 there will be an estimated 191 fellowships funded in the Institute's five program areas: Population and Reproduction, Perinatal Biology and Infant Mortality, Growth and Development, Adult Development and Aging, and Mental Retardation. Approximately 125 noncompeting continuations and 66 competing fellowships will be funded.

Objectives in 1972: In 1972 there will be a decrease of 12 fellowships and $133,000 in this activity.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Training Grants (Public Health Service Act, Title IV, Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$9,085,000	Indefinite	--	$9,085,000

Purpose: The training grant programs of the Institute are designed to: 1) attract individuals to careers in the field of child health and human development; and 2) produce investigators who will contribute significantly to the mission of the Institute.

Explanation: The goal of the training grants is to produce research investigators capable of increasing knowledge of human development not only in terms of physical form and function, but also in terms of mental, emotional, intellectual and social development.

Training grants are available to institutions which can provide excellent training programs for both predoctoral and postdoctoral trainees. These programs prepare both laboratory and clinical scientists for careers in the area of child health and human development.

Accomplishments in 1971: In 1971 an estimated 116 graduate training grants will be funded in the Institute's five program areas: Population and Reproduction, Perinatal Biology and Infant Mortality, Growth and Development, Adult Development and Aging, and Mental Retardation. Approximately 10 new grants and 106 noncompeting and competing continuations grants will be awarded.

Objectives for 1972: In 1971 an estimated 116 research training grants will be supported. In 1972, the Institute will continue to fund this program at the same level.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Laboratory and Clinical Research (Public Health Service Act, Title IV, Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
265	$9,254,000	Indefinite	281	$11,517,000

Purpose: Conducts research in five major program areas of child health and human development: reproduction and population, perinatal biology and infant mortality, growth and development, adult development and aging and mental retardation.

Explanation: Ten laboratories and branches conduct the Intramural Research operations in the porgram areas of the Institute. These include the Developmental Biology Branch, the Social and Behavioral Sciences Branch, the Reproduction Research Branch, the Laboratory of Biomedical Sciences, the Behavioral Biology Branch, the Children's Diagnostic and Study Branch, and the Gerontology Research Center (Baltimore), composed of the Laboratory of Molecular Aging, the Laboratory of Behavioral Sciences, the Laboratory of Cellular and Comparative Physiology, and the Clinical Physiology Branch.

Accomplishments in 1971: The intramural research program will make significant advances in the following areas: methods for examining the primate menstrual cycle in detail to permit the use of this animal model for the studies of human reproductive biology will be developed: evaluation of the effectiveness of preschool stimulation will be conducted in various environments so as to develop the most effective way to prepare children from deprived environments for adaptation to school situations; studies relating gene structure to cell function will be conducted and will open new avenues for the study of mental retardation; and human volunteers will be involved in our longitudinal studies in the physiological, biochemical, and psychological aspects of aging. The establishment of two new branches will strengthen our efforts in the development of diagnostic and therapeutic aids to improve the health of the mother, her fetus, and the new born infant.

Objectives for 1972: Sixteen positions will be added in intramural research to facilitate research efforts which will be expanded in the area of population and and reproduction, child health and aging. Particular emphasis will be placed on broadening the scientific bases of reproductive biology necessary for the development of specific contraceptive agents. To define the processes of fetal and early childhood development, programs have been initiated in developmental biochemistry, information transfer, neurophysiology, child psychology, and environmental influences on childhood maturation. Clinical programs in the high risk obstetrical patient and in the physiology of the neonatal period will be initiated.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Collaborative Research and Development (Public Health Service Act, Title IV, Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
40	$15,469,000	Indefinite	45	$18,521,000

Purpose: Supplements the Institute's five research programs primarily through the contract mechanism and maintains and advances program liaison through support of interdisciplinary research conferences and symposia.

Explanation: Most of the funds in this activity support the contract programs of the Center for Population Research. The Center administers contracts in three main areas: research in contraceptive development; research on the medical effects of existing contraceptives; and, research in the behavioral and social sciences to develop essential knowledge concerning the determinants and consequences of population change and the nature and magnitude of changes now in process. Child health programs utilizing contract funds concentrate on nutrition, early childhood development and mental retardation.

Accomplishments in 1971: The contraceptive development program will support approximately 120 contracts in four areas of reproductive biology espically identified as likely to contribute to the development of new methods of contraception and 25 in new initiative areas of drug and device development. These are studies of sperm, ovum, oviduct, and corpus luteum functions. The behavioral sciences program will support approximately 35 contracts in broad areas of behavioral and demographic studies. Contracts will be awarded for research on the medical effects of contraceptives now in use. Child Health contracts will support studies on the effect of malnutrition on the mother and developing fetus and on the effect of nutritional supplements during pregnancy.

Objectives in 1972: The program for fiscal year 1972 is designed to expand all aspects of the population and reproduction program with particular emphasis on the development of new contraceptives. Five positions will be added to conduct research which will include identification of testing facilities for rapid exploitation of new contraceptive leads; support of drug and device development; studies of local rather than systemic methods and research on improved methods of sterilization and abortion.

In addition, research will expand in the field of early childhood development including the related aspects of nutrition and mental retardation.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Biometry, Epidemiology, and Field Studies (Public Health Service Act, Title IV, Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
24	$2,200,000	Indefinite	24	$2,227,000

Purpose: Supports the Institute's scientific staff in planning and conducting epidemiologic and biometric investigations and conducts research in epidemiological and biometric theory, techniques, and methods; and collects and analyzes program statistics for the Institute's programs and executes statistical studies for use in program planning, development, and evaluation.

Explanation: Through the research contract mechanism, this activity supports the Institute's scientific staff in planning and conducting studies dealing with the incidence, distribution and control of health problems in certain populations. It supports development of more effective and reliable means for measuring health problems, through the collection and analysis of health data for use in initiating and evaluating scientific programs.

Accomplishments in 1971: The majority of the funds support research contracts in the Institute's five program areas: Population and Reproduction, Perinatal Biology and Infant Mortality, Growth and Development, Adult Development and Aging, and Mental Retardation. Approximately $1,626,000 will be used in 1971 in support of these programs.

Objectives in 1972: A number of new epidemiologic studies and research contracts begun in FY 1971, on the safety of oral contraceptives, infant mortality, low birth weight babies, and related phenomena will be continued.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Training Activities (Public Health Service Act, Title, IV Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
4	$86,000	Indefinite	4	$93,000

Purpose: To provide long term scientific training for employees of the National Institute of Child Health and Human Development.

Explanation: The direct training program is one means of coping with the crucial problem of an insufficient number of trained scientists. It is a mechanism of support to the Institute's intramural, extramural, and biometry and epidemiology staff by providing supplementary or cross-disciplinary training to increase staff effectiveness.

Accomplishments in 1971: Four intramural scientists will complete their training at the end of FY 1971. These four men will return to active research in the intramural program in FY 1972.

Objectives for 1972: The Institute will again provide opportunitites for four staff members to broaden their knowledge by participating in long term training activities at excellent outside training centers.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Review and Approval (Public Health Service Act, Title IV, Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
92	$2,544,000	Indefinite	92	$2,808,000

Purpose: Administers the Institute's research grants, training grants, fellowships, and research contracts.

Explanation: This activity supports the Institute's extramural program staff and the grants and contracts management branch. These branches are responsible for the planning and development of research programs that will best serve the Institute's mission; reviewing and evaluating grant applications for presentation to the National Institute of Child Health and Human Development Advisory Council; providing council staff assistance and liaison with applicants and grantees; and, continuing surveillance of grants.

Accomplishments in 1971: Ths most significant event of FY 1971 will be the approval of the concept of combining the review of program projects with the review of training grants, research career development awards, and fellowships within the Institute's training review committees. This concept puts the emphasis on problems and programs rather than of the mechanisms of review. Five committees will be developed whose members will be outstanding experts in their field, but who are also fully cognizant of major problems of research support within the extramural branches. The staff will continue management of 1,023 grants including training grants and fellowships, and 221 research contracts

Objectives in 1972: The objectives of this activity in 1972 will be the administration of grants, awards and contracts in population, nutrition, early childhood development and mental retardation.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Program Direction (Public Health Service Act, Title IV, Part E)

1971 Available Appropriation		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
48	$1,029,000	Indefinite	48	$1,099,000

Purpose: Provides the general administration, planning, direction, and coordination of the Institute's programs.

Explanation: This activity funds the Office of the Director and related staff which consists of the Officer of Program Planning and Evaluation, and the administrative management offices. In addition to the Office of the Director, the positions and non-program funds for the Center for Population Research are included in this activity.

Accomplishments in 1971: During 1971 the staff of the Office of the Director continued to provide administrative management services and program guidance to the Institute's staff, in support of rapidly increasing programs.

The Center for Population Research succeeded in recruiting sufficient professional staff to direct the expansion of the research contracts program within the Center.

Objectives for 1972: In 1972, the Institute's program will increase by nearly $9 million and the main objective of the Office of the Director will be the continued effective management of this expanding program.

New Positions Requested

Fiscal Year 1972

	Grade	Number	Annual Salary
Laboratory and clinical research			
Medical Officer	GS-15	1	$21,589
Developmental Biologist	GS-15	1	21,589
Medical Officer	GS-14	1	18,531
Medical Officer	GS-13	1	15,812
Biochemist	GS-12	1	13,389
Biologist	GS-12	1	13,389
Chemist	GS-11	2	22,466
Biochemist	GS-11	2	22,466
Biologist	GS-11	1	11,233
Secretary	GS- 5	2	12,352
Technician	GS- 4	1	5,853
Secretary	GS- 4	2	11,706
		16	190,375
Collaborative research and development			
Medical Officer	GS-14	1	18,531
Health Scientist Administrator	GS-13	1	15,812
Health Scientist Administrator	GS-12	1	13,389
Secretary	GS- 5	1	6,176
Secretary	GS- 4	1	5,853
		5	59,761
Total new positions, all activities		21	250,136

FRIDAY, MAY 17, 1971.

NATIONAL EYE INSTITUTE

WITNESSES

DR. CARL KUPFER, DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. GEORGE T. BROOKS, ACTING ASSOCIATE DIRECTOR FOR EXTRAMURAL PROGRAMS, NATIONAL EYE INSTITUTE
JAMES G. HILL, EXECUTIVE OFFICER, NATIONAL EYE INSTITUTE
JAMES G. CULP, BUDGET OFFICER, NATIONAL EYE INSTITUTE
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
B. FRANK GARDNER, JR., ACTING ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

National Eye Institute

Object Classification (in thousands of dollars)

Identification code 09-30-0887-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	740	1,262	1,428
11.3	Positions other than permanent	25	84	84
11.5	Other personnel compensation	1	14	14
	Total personnel compensation	766	1,360	1,526
12.1	Personnel benefits: Civilian employees	79	134	148
21.0	Travel and transportation of persons	35	67	67
22.0	Transportation of things	8	17	17
23.0	Rent, communications, and utilities	8	18	19
24.0	Printing and reproduction	11	27	27
25.0	Other services	867	2,393	2,560
26.0	Supplies and materials	61	166	166
31.0	Equipment	224	367	268
41.0	Grants, subsidies, and contributions	20,746	25,428	27,636
99.0	Total obligations	22,805	29,977	32,434

Personnel Summary

Total number of permanent positions	87	103	113
Full-time equivalent of other positions	5	8	8
Average number of all employees	72	98	106
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0887-0-1-651	1970 actual	1971 est.	1972 est.
Program by activities:			
1. Grants:			
(a) Research	16,807	20,754	24,525
(b) Fellowships	865	1,676	876
(c) Training	2,959	2,998	2,225
Total, grants	20,631	25,428	27,636
2. Direct operations:			
(a) Laboratory and clinical research	857	1,861	2,955
(b) Collaborative research and development	359	1,332	332
(c) Biometry, epidemiology, and field studies	250	341	368
(d) Review and approval of grants	416	689	770
(e) Program direction	152	326	373
Total, direct operations	2,034	4,549	4,798

	Total program costs, funded [1]	22,665	29,977	32,434
	Change in selected resources [2]	140	----------	----------
10	Total obligations	22,805	29,977	32,434
	Financing:			
25	Unobligated balance lapsing	9	1,118	----------
	Budget authority	**22,814**	**31,095**	**32,434**

[1] Includes capital outlay as follows: 1970, $80 thousand; 1971, $367 thousand; 1972, $268 thousand.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $5,625 thousand; 1970, $5,765 thousand; 1971, $5,765 thousand; 1972, $5,765 thousand.

Program and Financing (in thousands of dollars)—**Continued**

Identification code 09-30-0887-0-1-651		1970 actual	1971 est.	1972 est.
	Budget authority:			
40	Appropriation	24,342	30,986	32,434
40	Portion withdrawn (Public Law 91-204, sec. 410)	−1,506	----------	----------
41	Transferred to other accounts	−22	−2	----------
43	**Appropriation (adjusted)**	**22,814**	**30,984**	**32,434**
46.10	**Proposed transfer for wage-board increases**	----------	**5**	----------
46.20	**Proposed transfer for civilian pay act increases**	----------	**90**	----------
46.30	**Proposed transfer for military pay act increases**	----------	**16**	----------
	Relation of obligations to outlays:			
71	Obligations incurred, net	22,805	31,095	32,434
72	Obligated balance, start of year	----------	12,925	22,722
74	Obligated balance, end of year	−12,925	−22,722	−29,058
90	Outlays, excluding pay increase supplemental	9,880	21,190	26,095
91.10	Outlays from wage-board supplemental	----------	5	----------
92.20	Outlays from civilian pay act supplemental	----------	88	2
91.30	Outlays from military pay act supplemental	----------	15	1

NOTES

Includes $1,086 thousand in 1971 and $1,106 thousand in 1972 for activities previously financed from (in thousands of dollars):

	1970
Research resources	107
National Institute of Neurological Diseases and Stroke	963

Includes $1,172 thousand in 1972 for activities previously financed from (in thousands of dollars):

	1970	*1971*
National Heart and Lung Institute	23	-----
National Institute of Dental Research	88	-----
National Institute of Arthritis and Metabolic Diseases	---	69
National Institute of Neurological Diseases and Stroke	984	1,088
Fogarty International Center	7	-----

Excludes $8 thousand in 1972 for activities transferred to: Office of the Director, 1970, $10 thousand; 1971, $8 thousand.
Excludes $773 thousand in 1972 for activities transferred to: Health Manpower, 1970, $773 thousand; 1971, $773 thousand.

INTRODUCTION OF DR. KUPFER AND ASSOCIATES

Mr. FLOOD. We continue with the National Institutes of Health. We now have the National Eye Institute. The presentation will be made by Dr. Carl Kupfer, the Director. Do you have anybody you would like to introduce, Doctor?

Dr. KUPFER. Yes, sir. To my far left is Dr. George Brooks, the Acting Associate Director for Extramural Programs, and to my immediate left is Mr. James Hill, the Executive Officer, National Eye Institute. If they will be answering any questions, a biography will be provided.

Mr. FLOOD. We will place your biographical sketch in the record at this point.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH

Name: Carl Kupfer, M.D.

Position: Director, National Eye Institute.

Birthplace and date: New York, N.Y., February 9, 1928.

Education: A.B., Yale University, 1948; M.D., the Johns Hopkins Medical School, 1952.

Experience: Present: Director, National Eye Institute, National Institutes of Health; 1966–70, Professor and chairman in Ophthalmology, University of Washington School of Medicine; research affiliate, University of Washington Primate Center; 1962–66, assistant professor in Ophthalmology, Harvard Medical School; 1960–62; instructor in ophthalmology, Harvard Medical School; 1958–60, research fellow in ophthalmology, Harvard Medical School; 1957–58, research fellow in ophthalmology, Wilmer Eye Institute, the Johns Hopkins Medical School; laboratory assistant, biostatistics, the John Hopkins Medical School; 1953–54, laboratory assistant, biostatistics, the Johns Hopkins Medical School; 1952–54, internship and assistant residency, Wilmer Eye Institute, the Johns Hopkins Hospital.

Association memberships: American Physiological Society; Association for Research in Vision and Ophthalmology; American Academy of Ophthalmology and Otolaryngology.

Publications: Author or coauthor of approximately 40 publications in clinical ophthalmology and the anatomy physiology and biochemistry of the visual system.

GENERAL STATEMENT

Mr. FLOOD. Please proceed, Doctor.

Dr. KUPFER. Mr. Chairman and members of the committee, I am pleased to be here today to discuss the progress that has been made by the National Eye Institute, and to present our plans and needs for the coming fiscal year. This is my second appearance before this distinguished committee on behalf of the Eye Institute.

I am glad to report that, since I last appeared before you, the Institute has become the Federal focus for research on vision and visual disorders. We have been able to create the basis for a fully functioning, independent program of vision research, as envisioned by the Congress in its passage of the National Eye Institute Act. We have filled important staff positions, improved our advisory structure, and reorganized our programs.

SIGNIFICANT ADVANCES IN RETINA RESEARCH

Most important, the past year has been marked by significant and exciting advances in research, most notably in the field of diseases of the retina, the eye tissue that converts light to nervous impulses. These impulses are transmitted to the brain, allowing us to see. Diseases of the retina and its connections with the brain account for 40 percent of all blindness in the United States and an untold amount of disability short of blindness. Because many retinal disorders are increasing at a rate faster than the increase in the general population, this area presents one of the greatest challenges to vision research.

The retina can be viewed directly with a simple instrument that all doctors have, the ophthalmoscope. This ability to view intact blood vessels and nervous tissue is unique with the eye. Thus, not only retinal disease, but related problems elsewhere in the body can be revealed through retinal examination. Changes in the choroid, a tissue rich in blood vessels which nourishes the overlying retina, may also indicate disease of the retina and other portions of the eye.

An understanding of retinal function is essential for advance against retinal disease. As the committee knows, there is much ferment and activity currently underway in this field of scientific research. Two Institute grantees have shared Nobel prizes for their work in studying the visual system. I would like therefore to emphasize research on the retina in my remarks today. I will also briefly discuss progress that has been made against other important diseases such as cataract, glaucoma, and corneal disease.

DIAGNOSIS OF DISEASES BY FLUORESCEIN ANGIOGRAPHY

I should first like to bring to the committee's attention a diagnostic technique—fluorescein angiography—which has been largely responsible for many recent advances in retinal studies. Fluorescein angiography was developed primarily by various Institute grantees and involves the intravenous injection of a fluorescent dye. Unlike other forms of angiography which require a fluoroscope or X-ray apparatus, this technique permits the direct viewing of the blood flow within the vessels of the retina and choroid by the examining physician. It has enabled doctors to improve diagnosis by enhancing their ability to differentiate among various kinds of disease of the retina and choroid, and to pinpoint the site of any leakage or blocking of blood flow in these tissues.

I would like to depart for a moment, if I may, and give you some photographic examples of this particular technique. These are some actual photographs taken of the retina as seen by the examining physician through the ophthalmoscope. I just might point out some of the structures of the retina. One sees the optic nerve in each of these photographs as that white disk. One sees the blood vessels of the retina, and then one sees a diffuse whiteness which is the dye in the choroid, the tissue underneath the retina. The photographs were taken after the fluorescent dye was introduced into the circulatory system.

Mr. FLOOD. Into the circulatory system? At what point?

Dr. KUPFER. In the vein in the arm, the usual intravenous injection. This is a harmless dye. One can see in this particular case of a young man who had decreased vision that the dye, which appears white, fills the arteries, and is just beginning to fill the veins. But what is of particular importance, and one of the major advances in the concept of retinal disease, is the appearance of a small white spot here, and as one looks at a photograph taken perhaps 5 seconds later, one now sees that the dye is in both the artery and veins, but this white spot has increased in size, and in point of fact it is the site of a leakage of the blood vessel supplying this part of the eye. About 15 minutes later, when all the dye has left the back of the eye, one can still see that this leakage of dye, which appears white, has even grown further in size. It is now known that certain types of disease in the back of the eye are caused by leakages from the blood vessels, and with this technique of fluorescein angiography, the particular blood vessel that is leaking can be identified. What is particularly gratifying is that this leakage can be sealed so not only is the diagnosis made, but the treatment indicated.

The last photograph indicates that this site, which is the site of the leakage, has been sealed by the use of a laser beam.

Mr. FLOOD. That white dot?

Dr. KUPFER. Just this whitish area, which is the same location of the leakage that was previously found by the fluorescein angiogram. This photograph is taken several weeks later after treatment. The idea is to obliterate this vessel, to seal this leak, and this leak was sealed by the use of a laser beam. One can see the scar that was left by this very tiny laser beam, which sealed the leak and cured the particular disease of the retina. In this particular case, the individual regained completely normal vision.

Mr. FLOOD. I was going to ask you and I may as well ask you now since you are developing this, how successful is this relatively new use of lasers to what I would call a spotweld of the detached retina?

Dr. KUPFER. This is a very good description.

Mr. FLOOD. How are we coming along on that?

Dr. KUPFER. It is quite successful. In this case the laser is being used for another purpose, to spotweld closed a leakage in a small blood vessel. In this case it is extremely successful. This is an example of the technique of fluorescein angiography, not only in terms of diagnosing what the problem is, but indicating where one should apply the treatment. I think as I speak further I can show other examples of this particular technique.

FLUORESCEIN ANGIOGRAPHY DETECTION OF TUMORS

The potential for fluorescein angiography as a diagnositc tool can be appreciated by noting its recent use in aiding the preoperative identification of intraocular tumors. Research indicates that the technique will enhance the physician's ability to detect malignant melanoma, a cancer in the eye which, in addition to causing severe visual loss, frequently endangers life.

Again, if I may, I would like to show an example.

Mr. FLOOD. This committee knows that there are over 100 kinds of cancers. Is cancer in the eye an uncommon condition? Let me put it another way: Does it happen very often?

Dr. KUPFER. No, sir. I would say that it represents perhaps 1 percent of all the blindness, so it doesn't represent a major cause.

Mr. FLOOD. Would you know the reason for that kind of cancer? What would cause that kind of cancer?

Dr. KUPFER. I don't know, sir.

Mr. SMITH. It is very prevalent in some animals; but there is no correlation?

Dr. KUPFER. No, sir. You are quite correct on that. The ophthalmologist is confronted with the question, when one sees a growth in the back of the eye, which one can see with the ophthalmoscope, is it benign or is it malignant? Fluorescein angiography helps make this distinction. At the top is a picture of the retina after the fluorescein has been introduced into the blood vessels, and one notices that the tumor here is very much filled with the dye, which would indicate that there are many, many blood vessels in this tumor, and we now know that usually, when there are many blood vessels in a tumor such as shown here, that this indicates that the tumor is benign.

Mr. FLOOD. How did the tumor get there?

Dr. KUPFER. The tumor begins in the tissue underneath the retina, the choroid.

Mr. FLOOD. How does it begin?

Dr. KUPFER. It begins in the fashion of some cells which stop maintaining their usual normal situation, and begin to divide in no regular fashion. I would say that a tumor by definition is a mass of new tissue.

Mr. FLOOD. When a cell divides by assexual reproduction, the cell——

Dr. KUPFER. The usual controls over the division of the cell are removed, and this cell now begins to divide.

Mr. FLOOD. Chain lightning?

Dr. KUPFER. Perhaps so, without the restraints that one usually sees. The characteristics of a benign tumor in general is that there are many, many blood vessels in the tumor and we can visualize these blood vessels by using this dye.

Mr. FLOOD. Are those blood vessels in any tumor indigenous to that particular tumor?

Dr. KUPFER. Yes, sir. As a tumor grows it must depend upon blood vessels for the supply of nutrition.

Mr. FLOOD. Can it create its own blood vessels?

Dr. KUPFER. Yes, sir. In this case of the so-called malignant melanoma, which can be seen in this picture, one notices that there are almost no blood vessels.

Mr. FLOOD. What do you mean by malignant as distinguished from benign? Here is a tumor. You say tumor one is benign, tumor two is malignant.

Dr. KUPFER. Yes, sir. A benign tumor in general is not life threatening. It will not grow in an uncontrolled fashion, and then break off and seed other parts of the body.

Mr. FLOOD. Why is tumor two benign and tumor one is not?

Dr. KUPFER. Sir, this is one of the very important questions for which answers are not available yet.

Mr. FLOOD. But somebody is looking for them, of course.

Dr. KUPFER. Yes, sir. I think the National Cancer Institute would very much like the answer to these questions.

Mr. FLOOD. If the tumor in the eye, for instance, is benign, can that infect the rest of the body?

Dr. KUPFER. No, sir, it cannot. It will just stay in the eye, and very often will not threaten the integrity of the eye. The important thing is to be able to determine which growth in the eye is benign and which growth in the eye is malignant.

Mr. FLOOD. Can a malignant tumor of the stomach infect the eye?

Dr. KUPFER. Yes, sir; by metastasis. In the case of the malignant tumor, the characteristic picture is a relative absence of blood vessels. The explanation here is that if the tumor grows rapidly it may outgrow its blood supply and therefore there is relatively little blood supply. Therefore the technique of fluorescein angiography helps distinguish between a benign tumor which can be left in the eye and treated in a conservative manner and the malignant tumor which requires the removal of the eye to save the life of the patient.

RESEARCH ON DIABETIC RETINOPATHY

It has also proved its value as a research tool. Fluorescein angiography has increasingly implicated the choroid in a number of retinal disorders. Studies of certain diseases of the macula, the area of the retina subserving fine vision, in particular have pinpointed choroidal lesions as the source of damage.

Blindness associated with diabetes accounts for almost 15 percent of new cases of adult blindness. The principal kind of diabetes-related blindness affects the retina where a condition called diabetic retinopathy develops.

CONSTRUCTION OF THE HUMAN EYE

Mr. FLOOD. What is the retina?

Dr. KUPFER. The retina is the seeing part of the eye on which light falls. The retina takes the light and converts it into a nervous impluse which then travels to the brain and allows us to see.

Mr. FLOOD. Without the retina you have no eye?

Dr. KUPFER. You have no vision.

In this condition, new fragile blood vessels grow into the vitreous, the clear gel which fills the eyeball.

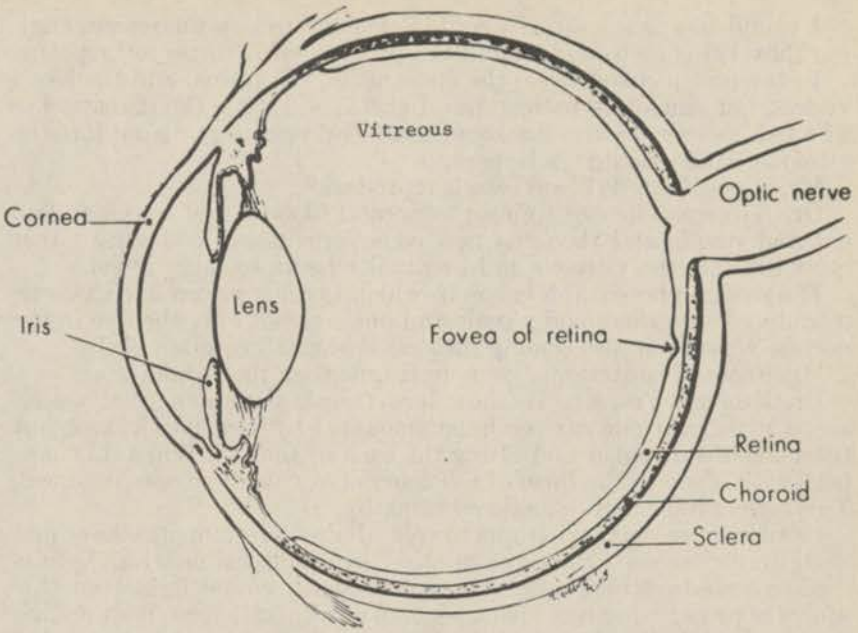
Mr. FLOOD. What is the eyeball?

Dr. KUPFER. The eyeball is the spherical structure within the orbit that contains the retina in the back and the cornea and lens in the front. The latter two structures focus light coming into the eye onto the retina.

Mr. FLOOD. I wish for the record you would briefly describe the parts of the eye.

Dr. KUPFER. Yes, sir, we will be happy to.

(The information follows:)



1. Cornea: Clear, transparent portion of the outer coat of the eyeball through which light enters the eye.
2. Sclera: The white part of the eye—a tough covering which, with the cornea, forms the external, protective coat of the eye.
3. Iris: Colored, circular membrane, suspended behind the cornea and immediately in front of the lens. The iris regulates the amount of light entering the eye by changing the size of the pupil.
4. Lens: Transparent, colorless body which brings the rays of light to focus upon the retina.
5. Vitreous: Transparent, colorless mass of soft, gelatinous material filling the eyeball behind the lens.
6. Retina: Innermost coat of the eye, formed of light-sensitive nerve fibers which transmit impulses to the brain via the optic nerve.
7. Fovea: The small, indented portion of the central retina which enables fine or reading vision.
8. Choroid: The vascular, intermediate coat which furnishes nourishment to the retina and other parts of the eye.
9. Optic nerve: The nerve which carries messages from the retina to the brain.

Dr. KUPFER. These new vessels hemorrhage into the vitreous and blood is dispersed. The blood may be eventually absorbed, with only temporary visual impairment, or if the patient is less fortunate, fibrous scar tissue may form leading to detachment of the retina from the choroid, and blindness.

Mr. FLOOD. Trauma can do this, too, of course.

Dr. KUPFER. Yes, sir. The exact mechanism causing this vascular breakdown is unknown, but it is a frequent complication of longstanding diabetes. An estimated 75 percent of all people with diabetes for 15 years or more will suffer some degree of retinopathy.

As a result of improved life expectancy, this condition is becoming the leading cause of new adult blindness in many States.

I would like again, sir, if I could demonstrate how fluorescein angiography helps us to understand the problem of diabetic retinopathy.

In the first picture we see the optic nerve, the retina, and the blood vessels, but since this patient has diabetes and since the diabetes has affected his eyes, he also has some new blood vessels going out into the vitreous. These should not be here.

Mr. FLOOD. How do blood vessels reproduce?

Dr. KUPFER. The cell lining the normal blood vessel begins to bud out and divide and then the new cells form new blood vessels that grow out into the vitreous and eventually begin to carry blood.

The second photograph is one in which the fluorescein dye has been introduced into the blood vessels and one sees not only the dye in the normal vessels but also coming into the abnormal, fragile vessels.

Mr. FLOOD. The abnormal is more fragile than the normal one?

Dr. KUPFER. Yes, sir. To show how fragile these abnormal vessels are, a little later one can see huge amounts of fluorescein leaking out from the blood vessels and filling the back of the eye. When this happens with blood in the form of a hemorrhage, this can cause blindness. This is the problem of diabetic retinopathy.

Until very recently, attempts to treat diabetic retinopathy have met with limited success. Photocoagulation, in which visible white light is used to occlude retinal vessel breaks, has been used but light from this source is projected in too wide a beam to concentrate selectively on fine vessels. During the past year Institute grantees have developed and begun evaluation of new methods of photocoagulation, notably the use of lasers in conjunction with fluorescein angiography which delineates the area to be treated.

As planned last year, the Institute has begun supporting a cooperative project, involving the pooling of patient results and a unified research plan to determine the effectiveness of treating diabetic retinopathy.

RESEARCH ON TREATMENT OF RETINAL DETACHMENT

Research is also helping to find better ways of treating retinal detachment resulting from other causes. NEI grantees have explored the use of cryosurgery, intense cold, in reattaching the retina. Several studies indicate that cryosurgery may enable the treatment of some retinal detachments on an outpatient basis without need for hospitalization.

Over the past two decades research has made it possible to reduce substantially the hospital stay for treating detached retina. Now, with this new advance, certain patients will not need hospitalization at all—a further savings in medical costs and patient comfort.

DEVELOPMENT OF THE LASER BEAM

Mr. FLOOD. This may not be in your shop. I happen to be on the subcommittee of Appropriations Committee for the Defense Department since it was established right after the war. Of course, we have done fantastic things and spent fantastic sums in research and development. The first time we became acquainted with the laser beam was through defense research. This was quite some time ago. It has been developed and redeveloped for use as a weapon.

Was it first discovered by the Defense research and development people or was it a separate and distinct discovery just generally in the field of science? Do you know offhand?

Dr. KUPFER. I would have to check that.

Mr. FLOOD. We got into research on fissionable material in Defense and now we are doing all sorts of good things with it. There are so many things that come out of research and development in Defense which many people thought were bad and yet have been developed to include so many, many good things.

I was wondering about the laser beam.

Dr. KUPFER. I have the impression it was developed by industry, if I am not mistaken. But, of course, the Defense Department research and development has greatly accelerated the development of it.

TREATMENT OF RETROLENTAL FIBROPLASIA

The committee has often heard of how NIH-supported research helped to establish that high levels of oxygen administered to newborn infants cause retrolental fibroplasia (RLF), a retinal disease causing blindness. However, in a number of premature nurseries, the necessary use of high levels of oxygen to save the lives of infants affected with respiratory disease has perpetuated the RLF problem. Research by Institute grantees is now aimed at treating RLF in these children.

Mr. FLOOD. Are you suggesting that the use of pure oxygen for any purpose regardless of age could produce blindness? You heard the prior witness testify one of the things they are experimenting with is to have the advanced-age group use pure oxygen to help breathing. Is there any danger to the eye?

Dr. KUPFER. No, sir; none at all.

COLOR BLINDNESS RESEARCH

In basic research on the retina, one of the Institute's own scientists is studying how color is transmitted through different parts of the visual system. This work is important because the first step in color vision occurs in the retina and may lead to a better understanding of color blindness and related defects.

Because of these and other advances in research on the retina, the National Eye Institute intends to continue and increase emphasis in this area in fiscal year 1972.

Mr. FLOOD. What is color blindness?

Dr. KUPFER. There are a number of people who can't differentiate one color from another.

Mr. FLOOD. Why?

Dr. KUPFER. There is some problem in the way the color light is perceived by the retina.

OTHER RESEARCH

Research on diseases of components of the visual system other than the retina is progressing. What promises to be a major new therapy in treating certain kinds of corneal disease is under development by NEI grantees using contact lenses made of a soft porous plastic. The medical use of these lenses includes the treatment of a serious chronic condition, the so-called "dry eye," a lack of tears which may result

from a number of conditions and which can lead to scarring of the cornea and blindness.

Mr. FLOOD. Does the contact lens do as much harm as it does good?

Dr. KUPFER. The contact lens does much more good than harm.

RESEARCH ON GLAUCOMA

In glaucoma research, studies employing fluorescein angiography have strongly suggested that it is the vessels of the choroid and not the retina which are first affected by increased intraoccular pressure. Therefore, the direction of research is shifting in the search for the cause of visual loss from this disorder.

Another finding is that the number of young patients with this potentially blinding condition is greater than previously suspected.

Mr. FLOOD. What do you mean by young?

Dr. KUPFER. Patients in their twenties and thirties.

An Institute grantee who has examined young people with glaucoma has stressed the importance of testing younger patients, especially when there is a family history of the disease.

Mr. FLOOD. What is glaucoma?

Dr. KUPFER. This is a disease of the eye manifested by increased pressure in the eyes eventually leading to loss of vision.

Mr. FLOOD. What kind of pressure?

Dr. KUPFER. The normal pressure in the eye is regulated at a certain level. If this pressure increases, the increased pressure can damage the optic nerve.

CAUSE AND TREATMENT OF CATARACTS

Surgical improvements in removing cataracts and in corneal transplantation, notably the use of finer suture material, have led to a shortening of the required hospital stay following these operations.

Mr. FLOOD. What is a cataract?

Dr. KUPFER. A cataract is an opacity——

Mr. FLOOD. Translate that.

Dr. KUPFER. Normally the lens in the eye is crystal clear. If the lens no longer is crystal clear, becomes opaque, this is referred to as a cataract.

Mr. FLOOD. What would cause that?

Dr. KUPFER. For the most part, the cause is unknown, but there are some types of cataracts such as the cataracts that occur in diabetes in which we do know the cause.

As the committee knows, surgery for removing cataracts is 95-percent successful—in fact, it is one of the most successful of all operative procedures. Here is another instance where research has directly contributed to reducing the cost of medical care.

INTRAMURAL RESEARCH

With increases provided in the 1971 appropriation we have been able to continue strengthening the research capability of our intramural program, working toward its becoming a national resource for vision research.

In our clinical program, patients are seen for whom a diagnosis has not been made and conventional therapy has not been successful.

Studies of glaucoma, degenerative disorders of the retina, and the treatment of inflammatory diseases with immunosuppressive and other new drugs are underway.

Presently, 26 beds in the NIH Clinical Center are being utilized for patient studies. Outpatients are also seen. Accordingly, our unique research capabilities presently offer us the opportunity to conduct a number of clinical studies which could not be conducted elsewhere. The Institute has been able to expand its clinical research program at a substantially reduced cost by housing patients who do not require bed care in rented facilities off the Bethesda campus but close enough for proper care and frequent observation.

RACIAL AND GEOGRAPHIC FACTORS IN EYE DISEASE

Mr. FLOOD. Speaking of the diseases of the eye, various types and kind, is there anything peculiar to race or color? We have many diseases peculiar to race and color, and geographical situations. What about the eye? Do black men have more trouble than red men or white men or yellow men with the eye?

Dr. KUPFER. This is a very interesting question and, in point of fact, just recently it has been shown that retinal detachment which is not infrequent among Caucasians is rare among the Negro in this country as well as in Africa.

Mr. FLOOD. What about geography? Is there anything peculiar to South Asia, Africa, in eye conditions?

Dr. KUPFER. I would say in some underdeveloped countries with poor facilities for maintaining personal hygiene the disease known as trachoma is very prevalent and as a matter of fact is the main cause of blindness the world over.

Mr. FLOOD. Have you ever been on the North African coast?

Dr. KUPFER. Just in Tangiers.

Mr. FLOOD. That is enough.

Dr. KUPFER. Our newly completed eye clinic has recently opened and has enabled us to intensify research activities in glaucoma and retinal diseases, conditions which do not usually require patients to be hospitalized.

ORGANIZATIONAL CHANGES

The Institute's intramural program, formerly constituted as the Opthalmology Branch, was reorganized as a clinical branch for patient studies an a Laboratory of Vision Research for basic investigations. A position of Director of Intramural Research was created to supervise both branches.

An Office of Biometry and Epidemiology has been created in response to the needs of the vision research community. The Office is the focal point in the Institute for conducting important statistical and epidemiological studies on the extent of eye disease, factors related to disease occurrence, and clinical trials of new treatments.

Mr. FLOOD. Are any eye conditions inherited?

Dr. KUPFER. They certainly are. Glaucoma would be an excellent example.

Mr. FLOOD. Are they infectious or contagious?

Dr. KUPFER. Eye diseases which are due to bacteria or a virus are contagious. Trachoma would be an excellent example.

It also provides statistical consultation to other Institute researchers as well as to grantees conducting complex, longitudinal collaborative studies. We have been very fortunate in recruiting an excellent and highly experienced individual to head this important new program.

Working closely with the National Center for Health Statistics, the Institute is helping to assure that the vision examinations to be included in the upcoming 4-year National Health Survey of 60,000 citizens will yield accurate and useful information from which we hope to obtain data on the national prevalence of ocular disease.

The basis for an active public information program, a subject of much interest to the committee last year, has been established. In addition to providing information on vision research, the Eye Institute has become a major source of referral within the Federal Government for all questions regarding visual health, including health care, rehabilitation, and even welfare services for the visually handicapped.

COORDINATION WITH EDUCATIONAL TV

Mr. FLOOD. Have you been in touch with the educational TV and radio people?

Dr. KUPFER. In terms of?

Mr. FLOOD. Bringing it to the attention of the public and young people; for instance, the Sesame Street program. Are you talking about something like that?

Dr. KUPFER. We have had discussions of eye care on television and on radio, and we have had exhibits but I——

Mr. FLOOD. Do you know Mr. Macy who used to be head of the Civil Service Commission?

Dr. KUPFER. No, sir.

Mr. FLOOD. Get in touch with him and tell him you were talking to me. He heads up the operations on the educational TV and public broadcasting. This is the kind of thing we have been talking to them about. You might mention we talked about this and see if you can get into the act in any way.

Dr. KUPFER. Excellent.

BUDGET REQUEST

In summary, the budget request for the National Eye Institute is $32,639,000 for 1972, compared with an operating level of $30,405,000 in 1971.

I shall be happy to answer any questions.

Mr. FLOOD. The overall figures show that you have an increase of $2,234,000, but that disappears and becomes a minus of over $3½ million when you take out the so-called "built-in" increases. So this is a pretty tight budget.

Do you agree with that?

Dr. KUPFER. Yes, sir.

BUDGET FOR RESEARCH GRANTS

Mr. FLOOD. Take a look at page 141. The table there shows that you are going to be able to fund 152 competing research grants in 1971, but will only be able to fund 92 under this budget for 1972. That is a cut of almost 40 percent.

How many approvable applications do you estimate you will have in 1972 compared to that 92 that you will be able to fund?

Dr. KUPFER. I think in addition to the 92, there will be approximately 130 applications that will be approved but unfunded.

Mr. FLOOD. How much would it cost in addition to what is now in the budget to fund as many in 1972 as you did in 1971?

Dr. KUPFER. It would be about $4 million.

REDUCTION IN FELLOWSHIPS

Mr. FLOOD. Take a look at page 143. There you are cutting back on the fellowships from 123 to 52. That is well over 50 percent. Why is your Institute being cut so much more than the average Institute? Is somebody mad at you? Who made this decision?

Dr. KUPFER. Mr. Chairman, I think this was a decision of the Office of Management and Budget.

Mr. FLOOD. They are back again.

You mean two or three 25-year-old arithmetical wonders down there? Don't answer that.

Dr. MARSTON. There was a policy decision at OMB to hold the dollar support of fellowships at the level of the 1971 budget request.

PRIORITY OF INTRAMURAL PROGRAM

Mr. FLOOD. I see you are requesting a program increase of $99,000 for 10 additional jobs for your intramural program?

Dr. KUPFER. Yes, sir.

Mr. FLOOD. Why do you give this priority to your direct research activities?

Dr. KUPFER. The 1971 budget contained funds for renovations and the purchase of equipment for a large increase in research space of the Bethesda in-house research facility. The funds in 1972 and the positions will be used to follow up on this opportunity.

This is a very high priority item to establish an intramural research facility that will be a national resource.

DEVELOPMENTS IN TREATMENT OF GLAUCOMA

Mr. FLOOD. For the record, will you tell us what new developments there are in detection and treatment of glaucoma?

Dr. KUPFER. Yes, sir.

(The information follows:)

RESEARCH PROGRESS IN GLAUCOMA AND CATARACTS

GLAUCOMA

Glaucoma is a group of diseases characterized by the elevation of pressure within the eye. The pressure elevation in susceptible individuals leads to damage of the optic nerve and if left untreated may progress to total irreversible blindness. The loss of vision can be arrested or prevented by medication or surgery. Glaucoma is initially symptomless; however, an irreparable visual loss may occur before the disease is detected. An important goal therefore is the early identification of individuals likely to lose vision so that treatment can be initiated.

Retinal blood vessels converge at the optic disc, a circular area in the back of the eye that is devoid of photosensitive cells where retinal nerve fibers also converge as they leave the eye. The size of the depression in the center of the

optic disc, the physiological cup, is genetically determined. Recently the relationship of the size of the cup to the size of the disk, the cup-disk ratio, has been studied as an aid in early diagnosis of glaucoma.

The cup-disk ratio is observed in individuals free of ocular complaints who had glaucomatous visual field defects. Such individuals exhibit the earliest clinical stage of glaucoma. One study showed that an enlargement of the optic cup occurs early in the course of glaucoma and parallels the magnitude of the vision defect. Furthermore, in the early stages of glaucoma the cup-disk ratio is characteristically unequal in two eyes. The cup-disk ratio, therefore, becomes an important tool in suspecting and detecting this otherwise symptomless (at this stage) disease. The simplicity of this procedure should be invaluable in reducing the frequency of the false positive test common to current procedures.

An investigation of the effect of exercise on intraocular pressures in human beings has confirmed that the pressure within the human eye falls after exercise. The largest drop in pressure and the greatest changes in blood chemistry occur immediately following exercise. Another study has shown that similar results are obtained in rabbits; thus, the rabbit provides an experimental model for further investigations. The animal model may provide a means by which further studies can explore the effect of blood chemistry on intraocular pressure.

Corticosteroids, a group of related compounds used to suppress inflammation, are known to increase intraocular pressure in the relatives of glaucoma patients. A corticosteroid provocative test has been developed which is becoming an important tool in investigating the genetics of primary open-angle glaucoma and identifying glaucoma-prone individuals. Questions have been raised, however, as to the possible irreversible introcular pressure and visual field changes induced by this short-term medication. A recent study has confirmed the safety of this provocative test. In 500 consecutive trials with topical steroids all elevations of intraocular pressure completely reversed upon discontinuance of the drug. The 4-year followup indicated no detectable permanent changes.

Nevertheless, it must be remembered that patients who are nearsighted or have a family history of glaucoma are especially prone to develop a rise in intraocular pressure in response to corticosteroid eye drops. Prolonged use of such medications to alleviate contact lens irritation discomfort may lead to the development of glaucoma and cataracts in high-risk groups. The need for precaution in prescribing corticosteroids for contact lens patients suffering from corneal irritation was illustrated by an Institute-supported study in which two young women developed both glaucoma leading to visual loss and cataracts in both eyes after prolonged unsupervised medication with cortisone.

CATARACT RESEARCH DEVELOPMENT

Mr. FLOOD. Do you have anything new to report regarding research on cataracts? Do that for the record, also.

Dr. KUPFER. Yes, sir.

(The information follows:)

CATARACT

Cataract is the loss of transparency or cloudiness of the ocular lens. The most common type is senile cataract which appears to be a part of the general aging process of the human body. Cataracts can also result from congenital defects, systemic and infectious diseases, and injuries to the eye. The exact cause of most kinds of cataracts remains uncertain, but changes in the normal balance of soluble and insoluble lens protein seem to be involved. The development of a medical procedure for the prevention and treatment of cataracts awaits a better understanding of the chemical nature of these opacities and of the metabolism of the lens.

Although cataract surgery has become a safe and satisfactory practice, technical improvements in the procedures are still being achieved. A 5-year evaluation has shown that an aspiration (suction) technique is superior to conventional surgery for removing cataracts in infancy, childhood, and adolescence and may also be used successfully in older patients.

In this procedure, the anterior chamber of the eye is entered through the clear cornea with a small tapered knife. The lens capsule is cut open and the lens material is stirred for several minutes. The knife is withdrawn, a hollow needle is inserted and the lens material is sucked out. The aspiration technique gen-

erally leads to better visual results and fewer postoperative complications than conventional techniques. The procedure is done in one session. A small incision simplifies postoperative care and shortens hospitalization. Congenital cataracts have long been a problem to ophthalmologists because conditions that interfere with normal retinal formation during infancy can cause irreversible vision loss. Ideally, congenital cataracts should be removed as early in life as possible, but the surgeon is faced with the difficult question of when to operate and what surgical technique to use. Now this single and simple aspiration procedure can remove the onus associated with congenital cataract surgery in the past.

Mr. FLOOD. Mrs. Reid?

EFFECTS OF DIET ON VISION

Mrs. REID. What effect does diet and nutrition have on the eyes? It has always been said that carrots were good for the eyes—is this really true?

Dr. KUPFER. I would first answer, Mrs. Reid, that just as proper diet and nutrition are essential for the health of all body tissues and organs, the same is true for the eyes. The folk wisdom that encourages the eating of carrots and drinking of carrot juice to improve vision is based on the high vitamin A content of that vegetable. Vitamin A is very important in the visual process. When light falls onto the retina the first thing that happens is that the vitamin A contained in the receptor cells undergoes change which initiates the process we call vision. Persons who are deficient in vitamin A may develop night blindness, although this would happen only after a long period of time and can be reversed if supplements are given. There is no evidence, however, that for healthy individuals intake of carrot juice or vitamin supplements will improve vision.

I might also add at this point that the new National Health Survey, which is now underway, could provide us with some interesting data on the relationship of nutrition to vision and visual disorders. We have played a very active part in cooperating with the National Center for Health Statistics to assure that vision examinations will be carried out during the survey in a manner which will yield some valuable information.

PROGRESS IN RESTORING LOST VISION

Mrs. REID. Are we making any progress in regard to persons who have been considered to be blind and then, through some means, have some of their sight restored?

Dr. KUPFER. Yes, very definitely. If we define "blindness" to mean legal blindness, the standard used by the Social Security Administration and other agencies to determine eligibility for assistance and tax benefits, there are many people who have been removed from this status through various means. One method is corneal transplantation which can often help persons blinded by diseases which scar the cornea. This is now a fairly routine procedure. But research is aimed at improving the outcome of this operation and to find better ways of preserving donor tissue. Cataract operations, which are 95-percent successful, dramatically restore vision to persons blind from this condition. Also, many individuals who cannot be helped through surgery or drugs can be assisted greatly by the proper fitting of specially designed low-vision aids. The Institute has supported the development of these devices.

DRUG TREATMENT FOR EYE DISORDERS

Mrs. REID. Are any studies or research being done on the use of drugs to prevent nearsightedness and other disorders?

Dr. KUPFER. Some ophthalmologists have claimed that the use of cycloplegic drugs, in fact the same drugs given by your doctor to dilate the pupils when he examines your eyes, can have a beneficial effect in retarding or halting the progression of nearsightedness. What is usually done is that short-acting drugs are prescribed so that they do not interfere very much with vision and used in conjunction with special bifocal glasses. At the present time one of our own doctors at the Institute is evaluating this treatment in sets of twins with similar degrees of nearsightedness. One twin receives only the usual spectacle correction while the other receives the drops and bifocals. It will be very interesting to see the outcome of this study. Of course, a major use of drugs in the prevention of blindness is in the treatment of glaucoma. Research is seeking more effective and longer acting medications to control this disease.

COORDINATION OF DIABETES RESEARCH

Mrs. REID. How are your efforts regarding blindness and diabetes coordinated with the programs of the National Institute of Arthritis cations to control this disease.

Dr. KUPFER. There is a close coordination. We have discussed this common interest on several occasions with officials of the Arthritis' Institute. We have also sought to define clearly our respective interests in this matter. Of course, NIAMD is interested in diabetes in all its manifestations, which includes a general interest in the eye complications. We are interested primarily in the eye and how disease may be prevented from causing blindness. Since there appears to be no clear relationship between overall control of diabetes by insulin or oral medication and the involvement of the eye, it appears that some other as yet unknown factor is at work here. I might add that the new cooperative study of the treatment of diabetic retinopathy which will be shortly underway with NEI support was developed in consultation with the NIAMD-supported group diabetes study.

Mrs. REID. That is all, Mr. Chairman.

Mr. FLOOD. Thank you very much.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Amounts Available for Obligation

	1971	1972
Appropriation	$30,986,000	$32,639,000
Real transfer to:		
"Departmental Management"	-2,000	---
"Office of the Director" (Proposed transfer for increased pay costs)	-461,000	---
"St. Elizabeths Hospital" (Proposed transfer for increased pay costs)	-494,000	---
Comparative transfers to:		
"Office of the Director"	-8,000	---
"Health Manpower"	-773,000	---
Comparative transfers from:		
"National Institute of Allergy and Infectious Diseases"	69,000	---
"National Institute of Neurological Diseases and Stroke"	1,088,000	---
Total, obligations	30,405,000	32,639,000

62-645 O - 71 - pt. 3 - 64

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
138	Research.....		$20,754,000		$23,535,000		$+2,781,000
	General research support grants.....		(1,551,000)		(1,381,000)		(-170,000)
	Scientific evaluation and planning.....		(25,000)		(25,000)		---
	Categorical clinical research centers.....		(686,000)		(686,000)		---
142	Fellowships.....		1,676,000		876,000		-800,000
143	Training.....		2,225,000		2,225,000		---
	Direct Operations:						
144	Laboratory and clinical research....	51	2,925,000	61	3,075,000	+10	+150,000
145	Collaborative research and development.....	--	1,332,000	--	1,332,000	--	---
146	Biometry, epidemiology, and field studies....	15	369,000	15	385,000	--	+16,000
147	Review and approval of grants.....	24	769,000	24	821,000	--	+52,000
147	Program direction.....	13	355,000	13	390,000	--	+35,000
	Total obligations...	103	30,405,000	113	32,639,000	+10	+2,234,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions.....	103	113	+10
Full-time equivalent of other positions.	8	8	--
Average number of all employees.....	98	106	+8
Personnel compensation:			
Permanent positions.....	$1,299,000	$1,525,000	+$226,000
Positions other than permanent.....	84,000	99,000	+15,000
Other personnel compensation.....	14,000	14,000	---
Total personnel compensation.....	1,397,000	1,638,000	+241,000
Personnel benefits.....	136,000	155,000	+19,000
Travel and transportation of persons.	67,000	67,000	---
Transportation of things.....	17,000	17,000	---
Rent, communications, and utilities..	18,000	19,000	+1,000
Printing and reproduction.....	27,000	27,000	---
Other services:			
Project contracts.....	1,332,000	1,332,000	---
Payment to NIH Management Fund....	1,733,000	1,819,000	+86,000
Other.....	490,000	495,000	+5,000
Supplies and materials.....	166,000	166,000	---
Equipment.....	367,000	268,000	-99,000
Grants, subsidies, and contributions.	24,655,000	26,636,000	+1,981,000
Total, obligations by object.....	30,405,000	32,639,000	+2,234,000

Summary of Changes

1971 estimated obligations	$30,405,000
1972 estimated obligations	32,639,000
Net change	+ 2,234,000

	Base Pos.	Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase costs	--	--	--	+ 85,000
2. Annualization of positions new in 1971	--	--	--	+ 52,000
3. Within-grade salary increases	--	--	--	+ 23,000
4. Extra day pay costs	--	--	--	+ 6,000
5. FTS rate increase	--	--	--	+ 1,000
6. Non-competing research grants	--	$ 11,450,000	--	+5,636,000
B. Program:				
1. Laboratory and clinical research	51	2,900,000	+10	+ 99,000
C. Payment to "National Institutes of Health Management Fund" for centrally-furnished services		1,733,000		+ 86,000
Total, increases	--	--	+10	+5,988,000
Decreases:				
A. Program:				
1. Competing research grants	--	7,042,000	--	-2,685,000
2. General research support grants	--	1,551,000	--	-170,000
3. Fellowships	--	1,676,000	--	-800,000
4. Laboratory and clinical research	51	2,900,000	--	-99,000
Total, decreases	--	--	--	-3,754,000
Total, Net Change	--	--	+10	+2,234,000

Explanation of Changes

Built-in Increases - These increases will provide: $85,000 for annualization of 1971 pay increase costs; $52,000 for the annualization of positions new in 1971; $23,000 for within grade salary increases; $6,000 for the cost of an extra day of pay; $1,000 for increased costs of using the Federal Telecommunications System; and $5,636,000 for the continuation of non-competing research grant awards.

Research Grants - The program decrease of $2,685,000 for competing research grants will result in a reduction of approximately 60 new and renewal awards in 1972. The request also includes a decrease of $170,000 for general research support grants, a program included in each NIH appropriation containing research grant projects, but administered separately by the Division of Research Resources.

Fellowships - The reduction of $800,000 in 1972 will result in 71 fewer awards than were funded in 1971.

Laboratory and Clinical Research - The budget request includes a decrease of $99,000 for equipment and an increase of a like amount to support 10 new positions for the intramural research program of the Institute.

Significant Items in House and Senate Appropriation Committee Reports

Items	Action Taken or to be Taken
1971 House Report	
(1) The Committee expressed its desire that the administrative structure of the Institute be adequate in jobs and salaries.	(1) The 1971 budget included an increase of sixteen positions. The Institute used these positions to appoint a Clinical Director, a Chief for the Office of Biometry and Epidemiology, and to recruit professional and technical staff in Program Direction and laboratory and clinical research activities. The 1972 budget request includes a moderate increase of 10 positions to strengthen the Laboratory of Vision Research and the Clinical Branch of the Institute's intramural research program.
1971 Senate Report	
(1) The Committee repeated, with greater emphasis, the concern it expressed in the previous year for the adequacy of positions allocated to the Institute.	(1) As noted above, the Institute was allocated sixteen new positions in 1971, and requests an additional ten positions in 1972 to strengthen the in-house research effort.
(2) The Committee Report noted that special opportunities exist for significant progress in several areas of vision research, particularly in retinal disease, corneal disease and glaucoma.	(2) The Institute has emphasized new projects in these areas, placing particular emphasis on diabetic retinopathy, and other retinal disorders. In 1972 further efforts will be undertaken to exploit opportunities for research progress in these areas, including more extensive use of research contracts to fund staff directed projects in drug therapy of glaucoma and the development of improved diagnostic techniques for retinal disorders.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation requested
Public Health Service Act Section 301--Research and Investigations in General.....	Indefinite	$ 32,639,000
Title IV, Part F--National Eye Institute....	Indefinite	32,639,000

PUBLIC HEALTH SERVICE ACT

The legislative authority which provides for the award of grants for research, research training and fellowships is included in section 301 of the Public Health Service Act.

Public Law 90-489
90th Congress, H.R. 12843
August 16, 1968

"Sec. 451. The Secretary is authorized to establish in the Public Health Service an institute for the conduct and support of research for new treatment and cures and training relating to blinding eye diseases and visual disorders, including research and training in the special health problems and requirements of the blind and in the basic and clinical sciences relating to the mechanism of the visual function and preservation of sight. The Secretary is also authorized to plan for research and training, especially against the main causes of blindness and loss of visual function."

Explanation of Transfers

Real transfer to:		
Departmental Management	-$2,000	To establish the Facilities Engineering and Construction Agency
Office of the Director	-461,000	Proposed transfer for increased pay costs
St. Elizabeths Hospital	-494,000	Proposed transfer for increased pay costs
Comparative transfer to:		
Office of the Director	-8,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director
Health Manpower	-773,000	Transfer of institutional support funds to Health Manpower
Comparative transfer from:		
National Institute of Arthritis and Metabolic Diseases	+69,000	To provide an equitable distribution of the Management Fund in 1972
National Institute of Neurological Diseases and Stroke	+1,088,000	To provide an equitable distribution of the Management Fund in 1972

Justification

National Eye Institute

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	103	1,533,000	113	1,793,000	+10	260,000
Other expenses.....	---	28,872,000	---	30,846,000	---	+1,974,000
Total.....	103	30,405,000	113	32,639,000	+10	+2,234,000

General Statement

The National Eye Institute was created in 1968 to conduct and support basic and applied research on disease problems of the eye and visual system. Institute programs are implemented through grants and contracts with individuals and research organizations working on problems of visual health, and through laboratory and clinical research conducted by Institute personnel.

Millions of Americans are socially and economically handicapped by blindness and visual impairment. Available statistics indicate that nearly 100,000,000 Americans have some form of eye disorder or impaired vision. Each year more than 350,000 more Americans are afflicted with serious visual disability. The resulting expenses of care, rehabilitation and treatment, as well as lost productivity, constitute an enormous cost to the nation. This great economic loss, the cost of a deplorable waste of human resources, requires a most vigorous program of research on the prevention of visual disorders, and on the care and rehabilitation of afflicted individuals. The National Eye Institute serves as the focal point for such an effort.

Institute scientists and grantees are engaged in research efforts to advance our understanding of the visual process and to attack the full range of vision disorders affecting large segments of the population. Their investigations have contributed significantly to our knowledge of normal visual function and to the development of more effective means for the prevention, diagnosis and treatment of retinal disorders, corneal disease, glaucoma, cataracts, and inflammatory diseases of the eye. Progress in each of these areas has been, and will continue to be, dependent upon the support of laboratory and clinical research in the wide variety of disciplines associated with vision.

Special opportunities exist for accelerating the application of current knowledge and technology to the management of corneal and retinal disease and glaucoma. A scientific base has been created for the further development of a soft corneal contact lens which has already proven useful in eliminating the pain of bullous keratopathy, a common result of corneal disease, and has often significantly increased visual acuity. Progress against retinal disease can be speeded through research to develop new techniques for "spot welding" the retina to the underlying choroid at the site of retinal detachment. In the clinical management of glaucoma, information presently available would permit the development of new and more effective drugs, less destructive surgical procedures, and improved early diagnosis.

Within the resources requested for the National Eye Institute in 1972, efforts will be sustained to exploit opportunities for advances in the prevention, diagnosis and treatment of retinal disorders. These studies will be primarily concerned with retinal detachment, diabetic retinopathy, and the elucidation of the means by which light is converted by the retina to electrical energy and coded to create the sense of sight. In addition, progress against glaucoma, cataract, developmental abnormalities, strabismus, and other visual disorders will be fostered through the continuation of essential ongoing studies on these problems.

Research Grants

	1971	1972	Increase or Decrease
Research projects.....	$18,492,000	$21,443,000	+$2,951,000
Special projects.....	2,262,000	2,092,000	- 170,000
Total research grants	20,754,000	23,535,000	+ 2,781,000

Introduction

The Institute sponsors over 400 research projects at universities, hospitals, research institutes, and other public and private nonprofit institutions. Through these grants the Institute stimulates and supports research on problems related to the prevention, diagnosis, and treatment of visual disorders, as well as fundamental studies essential to an understanding of the eye and the visual system. Grant-supported projects vary from the relatively circumscribed activities of an individual scientist to broadly-based programs that integrate the effort of groups of investigators in a variety of scientific disciplines. They include traditional research projects, research program projects, eye clinical research centers, and eye outpatient clinical research centers.

Program Plans in 1971 and 1972

Diseases of the Retina and Choroid

The retina is the photoreceptive tissue lining the eye that converts light into nervous impulses which are transmitted to the brain allowing us to see. It is nourished by the choroid, the adjacent specialized vascular tissue exterior to the retina. Disorders of these tissues include retinal detachment, diabetic retinopathy, retinal and macular degenerations, congenital anomalies, and circulatory disturbances. These disorders, most of which increase with advancing age, cause approximately 40 percent of the reported cases of blindness in the United States. With increasing longevity, the occurrence of these diseases is rising, and the therapy for some remains controversial.

In 1971 and 1972 the Institute will support studies to further evaluate the effectiveness of photocoagulation techniques to arrest or reverse the impaired vision and vascular proliferation characteristic of diabetic retinopathy and other forms of retinal disease. The observation that freezing the tissues (cryosurgery) is more beneficial than previous treatment for retinal detachment suggests that continued support for the development of this technique could eliminate the necessity for patient hospitalization. Investigations of ultrasonic therapy conducted by Institute grantees may lead to the means of hastening reabsorption of vitreous hemorrhages from the retina. Fluorescein angiography, a newly developed technique that permits direct viewing of the blood vessels of the retina and choroid, will be exploited to understand the effects that circulatory changes may have in producing disease states.

Investigations of the basic mechanisms of retinal function are essential for an understanding of visual disorders, their diagnosis and their treatment. For example, recent studies that relate the embryological development of photoreceptor cells with electroretinographic estimates of visual function portend new methods for the early diagnosis of visual impairments in infants and young children. During 1971 and 1972 support will be maintained for projects that investigate how light energy causes biochemical changes in the visual pigments, how these changes

generate electrical responses in retina cells, and how these bioelectric pulses are coded, processed and finally decoded in the brain to create the sensation of sight.

Corneal Disease

Despite the advent of effective antibiotics and anti-inflammatory agents, infectious diseases of the eye continue to be an important clinical problem. Keratitis and conjunctivitis, for example, affect large numbers of patients in all parts of the world. In FY 1971 and FY 1972 the Institute will support continued efforts to identify causative agents, to describe the development of disease in terms of host parasite relations, and to determine the epidemiology and natural history of infectious diseases, Emphasis will also be placed on the development of new medicinal and immunological treatments and on the surgical and prosthetic alleviation of damaged ocular tissue. These efforts will be enhanced by recent promising developments in the use of tissue adhesives to seal wounds and to fasten contact lenses on the cornea. Recent hypotheses that an infectious rather than an allergic agent may be responsible for certain types of corneal disease and that neonatal inclusion conjunctivitis may be ascribable to a trachoma infection will be examined. Efforts will be made to improve a vaccine against the trachoma agent, still the leading cause of blindness in the world.

Glaucoma

Glaucoma is a group of diseases characterized by an elevation of pressure within the eye that leads to damage of the optic nerve and a subsequent loss of vision. Visual loss can be arrested or prevented by medication or surgery, but since glaucoma is initially symptomless, an irreparable loss of vision may occur before the disease is discovered. An important research goal, therefore, is the early identification of individuals likely to lose vision so that treatment can be initiated. Approximately 2 percent of the population over the age of 40 are victims of glaucoma, and genetic studies suggest that about 4 percent of the total population may have an hereditary predisposition to develop this disease.

Epidemiological and genetic studies are needed to develop a means by which individuals predisposed to glaucoma may be identified. Such investigations will be stimulated and abetted by the recent observation that topically applied corticosteroids induce elevated intraocular pressures. The ability to induce elevated pressures also provides a new model for evaluating medications and for studying the body's normal mechanism for controlling ocular pressure. The fundamental nature of the abnormal situation will only be understood when the normal mechanisms are known. One of the most promising areas involves the role of the sympathetic nerve supply to the eye and its effect on regulating intraocular pressure by controlling the release of endogenous norepinephrine. Additional studies are also needed on both the inflow and the outflow of intraocular fluids, as well as on the exact mechanism by which elevated ocular pressures damage the optic nerve.

Cataract

Cataract is one of the leading causes of blindness in the United States. It accounts for approximately 22 percent of all blind persons in this country. Congenital defects, systemic and infectious diseases and injury can result in cataract formation. However, the most common type is senile cataract so called because it appears to be part of the general aging process in the human body. A cataract is a loss of transparency or a clouding of the ocular lens. While the exact causes of most varieties of cataracts remains uncertain, they seem to be related to changes in the normal balance of soluble and insoluble lens proteins. Technical advancements have made cataract surgery a safe and satisfactory practice, but the development of a medical treatment for cataract or for the prevention of

cataract awaits further research. Recently for the first time, experimental cataract has been successfully prevented in incubated lenses by the use of an inhibitor.

In 1972 the Institute will continue to support research on the mechanisms of cataract formation and inhibition, on the physical and chemical characteristics of lens proteins and changes in these proteins, and on the development of preventative medicine and medical treatment as a substitute for cataract surgery.

Oculomotor Disorders

Binocular vision is a complex process in which the brain must maintain the fixation of both eyes upon an object, moving or stationary, and integrate the incoming images from two retinas in a way that conveys the unique property of depth perception. Deficiencies in either the motor or sensory elements that contribute to this performance results in strabismus, a deviation of an eye which a patient cannot overcome. The habitual deviation of an eye may lead to amblyopia and the loss of visual acuity. To understand the sensory and motor elements that contribute to binocular vision, basic and clinical investigations are needed in: neuroanatomy, neurophysiology, the cerebral control of the oculomotor system, the accommodative mechanism, the nature of fusion, myopathic disorders of ocular motility, and the effects of aging on the oculomotor system. These investigations in 1971, and 1972 will be aided by a newly developed instrument that can record ocular movement by sensing the amount of infrared light reflected from the ocular surface when the eye is rotated. An animal model for studying amblyopia has become available as the result of an observation that visual behavior patterns of surgically induced strabismic monkeys and of monkeys unilaterally deprived of sight from birth is strikingly similar to that of strabismic and amblyopic human patients. Support will be provided for the development of new techniques to restore binocular vision skills and in the search for drugs that can reduce the need for surgery which remains the principle means for attempting to correct strabismus.

Other Research

Grant-supported studies will continue to investigate the treatment and the biochemical and pathological mechanisms of eye injuries that result from accidental exposure to external chemicals, penetrating foreign bodies, systemic poisoning, adverse side effects from drug therapy, and mechanical trauma. The Institute will also support the development of better instruments and techniques for microsurgical repair of eye wounds and for the localization and removal of both magnetic and non-magnetic foreign bodies that enter the eye. A further area of emphasis will be on biomedical engineering investigations to develop reading and mobility aids for the blind and near blind.

Summary

The 1972 budget request for research grant programs sponsored by the National Eye Institute is $23,535,000, a net increase of $2,781,000 over the 1971 level. An increase of $5,636,000 is requested for noncompeting research grants to permit the continuation of research projects awarded prior to 1972. The amount available for new and renewal grants is decreased from $7,042,000 in 1971 to $4,357,000 in 1972, a total reduction of $2,685,000. Support for Eye Categorical Clinical Research Centers is maintained at the 1971 level of $686,000, and the request includes a reduction of $170,000 in 1972 of the Institute's proportionate share of the General Research Support Grant program.

Research Grants Program Analysis

	1971 Estimate	1972 Estimate	Increase or Decrease
Corneal disease	$ 2,900,000	$ 3,100,000	+$ 200,000
Glaucoma	2,219,000	2,574,000	+355,000
Uveitis	370,000	429,000	+59,000
Cataract	1,538,000	2,043,000	+505,000
Chemical toxicity and physical trauma	370,000	429,000	+59,000
Retinal disease	4,808,000	5,576,000	+768,000
Choroidal vascular disease	546,000	845,000	+299,000
Developmental defects	916,000	1,275,000	+359,000
Disorders of visual system	3,900,000	4,100,000	+200,000
Diseases of the oculomotor system	925,000	1,072,000	+147,000
Subtotal	18,492,000	21,443,000	+2,951,000
General research support grants	1,551,000	1,381,000	-170,000
Scientific evaluation	25,000	25,000	---
Categorical clinical research centers	686,000	686,000	---
Total research grants	20,754,000	23,535,000	+2,781,000

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Noncompeting continuations	297	$11,450,000	408	$17,086,000	+111	+$5,636,000
Competing projects	152	6,992,000	92	4,307,000	-60	-2,685,000
Supplementals	(2)	50,000	(2)	50,000	--	---
Subtotal, regular program	449	18,492,000	500	21,443,000	+51	+2,951,000
General research support grants		1,551,000		1,381,000		-170,000
Scientific evaluation		25,000		25,000		---
Categorical clinical research centers		686,000		686,000		---
Total, research grants		20,754,000		23,535,000		+2,781,000

Fellowships

	1971	1972	Increase or Decrease
Total fellowships.....	$1,676,000	$876,000	-$800,000

The fellowships program of the National Eye Institute is directed toward increasing the number of individuals engaged in research and academic careers in the visual sciences. The program emphasizes the training of individuals already knowledgeable in the basic sciences related to vision research. Postdoctoral fellowships provide support for one to three years of training to individuals who have already earned a doctoral degree, but who have had little or no research experience. Special fellowships are awarded to more experienced individuals who find it highly productive to spend a year or two in research laboratories other than their own. Research career development awards are made to investigators of demonstrated ability who require several years of additional experience in order to develop a capability for independent investigation.

The budget request for 1972 will provide for approximately 52 fellowship awards of all types, a decrease of 71 awards.

Fellowship Program Analysis

	1971 Estimate	1972 Estimate	Increase or Decrease
Retinal and choroidal disorders..	$ 687,000	$420,000	-$267,000
Disorders of the visual system...	436,000	175,000	-261,000
Refractive anomalies.....	251,000	88,000	-163,000
Developmental defects.....	218,000	149,000	-69,000
Glaucoma.....	84,000	44,000	-40,000
Total.....	1,676,000	876,000	-800,000

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Continuations:						
Noncompeting.....	18	$427,000	14	$410,000	-4	-$17,000
Competing.....	7	82,000	5	52,000	-2	-30,000
New.....	98	1,167,000	33	414,000	-65	-753,000
Total.....	123	1,676,000	52	876,000	-71	-800,000

Fellowships (by type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Postdoctoral.....	35	$ 330,000	18	$170,000	-17	-$160,000
Special.....	63	723,000	10	108,000	-53	-615,000
Research career development.....	24	591,000	23	566,000	-1	-25,000
Research career.....	1	32,000	1	32,000	---	---
Total.....	123	1,676,000	52	876,000	-71	-800,000

Training Grants

	1971	1972	Increase or Decrease
Total training grants.....	$2,225,000	$2,225,000	---

Training grants supported by the National Eye Institute are awarded to institutions for establishing, improving, or expanding graduate training programs to prepare individuals for research and academic careers in the visual sciences. In 1971 and 1972 emphasis will be placed on advanced training linked to the objective of providing medical schools with full-time personnel for coordinating and conducting programs in investigative ophthalmology. These programs will produce scientists to develop the knowledge essential for improving the prevention and treatment of eye disorders and for training the next generation of investigators in vision research.

Funds for this program remain constant for 1971 and 1972. In the face of increasing costs for training, the number of grants will decrease from 47 in 1971 to 42 in 1972.

Distribution of Training Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Continuations:						
Noncompeting.....	42	$1,958,000	31	$1,568,000	-11	-$390,000
Competing.....	4	195,000	10	567,000	+6	+390,000
New.....	1	47,000	1	65,000	--	---
Scientific evaluation	(1)	25,000	(1)	25,000	--	---
Total.....	47	2,225,000	42	2,225,000	-5	---

Training Grants (by type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Graduate.....	47	$2,200,000	42	$2,200,000	-5	---
Scientific evaluation..	(1)	25,000	(1)	25,000	--	---
Total.....	47	2,225,000	42	2,225,000	-5	---

Laboratory and Clinical Research

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	51	$ 712,000	61	$ 896,000	+10	+$184,000
Other expenses.....	--	2,213,000	--	2,179,000	--	-34,000
Total.....	51	2,925,000	61	3,075,000	+10	+150,000

Funds appropriated for this activity support the NEI intramural research program. The program is comprised of a Laboratory of Vision Research focusing on the basic structure and function of the visual system, and a Clinical Branch focusing on the application of basic knowledge for improved health care and the prevention of visual disorders. The Institute is currently engaged in an intense effort to maintain and further develop a research environment which will provide the physical resources, scientific leadership and administrative management necessary to permit the opportunity for high quality research to be performed and for rapid translation of results to clinical application.

Talented investigators representing a wide variety of scientific disciplines are performing important basic and clinical studies of retinal disease, glaucoma, infectious diseases of the eye, and other physically and economically debilitating visual disorders. These efforts have recently led to significant research advances, demonstrating the need for continuation and strengthening of the intramural program. Through studies of the development of visual tissues in embryos, one investigator has increased our understanding of congenital diseases of the eye and of refractive errors, the most common form of visual impairment. The first description of color vision at the level of a single nerve cell has been accomplished by another investigator, providing much needed information for the understanding of normal and abnormal retinal function. In addition, the possibility of long term and even permanent management of retinal degeneration has been indicated in experiments which have resulted in the reversal of a degenerative disease of the retina. Another Institute scientist, in collaboration with investigators from the National Institute of Arthritis and Metabolic Diseases, has developed a simple technique for the biochemical diagnosis of cystinosis, a hereditary disorder. The discovery by another investigator that a certain drug can increase the rate of aqueous humor formation has advanced the Institute's research on glaucoma.

In terms of organization and program context, the intramural program has been strengthened by the appointment of a Clinical Director; the centralization of technical and administrative support and the appointment of an administrative officer; the establishment of a new eye clinic in the NIH Clinical Center, and major renovations and equipment purchases for new laboratory facilities.

In addition, the Institute is currently exploring a plan to intensify its clinical research program at reduced cost by renting nearby housing facilities to maintain patients whose condition does not require bed care. Expenses under this arrangement would include the cost of rented facilities, and travel and subsistence for patients and a parent or guardian. These patients are needed if research is to go forward to the fullest extent within the capabilities of NEI staff and the facilities of the Clinical Center.

Program Plans 1972

In 1972 additional laboratory facilities now under renovation will be available for the expansion of intramural research programs. These facilities will permit the Institute to undertake a major expansion of efforts in the anatomical, physiological, and biochemical investigation of the visual system through the extension and exploitation of such recent advances as were previously mentioned. Implementation of this program will require increased capabilities in biochemistry, neurophysiology, and electronmicroscopy. In addition, technical personnel are required to provide the necessary support to attract competent senior investigators in these areas.

The budget request of $3,075,000 for 1972 includes an increase of 10 new positions to permit implementation of these plans. The requested positions will be financed through a reduction of equipment expenditures and the utilization of funds budgeted in 1971 to equip the newly assigned laboratory space. Also included are increases of $42,000 for annualization of 1971 pay increase costs, $34,000 for the annualization of positions new in 1971, $12,000 for within-grade salary advances, $2,000 for an extra-day pay costs, and $60,000 for the National Institutes of Health management fund for centrally furnished services.

Collaborative Research and Development

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	--	---	--	---	--	---
Other expenses.....	--	$1,332,000	--	$1,332,000	--	---
Total.....	--	1,332,000	--	1,332,000	--	---

This activity provides support for research and development contracts with universities, non-profit research laboratories, or industrial concerns in areas where there is promise of improving and accelerating the application of knowledge and technology to the management of diseases of the visual system. The Institute is currently emphasizing those areas which will extend and compliment the intramural research effort through the support of NEI staff-directed projects aimed at basic improvements in current methodologies and techniques utilized for research, diagnosis and health care and prevention systems.

In 1972 the Institute will use funds appropriated for this activity to implement a major new effort to exploit opportunities for significant advances in the areas of corneal and retinal diseases and glaucoma. Efforts in such areas as the development of artificial tears, laser "spot welding" of the retina, and the development of new microsurgical techniques offer the possibility of rapid payoff and a significantly improved capability in the treatment of these visual disorders. Development of new examination methods for retinal disorders through advances in bioengineering and instrumentation, development of animal models for retinal disease, combination drug therapy of glaucoma, and purification of ocular tissue fractions

62-645 O - 71 - pt. 3 - 65

are other areas which will be considered for funding.

The budget request of $1,332,000 will provide the same level of support as in 1971.

Biometry, Epidemiology and Field Studies

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	15	$218,000	15	$230,000	--	+$12,000
Other expenses.....	--	151,000	--	155,000	--	+4,000
Total.....	15	369,000	15	385,000	--	+16,000

This activity provides support for studies on the incidence and prevalence of visual disorders, the application of statistical techniques to analyses of the distribution and natural history of visual disorders among selected population groups, and consultation to Institute staff on mathematical and statistical matters, data processing, and computer technology.

In 1972, efforts toward defining the extent of visual problems by disease category will be continued and strengthened through collaboration with the National Health Survey. Through analysis of data on twins collected by the NEI and others, an effort will be undertaken to rank the major eye diseases as to which are more associated with heredity and which are more associated with environmental factors. If one or more of the major eye diseases is found to be importantly related to environmental factors, the program will then concentrate epidemiologic studies in that direction with emphasis on variations in geographic prevalence and identification of factors associated with high prevalence within individual geographic areas.

The budget request of $385,000 includes increases of $8,000 for annualization of 1971 pay increase costs, $1,000 for one extra day of pay costs, $3,000 for within-grade salary increases, and $4,000 for the National Institutes of Health Management Fund for centrally furnished services.

Review and Approval

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	24	$349,000	24	$382,000	--	+$33,000
Other expenses	--	420,000	--	439,000	--	+19,000
Total	24	769,000	24	821,000	--	+52,000

Funds requested for this activity will provide support for professional and technical staff responsible for the administration of the Institute's research and training grant programs. Responsibilities of staff associated with this activity include routine processing of grant applications and the preparation of recommendations and analyses of grant programs for consideration by the Director and the National Advisory Eye Council.

The budget request of $821,000 includes increases of $26,000 for annualization of 1971 pay increase costs, $2,000 for one extra day of pay costs, $5,000 for within-grade salary increases, $18,000 for the National Institutes of Health Management Fund for centrally furnished services, and $1,000 for increased costs of using the Federal Telecommunications System.

Program Direction

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	13	$254,000	13	$285,000	--	+$31,000
Other expenses	--	101,000	--	105,000	--	+4,000
Total	13	355,000	13	390,000	--	+35,000

This activity provides for the overall administration and direction of Institute programs. The Director and his staff provide professional leadership and technical guidance to the varied activities of the Institute.

In 1972 the Institute plans to promote its capability for effective program management through further training of personnel and centralization of administrative services.

The budget request of $390,000 includes an increase of $9,000 for annualization of 1971 pay increase costs, $1,000 for one extra day's pay costs, $18,000 for annualization of positions new in 1971, $3,000 for within-grade salary increases, and $4,000 for the NIH Management fund for centrally furnished services.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Research Grants (Public Health Service Act, Title IV, Part F)

1971			1972	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$20,754,000	Indefinite	--	$23,535,000

Purpose: The research grants program of the National Eye Institute supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system to increase the knowledge necessary to solve vision and vision-related problems of mankind.

Explanation: The Institute sponsors over 400 research grant projects at universities, hospitals, research institutions, and other private or non-profit institutions. Projects vary from the activities of an individual scientist to broadly-based programs that integrate the effort of groups of investigators in a variety of scientific disciplines.

Accomplishments in 1971: In 1971 the National Eye Institute supported approximately 449 research grants in a concerted effort to increase knowledge on many fronts in the field of vision research. Institute grantees added important basic knowledge to our understanding of the visual system, and have developed new diagnostic and therapeutic techniques to enhance the prevention and control of retinal disorders, glaucoma, cataract, and other disabling conditions of the eye and visual system.

Objectives for 1972: In 1972 the Institute will continue to support essential ongoing research funded under this activity and will award approximately 92 competing grants to outstanding investigators in the field of vision research. Areas to be emphasized include glaucoma, diseases of the retina and cornea, and oculomotor disorders.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Training Grants (Public Health Service Act, Title IV, Part F)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$2,225,000	Indefinite	--	$2,225,000

Purpose: Training grants provide support to academic institutions for the establishment, improvement or expansion of training programs to prepare scientists for research and academic careers in the field of vision research.

Explanation: Support for this activity is funded through the grant mechanism, under the direction of the National Eye Institute extramural staff.

Accomplishments in 1971: In 1971 approximately 47 grants in the amount of $2,225,000 were awarded to institutions to train research investigators in the area of vision and visual disorders.

Objectives for 1972: The budget request for 1972 will provide for the support of an estimated 42 training grants, representing approximately 215 full-time equivalent trainees. Training programs are linked to the objective of providing medical schools with advanced personnel to conduct programs in investigative ophthalmology.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Fellowships (Public Health Service Act, Title IV, Part F)

1971			1972	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$1,676,000	Indefinite	--	$876,000

Purpose: The National Eye Institute fellowship program supports the national vision research effort through the provision of advanced research training in sciences related to the eye and the visual system.

Explanation: The program sponsors advanced research training for individuals whose career development extends from the immediate postdoctoral period through advanced stages of research attainment. Awards are made to individuals in the form of postdoctoral fellowships, special fellowships, research career development awards, and research career awards.

Accomplishments in 1971: In 1971 approximately 123 fellowships in the amount of $1,676,000 were awarded, improving the nation's vision research capability in the fields of anatomy, neuro-ophthalmology, physiology, optics, and ophthalmic pathology.

Objectives for 1972: The estimate for 1972 will provide for approximately 52 fellowship awards, a decrease of 71 awards from 1971.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Laboratory and Clinical Research (Public Health Service Act, Title IV, Part F)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
51	$2,925,000	Indefinite	61	$3,075,000

Purpose: This activity encompasses the in-house laboratory and clinical research program conducted by staff of the National Eye Institute. The program supports integrated laboratory and clinical studies related to the causation, diagnosis, therapy and prevention of retinal disease, glaucoma, cataracts, and other visual disorders.

Explanation: Approximately 50 professional and technical personnel are supported in this activity. Funds are provided for equipping and operating modern facilities for scientific research, including support for clinical studies utilizing out-patient facilities and 26 beds in the NIH Clinical Center.

Accomplishments in 1971: In 1971 a new eye clinic was established in the NIH Clinical Center, a laboratory of vision research and clinical branch based on the ophthalmology program transferred from NINDS in 1970 was established, and scientific and technical support services were centralized under an administrative officer. Significant scientific advances were made in the areas of hereditary disease, immunology, glaucoma, and retinal disease.

Objectives for 1972: Additional laboratory facilities currently under renovation will permit the Institute to undertake a more extensive effort in the anatomical, physiological, and biochemical investigation of the visual system. Particular emphasis will be placed on investigations of the retina.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Collaborative Research and Development (Public Health Service Act, Title IV, Part F)

1971			1972	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$1,332,000	Indefinite	--	$1,332,000

Purpose: This activity supports the Institute's targeted research and development program on the prevention, diagnosis and treatment of visual disorders.

Explanation: Research and development supported by this activity is funded through contracts and performed in collaboration with other federal agencies, universities, non-profit laboratories, and industrial concerns.

Accomplishments in 1971: In 1971 the Institute continued its support of efforts to improve diagnostic techniques and to evaluate the need for vision manpower. In addition, Institute staff initiated programs to improve the scientific basis for visual care, particularly in instrumentation technology and examination procedures aimed at early detection and prevention of visual disorders.

Objectives for 1972: In 1972 the Institute will use funds appropriated for this activity to maintain its targeted research emphasis initiated in 1971 and implement a major new collaborative effort in the areas of corneal and retinal disease and glaucoma.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Biometry, Epidemiology and Field Studies (Public Health Service Act, Title IV, Part F)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
15	$369,000	Indefinite	15	$385,000

Purpose: This activity constitutes a program for the collection, analysis and dissemination of statistical data on visual disorders in selected population groups.

Explanation: Support is provided for the Office of Biometry and Epidemiology. The Office is staffed by 15 professional and technical personnel responsible for the design and performance of mathematical and statistical studies on the incidence and prevalence of visual disorders.

Accomplishments in 1971: With the appointment of the Chief, Office of Biometry and Epidemiology, this activity has been strengthened to provide biostatistical consultation for in-house and extramural programs on a continuing basis. Selected population groups have been studied to determine the role of inheritance, age and other factors of potential significance to the etiology of glaucoma, myopia, and other visual disorders.

Objectives in 1972: During 1972 the Office of Biometry and Epidemiology plans to implement clinical field studies to further investigate environmental and genetic factors related to the occurrence of ocular disease, including evaluation of possible therapeutic and preventive measures.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Review and Approval (Public Health Service Act, Title IV, Part F)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
24	$769,000	Indefinite	24	$821,000

Purpose: This activity provides scientific and administrative direction for all grant supported research and training programs of the National Eye Institute.

Explanation: Support is provided for a staff of 24 professional and administrative personnel to evaluate and administer the extramural programs of the Institute. Positions receiving support include Health Scientist Administrators, Grants Management Specialists, and related clerical personnel.

Accomplishments in 1971: During 1971 the review and approval function continued to meet Institute needs for leadership of extramural visual research programs.

Objectives for 1972: During 1972 the Institute will continue its efforts to enhance the availability of needed information on grant programs. Specifically, the Institute plans to develop an improved information system to meet the needs of scientific and administrative personnel responsible for monitoring and and evaluating extramural programs.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Program Direction (Public Health Service Act, Title IV, Part F)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
13	$355,000	Indefinite	13	$390,000

Purpose: This activity provides support for the Institute Director and his immediate staff.

Explanation: Funds are made available for the Institute Director and personnel assigned to his immediate office to provide overall scientific and administrative direction of Institute programs. Positions supported include Director, Executive Officer, Budget Officer, and associated clerical and administrative staff.

Accomplishments in 1971: The National Eye Institute became operational with the appointment of its Director in January of 1970. Under his leadership in 1971 the administrative structure of the Institute was strengthened to provide service and support for the in-house and extramural vision-research programs of the Institute. Several important administrative positions were filled to provide a more effective capability for management of these programs.

Objectives for 1972: During 1972 the Office of the Director will continue to function as the focal point for providing direction and coordination to Institute programs.

New Positions Requested
Fiscal Year 1972

	Grade	Number	Annual Salary
Laboratory and Clinical Research			
Clinical Ophthalmologist.....	GS-14	1	$ 20,815
Physiologist.....	GS-13	1	17,761
Biochemist.....	GS-13	1	17,761
Electronmicroscopist.....	GS-12	1	15,040
Technician.....	GS-9	3	31,410
Administrative Assistant.....	GS-7	1	8,582
Clerk Typist.....	GS-5	2	13,876
Total, new positions.....		10	125,245

MONDAY, MAY 10, 1971.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

WITNESSES

DR. DAVID P. RALL, DIRECTOR

DR. ROBERT W. BERLINER, DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
GEORGE M. KINGMAN, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
BENJAMIN A. ORRINGER, BUDGET OFFICER, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
B. FRANK GARDNER, ACTING ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

National Institute of Environmental Health Sciences

Object Classification (in thousands of dollars)

Identification code 09-30-0862-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	2,064	2,683	2,823
11.3	Positions other than permanent	50	60	60
11.5	Other personnel compensation	18	22	22
	Total personnel compensation	2,132	2,765	2,905
12.1	Personnel benefits: Civilian employees	191	282	295
21.0	Travel and transportation of persons	149	166	242
22.0	Transportation of things	14	25	30
23.0	Rent, communications, and utilities	335	512	807
24.0	Printing and reproduction	19	25	33
25.0	Other services	1,695	2,513	4,498
26.0	Supplies and materials	468	635	927
31.0	Equipment	567	783	1,277
41.0	Grants, subsidies, and contributions	11,684	12,361	14,025
99.0	Total obligations	17,254	20,067	25,039

Personnel Summary

Total number of permanent positions	202	235	263
Full-time equivalent of other positions	12	12	12
Average number of all employees	214	230	248
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0862-0-1-651		1970 actual	1971 est.	1972 est.
	Program by activities:			
	1. Grants:			
	(a) Research	6,990	8,980	10,478
	(b) Fellowships	215	264	264
	(c) Training	3,622	3,117	3,283
	Total grants	10,827	12,361	14,025
	2. Direct operations:			
	(a) Laboratory and clinical research	3,561	5,355	7,139
	(b) Collaborative research and development	1,005	1,484	2,995
	(c) Review and approval	344	477	488
	(d) Program direction	388	390	392
	Total direct operations	5,298	7,706	11,014
	Total program costs, funded [1]	16,125	20,067	25,039
	Change in selected resources [2]	1,129	----------	----------
10	Total obligations	17,254	20,067	25,039
	Financing:			
25	Unobligated balance lapsing	164	738	----------
	Budget authority	**17,418**	**20,805**	**25,039**

Program and Financing (in thousands of dollars)

Identification code 09-30-0862-0-1-651		1970 actual	1971 est.	1972 est.
	Budget authority:			
40	Appropriation	18,328	20,620	25,039
40	Portion withdrawn (Public Law 91-204, sec. 410)	−755	----------	----------
41	Transferred to other accounts	−155	----------	----------
43	**Appropriation (adjusted)**	**17,418**	**20,620**	**25,039**
46.10	**Proposed transfer for wage-board pay increases**	----------	**9**	----------
46.20	**Proposed transfer for civilian pay act increases**	----------	**158**	----------
46.30	**Proposed transfer for military pay act increases**	----------	**18**	----------
	Relation of obligations to outlays:			
71	Obligations incurred, net	17,254	20,067	25,039
72	Obligated balance, start of year	12,222	12,118	12,705
74	Obligated balance, end of year	−12,118	−12,705	−14,680
77	Adjustments in expired accounts	−394	----------	----------
90	Outlays, excluding pay increase supplemental	16,964	19,298	23,061
91.10	Outlays from wage-board supplemental	----------	9	----------
91.20	Outlays from civilian pay act supplemental	----------	155	3
91.30	Outlays from military pay act supplemental	----------	18	----------

[1] Includes capital outlay as follows: 1970, $434 thousand; 1971, $643 thousand; 1972, $723 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $6,267 thousand; 1970, $7,396 thousand; 1971, $7,396 thousand; 1972, $7,396 thousand.

NOTES

Includes $140 thousand in 1972 for activities previously financed from (in thousands of dollars):

	1970	*1971*
National Cancer Institute	86	--
Division of Biologics Standards	--	135

Includes $162 thousand in 1971 and $162 thousand in 1972 for activities previously financed from: Research resources, 1970, $162 thousand.

Excludes $22 thousand in 1972 for activities transferred to: Office of the director, 1970, $23 thousand; 1971, $22 thousand.

Excludes $274 thousand in 1972 for activities transferred to Health Manpower, 1970, $274 thousand; 1971, $274 thousand.

INTRODUCTION OF DR. RALL AND ASSOCIATES

Mr. FLOOD. The committee will come to order.

We continue with the National Institutes of Health, and we have now the Institute of Environmental Health Sciences. The presentation will be made by Dr. David P. Rall.

I see we have your biographical sketch which we will place in the record.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH OF DAVID P. RALL, M.D., PH. D.

Position: Director, National Institute of Environmental Health Sciences.
Birthplace and date: Aurora, Ill., August 3, 1926.
Education:
B.A., North Central College, 1946.
M.S., Northwestern University, 1948.
Ph.D., Northwestern University, 1951.
M.D., Northwestern University, 1951.
Experience:
Director, National Institute of Environmental Health Sciences, 1971–present.
Associate Scientific Director for Experimental Therapeutics, National Cancer Institute, 1966–71.
Chief, Laboratory of Chemical Pharmacology, National Cancer Institute, 1963–69.
Head, Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch, National Cancer Institute, 1958–63.
Scientist, Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch, National Cancer Institute, 1955–58.
Scientist, Laboratory of Chemical Pharmacology, National Cancer Institute, 1953–55.
Research associate in pharmacology, Northwestern University, 1950.
Assistant in pharmacology, Northwestern University, 1949–50.
Baxter fellow in pharmacology, Northwestern University, 1947–49.
Association memberships:
Society for Experimental Biology and Medicine.
American Society for Pharmacology and Experimental Therapeutics.
American Association for Cancer Research.
Washington Academy of Sciences.
American Society for Clinical Investigation.
Fellow, American Association for Advancement of Science.
Special awards, citations, or publications:
Chairman, HEW Departmental Committee on Drug Research and Regulations, 1970.
Editorial Board, Pharmacological Reviews, 1969–present.
Chairman, National Institute of General Medical Science Pharmacology-Toxicology Review Committee, 1967–69.
Editorial Board, Cancer Research, 1964–present.
Member, Graduate Council, George Washington University, 1962–present.
Editorial Board, Proceedings of the Society for Experimental Biology and Medicine, 1962–65.
Lecturer in physiology, Medical School, George Washington University, 1958–62.
Meritorious Service Medal; Dr. Rall has authored and coauthored many published papers relating to comparative pharmacology, cancer chemotherapy, blood-brain barrier, blood CSF barrier, pesticide toxicology, and drug research and regulation.

Mr. FLOOD. Would you like us to meet some of your people?

Dr. RALL. I would like to introduce Mr. Kingman and Mr. Orringer.

Mr. FLOOD. If they are called on, have their biographical sketches placed in the record also.

(The information follows:)

BIOGRAPHICAL SKETCH OF MR. GEORGE M. KINGMAN

Position: Executive Officer, National Institute of Environmental Health Sciences.
Birthplace and date: Ft. Leavenworth, Kans., December 25, 1929.
Education: B.S. Northwestern University, 1955.
Experience:
Executive Officer, National Institute of Environmental Health Sciences, 1967–present.
Assistant Executive Officer, National Institute of Mental Health, 1963–67.
Administrative Officer for Extramural Programs, National Institute of Mental Health, 1961–63.
Budget Officer, National Institute of Mental Health, 1958–61.
Budget Examiner, National Institute of Dental Research, 1958.
Budget Examiner (trainee), National Institute of Neurological Diseases and Blindness, 1957–58.
Management Intern, Division of Business Operations, 1956–57.
Private industry, 1955–56.
Military service, 1950–53.
Association memberships:
American Society for Public Administration.
The Academy of Political Science.
Special awards, citations, or publications: 1962 Department of Health, Education, and Welfare Candidate for William A. Jump Award.

GENERAL STATEMENT

Mr. FLOOD. You have a prepared statement, Doctor. How do you wish to proceed?

Dr. RALL. May I read it?

Mr. FLOOD. Suppose you do.

Dr. RALL. Mr. Chairman and members of the committee, I am pleased for the opportunity to speak to the committee about the National Institute of Environmental Health Sciences and to supply you with information which will help you in making the budgetary decisions for the coming year.

During the few weeks that I have been Director of NIEHS, I have thoroughly reviewed the personnel situation, the facilities, the programs, and the philosophy of the Institute.

Mr. FLOOD. How long have you been on board, Doctor?

Dr. RALL. Technically since the 13th of April.

THE MISSION AND ACCOMPLISHMENTS OF NIEHS

It is indeed a tribute to my predecessor, Dr. Paul Kotin, to report to you the results of this review. The NIEHS has progressed remarkably during its first 5 years of existence. Strictures on funding and employment have restrained the growth of programs whose inherent quality and importance should in another time have developed more rapidly. Nevertheless, major strides have been made. The foundation established under Paul Kotin's direction and the substantial edifice built by him will long support programs of urgent national need.

The mission of our Institute is to provide a scientific foundation to assist the control agencies in their efforts to resolve environmental health problems. We seek to identify and better understand the chemical, physical, and biological factors in the environment which are most likely to affect man's health. For agencies like the newly created Environmental Protection Agency, this knowledge forms the basis for establishing effective control measures.

Environmental health problems can arise in unpredictable ways. In fact, it seems that is true more often than not; therefore, the Institute programs have been organized with flexibility in mind. Whether the problem at hand is a new and urgent one requiring the immediate marshalling of resources or one whose subtlety and ubiquity requires a long-term investment of resources, NIEHS is able to act effectively. I have long been convinced that this dual approach has a synergism of its own. Long-term research can be stimulated by ad hoc problem-solving efforts, and urgent problem solving is expedited because of the related basic research.

During my research career at the National Cancer Institute, I was deeply involved in such a mixture of long term basic and short term pragmatic research programs, and I intend to continue the development of this effective approach at the NIEHS.

There is another characteristic of this Institute which I hope to maintain and refine: that is, the recognition that no single classification adequately encompasses the many interactions which can yield environmental situations with potential deleterious human health effects. It is not enough to base programs exclusively upon study of agents, or only on study of cellular effects, or simply on study of disease endpoints, or on the environmental sector from which they originate; rather, each of these categories must be encompassed in a broad approach to the study of environmental health.

These are generalizations about the organization Paul Kotin and his staff established. I would now like to cite briefly a few specific examples from the past year which illustrate the way in which the Institute strives to carry out its mission.

THE "DETERGENTS DILEMMA"

You are no doubt familiar with some of the problems associated with developing chemicals to satisfy the conflicting demands of the American housewife for clean clothes on one hand and the guardians of public health and the conservationists who wish to preserve our health and our ecological balance on the other hand. NIEHS has had a notable part to play in the resolution of this dilemma during 1970 and 1971.

The detergents industry developed a compound known as NTA (its chemical name is nitrilotriacetic acid) in the hope of using it as a substitute for the troublesome poly phosphates traditionally used. They conducted environmental and toxicological studies which showed that NTA was biodegradable and by itself nontoxic. They envisioned use of more than 1 billion pounds of the chemical in household detergents by 1975.

Before irreversible commitments were made, NIEHS was asked by the Federal Water Quality Administration (FWQA) to study the toxicity of NTA in chemical association (chelates) with some heavy metals which may be present in water supplies. The Institute found that chelates, combinations of cadmium and methyl mercury, with NTA appeared to be more toxic than the metal salts alone. When the results were known, representatives of the detergents industry met

62-645 O—71—pt. 3——66

with officials of EPA and the Surgeon General's office and voluntarily modified plans for immediate use of NTA.

This case illustrates two important points: First, basic research programs in teratology and pharmacology enabled NIEHS to clarify an urgent and immediate national problem; second, the results led to constructive scientific action on industry's side to confirm or further advance the elucidation of this potential health hazard.

Mr. FLOOD. How did this thing surface all of a sudden? Detergents have been around a long time. All of a sudden there are headlines in the news media and everybody knows about it. It is on everybody's tongue and nobody seemed to know a thing about it for years. What happened?

Dr. RALL. It is just in the last few years that the role of phosphates in stream pollution was recognized and the detergent industry has developed this compound, NTA as a substitute. It has been used just to a very limited extent.

Mr. FLOOD. I suppose you fellows suspected at once when they used it it should be looked at?

Dr. RALL. Absolutely. In fact we believe that it is mutually advantageous for scientists to study these new compounds prior to industry's investing large amounts in "tooling up" costs.

MERCURY INTOXICATION

Another Institute program which gained my early attention concerns studies of organic mercury compounds. You are probably aware of the heightened concern during the past year over mercury's possible effects on man. That concern resulted from the realization that metallic mercury in water supplies is not stable or inert as we once assumed, but, rather that it is converted by bacterial action into methyl mercury —an organic compound readily taken up in the food chain which reaches man.

Mr. FLOOD. Does the body carry a certain amount of mercury anyhow?

Dr. RALL. Yes, we are all exposed to very low levels of mercury.

Mr. FLOOD. And everybody undoubtedly has a certain level of mercury?

Dr. RALL. Yes.

Mr. FLOOD. It is a question of degree as to when it becomes dangerous?

Dr. RALL. That is right.

Mr. FLOOD. Mr. X has exceeded the minimum. How will it affect the body?

Dr. RALL. In a very frightening way because their effects are irreversible. The Japanese about 10 years ago experienced methyl mercury problems in one of their bays, Minamata Bay.

Mr. FLOOD. That is where the people were consuming the fish?

Dr. RALL. Yes, which had the mercury in it. They got nerve damage.

Mr. FLOOD. Does it center in one place?

Dr. RALL. It is fairly well distributed in the body.

Mr. FLOOD. What is the normal? At what point does it become dangerous?

Dr. RALL. In terms of how much you take in the body?

Mr. FLOOD. Yes.

Dr. RALL. Something less than $^3/_{10}$ of a miligram a day is the maximum amount you should take in. This would correspond to eating about 6 ounces of contaminated swordfish every day. This would be the point where you would begin to get into trouble.

MERCURY IN TUNA AND OTHER FISH

Mr. FLOOD. What happened to our friend, the tuna? Is that off the market?

Dr. RALL. It is an interesting story.

Mr. FLOOD. Was it just the canned tuna?

Dr. RALL. No live tuna has mercury, also, but as fish grow they eat smaller fish which are contaminated with methyl mercury. They accumulate it and then as they grow older the bigger fish have more. The swordfish, which is about 500 pounds, has much more than the tuna because most of our commercial tuna are about 50 pounds.

Mr. FLOOD. Where are we regarding tuna right now?

Dr. RALL. As I understand, the fishermen are concentrating on catching 50 and 75 pound tuna which are quite safe and are turning down the 500 pound tuna which the sports fishermen like.

Mr. SMITH. For a couple of years they were wrought up about fish in the rivers containing mercury, and they were blaming the farmers because they use a mercury solution on seed corn and surface water drains to the nearby streams. Then later we find out fish way out in the ocean which were never exposed to the river water involved contain more mercury than those in the rivers.

Why was it a couple of years before they discovered that?

Dr. RALL. It may be runoff from the land because many of the tuna and swordfish are taken off the Continental Shelf not too far out. In fact, however, we do not know yet.

Mr. SMITH. It didn't run off the land where the corn was planted. The water out in the ocean is greatly diluted with rain falling in the ocean and water which ran off there a good many years ago.

Dr. RALL. But there was some methyl mercury in those fish.

Mr. SMITH. But less in the river fish than those in the ocean.

Dr. RALL. Again it is the concentrating business. As a fish eats more contaminated fish of plankton, or whatever the fish eats, you concentrate more and more mercury. So a little fish, a river fish, which is maybe 5 pounds, would have a relatively low level.

Mr. FLOOD. Proceed.

STUDY OF METHYL MERCURY

Dr. RALL. The NIEHS approach to study of methyl mercury demonstrates important points about the way in which the Institute functions. This study involves a multifaceted, multidisciplined approach which makes the most efficient use of the broad array of scientific disciplines represented on the Institute staff. The full range of fundamental biological effects of methyl mercury in man is being examined in this effort:

> Pathologists and veterinarians are examining in animal models, at both the gross and molecular levels, the pathologic changes from ingestion of the compound to determine fundamental mech-

anisms of action in brain, kidney, liver, spleen and other organs and to relate blood concentration of the metal to toxicity.

Mr. FLOOD. It may not be your shop, but what is the function of the spleen?

Dr. RALL. The spleen destroys old red cells in man and also has some function in the mouse for instance, in making new blood cells.

Mr. FLOOD. Apparently it is not a very essential thing; is it?

Dr. RALL. No; it is not.

Biochemists are studying the effects of methyl mercury on cell components and enzyme systems;

Pharmacologists are studying the effects of the compound on fetal development in experimental animals.

All these efforts seek methods for earlier diagnosis and possible reversal and repair of what today are the inevitable and dreadful results of methyl mercury ingestion.

STUDIES OF LEAD AND NITRATE-NITRITE

Lead is another heavy metal which can be toxic; we have been studying and now understand better the way the body handles lead during and following chronic exposure.

Mr. FLOOD. Does the body acquire lead other than by eating paint off walls or something?

Dr. RALL. We probably acquire most of our lead by inhalation from lead fumes; this is so particularly in cities with a lot of automobiles.

Mr. MICHEL. What did I read about several employees in HEW raising questions about the lead poisoning prevention program? I had a release on my desk this morning.

Dr. RALL. I don't know anything about that.

Mr. MICHEL. It was some doctors in HEW. You don't know about that, Mr. Miller?

Mr. MILLER. No.

(Discussion off the record.)

Mr. FLOOD. Proceed.

Dr. RALL. Another problem relates to nitrate-nitrite exposure. We, in collaboration with our university-based environmental health sciences centers, have explored and delineated the extent of disease from nitrite exposure. Specifically, these investigations indicate that current levels in baby food in the United States present no health problem.

MERCURY HAZARDS IN HOUSEHOLD GOODS

Mr. FLOOD. I mentioned a moment ago, off the record, a certain type of tooth brush you people have ruled off the market because of potential danger from mercury.

How did you stumble on that?

Dr. RALL. That was an action of the Food and Drug Administration.

Mr. FLOOD. Did some spies tell them?

Dr. RALL. I think it was known it contained mercury. Mercury is very good for preventing the growth of mold. Many products have low concentrations of methyl mercury.

Mr. FLOOD. Let us ask you the same thing about large food chains. Although we have been hearing about this for some time—maybe a year

or 2—very recently certain of the large food chains have agreed to remove from the market certain English tableware because of the clear hazard of lead poisoning. How would you happen to pick that up, a plate instead of a water pitcher? Didn't we also have trouble with some California people who manufactured tableware of the same sort?

Dr. BERLINER. I think I can answer the question how we got onto this particular one. Several children were admitted to a hospital in Canada with severe lead poisoning, and it turned out that the lead poisoning had come from fruit juice that had been stored in a lead glazed container.

Mr. FLOOD. A lead glazed container?

Dr. BERLINER. Yes. The glaze put on the earthenware contained lead.

Dr. RALL. There was inadequate firing of the earthenware.

This is a fascinating story. It was apple juice, and the mother kept the jug full of apple juice for the children to drink when they came home. Apple juice is acid enough to remove the lead from the glaze.

Mrs. REID. If the Chairman will yield, don't some cosmetics contain mercury?

Dr. RALL. I don't know.

Mrs. REID. I thought I had read that there are some that contain small amounts of mercury.

MERCURY AND ITS COMPOUNDS

Dr. RALL. There are two things to remember. One is the metallic mercury or the regular salts of mercury are not terribly toxic. Mercury salts are not very good but they are not very bad either. It is the organic mercury compound, like methyl mercury that is very toxic.

Mr. FLOOD. You mentioned two kinds of mercury. What are they?

Dr. RALL. One is metallic mercury, the regular salts, the silver metal or quicksilver with chlorine or something like that. They act very differently.

Mr. FLOOD. And the other one?

Dr. RALL. The organic compound with carbon attached.

Mrs. REID. You are not aware of any cosmetics containing mercury?

Dr. RALL. They may have some elemental mercury and mercury salts, but it is the organic mercury that is dangerous.

Mr. MILLER. May I make one point, Mr. Chairman? This Institute has no inspection or enforcement function. The decision as to whether or not something stays on the market is a determination made by the Food and Drug Administration.

Dr. RALL. We are very interested in the specific problem you raised—how these potential hazards come to somebody's attention. This is a very serious problem. It is apparent that in the future we must be more aggressive in seeking and finding these potential problems. I am setting up a special group within the Institute whose job it will be to search the chemical literature and maintain a continuing overview of the field and find out what is going on.

Mr. FLOOD. You are a doctor of what?

Dr. RALL. Doctor of medicine and also of pharmacology.

Mr. FLOOD. Of course pharmacology is your thing?

Dr. RALL. Right.

These efforts emphasize the role NIEHS is playing in performing broadly based fundamental studies on the environmental fate and potential adverse effects of common chemicals. They demonstrate the ability of this Institute to assemble quickly an ad hoc team of scientists of many disciplines to contribute their expertise in resolution of an urgent national problem.

With your help, I hope that we can strengthen and extend this important Institute capability.

1972 BUDGET

More than $25 million is requested for operations of this Institute during 1972. That figure is approximately a $5 million increase over this year's operating level. I can assure you that what appears to be a major increase is needed and in fact is modest in relation to the problems which demand our solution.

USE OF NEW FACILITIES

We shall soon begin to use laboratory and special purpose facilities which have been completed during the present fiscal year. These facilities represent the first major addition of laboratory space to our intramural program. We have earmarked nearly $2 million of our requested increase and all 28 proposed new positions to begin to take advantage of the new and unique research capabilities and opportunities made possible by these new facilities. There are three buildings which make up these new facilities: An animal holding facility, an aerotoxicology research facility and a laboratory building.

Mr. FLOOD. By building what do you mean? A Taj Mahal of some sort? How big are these buildings?

Mr. KINGMAN. A round figure for the construction cost is about $3 million for these additional buildings.

Mr. FLOOD. Each?

Mr. KINGMAN. In total. It was built as a complex of three buildings.

Mr. FLOOD. Around a plaza or a center? We are still concerned about scattering buildings around and people running back and forth from one to another.

Mr. KINGMAN. The reason there are three separate structures is that the experiments carried out in each must be isolated from the experiments carried out in the others. The number of buildings was determined by the research that is to be carried out within each, rather than an effort to fulfill an esthetic concept.

For example, as Dr. Rall will discuss later, many of the experiments which will be carried out involve a deliberate exposure of animals over a long time to low doses of toxic substances singly and in combination. It is important that these experiments not be ruined by unintentional contamination from other substances.

Mr. FLOOD. You do have a complex of three buildings?

Mr. KINGMAN. Yes.

Mr. FLOOD. And they are what?

SPECIAL ANIMAL HOLDING FACILITY

Dr. RALL. One is a special animal holding facility.

Mr. FLOOD. What does that mean?

Dr. RALL. We want to keep the experimental animals for their lifetime and keep them under very highly controlled environmental conditions from early years up, and expose them deliberately to various toxic substances.

Mr. FLOOD. So you put a calf in this building——

Dr. RALL. These are mostly mice and rats.

Mr. SMITH. Are most born by ceasarian operation?

Mr. FLOOD. What is the benefit of that?

Dr. RALL. They start out with almost no germ contamination in what is essentially a germ-free environment.

Mr. FLOOD. Where is this located?

Dr. RALL. North Carolina.

Mr. FLOOD. What is peculiar or special in the body structure, for your purposes, of mice and rats as distinguished from any other animal? Why a mouse?

Dr. RALL. I suspect it is appropriate you ask this in the appropriation hearing. It is because they are inexpensive. They take very little space to house and have only about a 2-year life span.

The animal building will permit us to isolate test animals in environments over which we have nearly absolute control. The air in this facility will be repeatedly filtered and exchanged every 5 or 6 minutes to insure its purity; workers entering the area will take elaborate precautions to prevent introduction of unwanted infectious agents; temperature, lighting, and humidity are under special control. For the first time, we will be able to begin a whole new range of experiments to determine the specific and unique effects of a vast series of environmental components about which previously we could only speculate.

AEROTOXICOLOGY FACILITY

In the aerotoxicology facility there will be exposure chambers in which laboratory animals can be exposed to suspected toxic agents to which man is exposed in aerosol form.

Mr. FLOOD. What is aerosol?

Dr. RALL. This is when a compound is blasted into the air so it becomes essentially airborne. It is forced into the air under pressure and vaporized.

Mr. FLOOD. Who would want to do that and for what purpose?

Dr. RALL. We use it in shaving cream and other pressurized cans.

In these chambers we hope to gain better understanding of the effects of many common aerosol products ranging from hairsprays to bug bombs and other pesticide sprays.

Adjacent to the specialized facilities are additional laboratories of the most modern design.

Mr. FLOOD. Can you walk from one building to the other?

Dr. RALL. Yes.

Mr. FLOOD. Are they all going to be in the triangle?

Dr. RALL. Yes.

Mr. FLOOD. I gather they are a complex?

RESEARCH ON MICROWAVES AND NOISE

Dr. RALL. A group attached to our other buildings. We will be able to begin intramural research on important physical agents in the environment including microwaves and noise, as well as extend ongoing research.

Mr. FLOOD. You treat that very casually.

Dr. RALL. No, sir; it is important.

Mr. FLOOD. Why don't you say something more about it?

Dr. RALL. I think these two areas—noise and microwave research—are extremely important ones which have received inadequate attention by the scientific community. We think these new facilities will permit us to make real progress in these areas.

Mr. FLOOD. We have heard very little, until the last relatively few years, about pollution and ecology. We understand pollution is not only water and air, but several other things, including noise. How can microwaves pollute something? What is it?

Dr. RALL. Microwaves are being used more and more widely in special ovens to cook and heat food extremely rapidly.

Mr. FLOOD. What generates a microwave? Put that in the record.

(The information follows:)

A microwave is an electromagnetic radiation having a very long wavelength. Microwaves are generated by passing an electric current through a special tube.

Dr. RALL. These are the ovens that will cook a steak in 5 minutes.

Mr. FLOOD. That is radiation?

Dr. RALL. It is a very long wavelength electromagnetic.

Mr. FLOOD. Do you know—if you don't, have the record show—from what distance would the user be subjected to this danger—2 feet, 4 feet, all the way across the kitchen, or what?

Dr. RALL. The oven should be designed to shield you from the radiation. The problem is it is very hard to estimate what the dose of radiation is and how much radiation people are getting. Until we have adequate dosemitry measures, it is almost impossible to evaluate the potential health hazard. Our research is aimed at developing these measures.

Mr. FLOOD. I went to a friend's party one night and they had one of these things. They showed me how to work it. Am I radiated? I fooled around there about a half hour with it.

Dr. RALL. The ones on the market now are apparently quite safe.

Mr. FLOOD. This is not one exposure?

Dr. RALL. No, sir.

Mr. FLOOD. This is a time element in usage?

Dr. RALL. Yes.

Mr. FLOOD. And you have to be close to it?

Dr. RALL. Yes.

Mr. FLOOD. And if it is not turned on, there is no danger?

Dr. RALL. We believe it is perfectly safe.

NOISE POLLUTION RESEARCH

Mr. FLOOD. How does noise pollute? Mere noise?

Dr. RALL. We do not know very much about the general health effects today. I remember there was a special report last year that Dr. Kotin submitted on noise.

Mr. FLOOD. Yes; we have that.

Dr. RALL. I think we must simply do some experimenting and find out. Noise can startle people and can make them tense. Does this affect our body function? Does this affect our metabolism?

Mr. FLOOD. I spoke to a college group last year after receiving Dr. Kotin's report and read excerpts from it, and one of the bright young people wanted to pin me down on noise. All I could talk about were jets and how people who work at airports were affected.

Over at National Airport about that time I saw two fellows with these earmuffs on. I asked the one fellow what did they do, and he let me put it on. He told me that, without them, the noise actually destroyed the hearing—just the mere volume. What is the ecological problem of noise pollution? We don't know much about that; do we?

Dr. RALL. No. What we want to investigate is whether noise affects the normal body functions other than hearing.

EFFECTS OF NOISE ON BODY FUNCTIONS

Mr. FLOOD. How does it affect the normal body functions of any kind? We can see how it affects nerves. Too much noise gives you the jitters—the blowing of a horn. We have known that for years.

But taking the words ecology and pollution as they are now embraced, we just haven't heard much about how noise pollutes. Will you give us something more on that?

Dr. RALL. We will be prepared to discuss this matter at greater length next year. It is an important area.

Mr. FLOOD. It is important because I didn't have the answer.

Dr. RALL. And neither do I.

Mr. MICHEL. I hope we also have a discussion of where we are. We already know that, from an occupational standpoint, noise can cause a loss of hearing. We know sharp sounds are injurious. I wonder what else we can find out. Many animals' lives depend on their ability to detect a shocking noise which pushes a reflex button to get them to safety or they lose their life. I hope we don't go back and rework a lot of these things already known.

Mr. FLOOD. What I am driving at—and you mentioned body functions— how does it pollute the environment? How does it affect the heart, or the lungs, or the liver, or kidneys, or the brain?

Dr. RALL. That is exactly what we want to find out.

Mr. FLOOD. Do you have a target on this or is this just one of those things you have wandering around?

Dr. RALL. We have one person who is actively working on that.

Mr. FLOOD. People have developed a great concern about noise for many, many reasons and we have little to tell them. Do I just say you have one person looking into it?

Dr. RALL. The way we ought to start is to try to get a feeling for whether we can set up good experimental systems and see whether we can develop the methodology to see if noise affects the people. Then based upon those efforts we may well ask you to support a more extensive research program.

Mr. FLOOD. Will this take generations to find out?

Dr. RALL. It shouldn't take generations. It is awfully hard to put a time frame on a scientific problem. I hope to have some information next year at this time.

Mr. FLOOD. I hope you get your hope.

Mrs. REID. If the chairman will yield, there are many young people today who can't seem to study unless they have music blaring. Are you going to go into this, also; the effect of this kind of noisy music on young people today?

I went down to the University of Virginia last year and chaperoned one of their dances. You could not carry on a conversation with anyone because the music was so deafening. I wonder if this is part of your experimentation: what noise is doing to young people?

Dr. RALL. I expect it is more the other Institute's problems.

Mrs. REID. This would not be part of your concern?

Dr. RALL. Our primary concern would be on bodily function.

Mrs. REID. I think this could affect bodily functions.

OTHER AGENCIES' RESEARCH ON NOISE

Mr. SHRIVER. There are other agencies of Government involved in this problem, and industry is doing a lot of work in connection with elimination of noise. The chairman mentioned jet noise. I know the Boeing Co. has been working on this problem. They have cut down one-half in the noise of jets.

Mr. FLOOD. They have volunteered to do that.

Mr. SHRIVER. They would also like to have a contract to work on it more.

Mr. FLOOD. I know about Boeing. I have been on the Defense Appropriations Subcommittee for many years. We have talked about this for a number of years, especially about our big guns. Then we asked the Navy people about the 16-inch guns and we never got anything from them. They knew there was noise. A 16-inch gun makes noise and even some of the Navy people knew that. There was nothing about the effect upon the sailors or the gunners.

Dr. RALL. There is a report that the Environmental Protection Agency has put out——

Mr. FLOOD. On bodily effects?

Dr. RALL. This is a general review and includes that. This is the Goldman report. Would you be interested in a copy of this?

Mr. FLOOD. That is a very recent one.

Dr. RALL. It just came out.

Mr. FLOOD. I know about that. Let the members have a copy of that. I read about a two-page analysis of that in some university journal in the last couple of months.

RESEARCH GRANT AND CONTRACT NEEDS

Dr. RALL. We are also asking for approximately $2½ million additional for grant-supported research. We are confident that we will continue to attract increasing numbers of scientists to fill in the vast knowledge gaps in this important area of research. Our concern this year is that we have been unable to fund all the high-quality research which has been proposed for support. We are certain that the amount requested will better use the talent available in our universities, and will permit important advances in research in the field of environmental health.

We are asking, too, for a $1-million increase for contract research. This money will enable us to take advantage of research opportunities which must be pursued now but which cannot be handled within resources available in our own laboratories.

SUMMARY

Mr. Chairman, I am very pleased for the opportunity to tell you of the progress which the NIEHS has made with the committee's encouragement and support. I am excited at the prospect of building upon such a solid foundation, and I am anxious to continue the development of this program which is of such grave national urgency.

Mr. Chairman, our budget request for 1972 is for $25,271,000, an increase of $5,281,000 over the 1971 level of $19,990,000. The increase includes $2,438,000 for grants and $2,843,000 for direct operations.

I shall be pleased to answer your questions.

RELATIONSHIP WITH ENVIRONMENTAL PROTECTION AGENCY

Mr. FLOOD. Doctor, we are glad to have you onboard. Can you tell us why it was decided not to include your shop either in the whole or in part in this new Environmental Protection Agency? Frankly, I was surprised. How did you escape the net?

Dr. RALL. Those decisions were made prior to the time I joined the Institute.

Mr. FLOOD. Does anybody know the answer?

Mr. KINGMAN. Yes.

Mr. FLOOD. How long have you been onboard?

Mr. KINGMAN. With the Institute 4 years and with the Public Health Service about 15.

I think the decision was based primarily upon the fact the Environmental Protection Agency is conceived as a control and regulatory agency rather than as a health research organization. It is our experience that health research organizations are generally more effective when operated in conjunction with other health research organizations. As the principal health research organization in the Federal government is the NIH it was believed appropriate that the NIEHS should continue within it.

Mr. FLOOD. We are glad they let you alone.

Mr. KINGMAN. We are, too.

Mr. FLOOD. We are concerned about the proposal to give birth to a separate cancer agency. We are concerned about any attempt to take the NIH apart.

REQUESTED BUDGET INCREASES

As you said, Doctor, you have a good, solid increase for both your extramural and your intramural program. Why are you such a sacred cow? How do you rate this treatment? We have had a parade of your brother institutes who didn't do so well.

Dr. RALL. I think the main reason is increasing concern over problems of toxic elements within our environment which we are not entirely aware of in many instances. When we are aware of them, we frequently don't understand how they work or how we can avoid them, or, if they are going to stay in our environment, how we can develop antidotes for them.

ENVIRONMENTAL HEALTH SCIENCE CENTERS

Mr. FLOOD. I believe you now have six Environmental Health Science Centers and are requesting funds for one more.

Dr. RALL. That is right.

Mr. FLOOD. Will you tell us where the six are located and why they are located there?

Dr. RALL. They are located where the scientific experts are. As they develop we look for the best possible ones.

One center is at Harvard in Boston, Mass.; another is New York University at New York; Vanderbilt in Nashville, Tenn.; Washington University in St. Louis, Mo.; Oregon State University at Corvallis, Oreg.; and the University of Cincinnati in Cincinnati, Ohio.

Mr. FLOOD. Do they seek these out? Do you knock on the door and say "Good morning, President Jones, how would you like a center this morning?" Or do they seek these?

Dr. RALL. I can't speak to the long history of these centers. But in general, centers develop because there is an effective group of scientists working together whose programs become of such a magnitude that they warrant support in this manner.

Mr. FLOOD. How much does each center get, do they get the same, and how do you determine the level of funding?

Dr. RALL. Our total funding for centers this year is $3.1 million.

Mr. FLOOD. How much does each get and what is your yardstick?

Dr. RALL. They vary in size and program, and range in funding from a quarter of a million dollars to $900,000.

Mr. FLOOD. Did you build the centers?

Mr. KINGMAN. In the sense of bricks and mortar?

Mr. FLOOD. Yes.

Mr. KINGMAN. No, sir. We have no construction grant authority in direct support of these centers. This program has been operating essentially at the same dollar level since the establishment of the institute. The size of each is predicated upon the individual need of the programs which are to be carried out within these centers.

Mr. FLOOD. How do you determine the level of funding? Why isn't it $6 million or $1 million? You have a yardstick of some kind.

Dr. RALL. I think perhaps a description of how we go through the review process might help.

The centers submit an annual request for how they would like to be supported within the limits established by our advisory groups. This is reviewed very carefully by our extramural scientific staff, and then our advisory council reviews it.

Then it is reviewed in the light of the needs of the other five centers. We work very closely with these centers.

We have meetings twice a year with the center directors and our staff and keep in very close touch.

CENTER RESEARCH ACTIVITIES

Mr. FLOOD. What activities are carried on at these centers? Why is it more efficient and more productive to support these centers than to do the research with your own personnel and your own facilities? If you are so good, why do you farm this business out?

Dr. RALL. One answer, of course, is that it does give different geographic dispersion to the research effort.

Mr. FLOOD. What does that have to do with it?

Dr. RALL. They are not all localized in Washington or in North Carolina. But that perhaps is not the most important reason.

The centers are in universities. They influence the universities to increase the awareness of the scientists within the university of environmental health problems, and we think this is very important.

Mr. FLOOD. What activities are carried on at the centers?

Dr. RALL. Primarily they do research as well as important and related training functions.

Mr. FLOOD. Do they all do the same thing?

Dr. RALL. They work on very different things.

Mr. FLOOD. Do you plan this and assure yourselves of this before you make the grant?

Dr. RALL. Yes.

Mr. FLOOD. They don't takeoff on their own?

Dr. RALL. No.

INITIATION OF HIGH PRIORITY PROJECTS

Mr. FLOOD. You have a program increase of $1,400,000 and 28 jobs for your direct laboratory and clinical research. Take a look at page 163. There you refer to "The initiation of long delayed high priority programs."

What are these high priority programs? How can something of high priority be long delayed? That seems to be a contradiction in terms.

Dr.RALL. They are a part of the basic research programs which we think are a main part of our institute. We want to determine better methods of estimating the toxicity of environmental agents. This is one of our major efforts.

We now know methyl mercury is highly toxic, but some other compounds are going to come along in the next 2 or 3 years. How do you determine whether or not these are going to be seriously toxic in man? We have got to find out more about how these compounds are handled by the human organism. How they are metabolized, stored excreted.

Mr. FLOOD. You said these are long delayed priorities. This isn't something you discovered overnight. This has been on the shelf. Why now?

Dr. RALL. The real factor here is that the three building complex will just become available to us at the end of this fiscal year and we can begin to move in and work in it. These facilities will permit studies which simply are not feasible in our earlier facilities.

PESTICIDES RESEARCH PROGRESS

Mr. FLOOD. Your largest research grant program is on pesticides. We have heard a lot about this for years. What new is there to report on that highly controversial subject? Is there anything new to tell us?

Dr. RALL. I don't think there is anything terribly encouraging to report. I think we are understanding the nature of the toxicity of the pesticides.

Pesticides were originally designed to kill some organisms. We are now finding many of them are somewhat more toxic to human beings and other valuable organisms than we realized.

Mr. FLOOD. What is a pesticide?

Dr. RALL. A pesticide can be a rodenticide against rodents, an insecticide against insects. Mercury is called a slimicide because it protects against fungus.

Mr. FLOOD. They can be liquids or gases or solids?

Dr. RALL. Absolutely.

Mr. FLOOD. Are these artificial? Do your chemists give birth to them?

Dr. RALL. Almost all of them are new chemical compounds that have been synthesized. If you remember, rotenones and pyrethrons and others were the pesticides I grew up with and are all natural products. Almost all of the new ones are newly synthesized chemicals.

Mr. FLOOD. Who uses them?

Dr. RALL. Everybody uses them. The farmer certainly uses them extensively. Housewives use them. And of course home gardeners use them extensively.

Mr. FLOOD. The point I want to make is, pesticides are not related only to agriculture?

Dr. RALL. Oh, no.

Mr. FLOOD. Do industries use pesticides?

Dr. RALL. It is almost impossible to find a segment of the population that doesn't use pesticides.

RESEARCH ON CHELATING AGENTS

Mr. FLOOD. Several times in your justification you refer to work you are doing with regard to chelating agents.

Dr. RALL. Yes.

Mr. FLOOD. What in the world is a chelating agent?

Dr. RALL. It is an agent which tightly binds a metal, as mercury for instance. NTA chelates mercury. It binds it tightly and changes all of its characteristics. Insoluble metal salts can be chelated by NTA or other compounds and rendered soluble.

Mr. FLOOD. Why is it important?

Dr. RALL. It can do two things. If you give some of these chelating agents to people, it can remove——

Mr. FLOOD. How would you give chelating agents to a person?

Dr. RALL. Citric acid is a chelating agent and citric acid is in lemon juice. So they can be natural products to. They can be chemical products.

Mr. FLOOD. They can be chemical products?

Dr. RALL. Yes. These are ingested. Two things can happen. Either they can remove normal and needed trace metals or they can dissolve trace metals and render them more toxic.

Mr. FLOOD. Are they good guys as well as bad guys?

Dr. RALL. I think they are like so many things—half of them are good and half of them are bad. Often the compound from chelation is more hazardous than the compound singly.

Mr. FLOOD. They are used through the whole spectrum of our economy I suppose and society?

Dr. RALL. Yes.

STUDIES RELATED TO GENETIC CHANGE IN MAN

Mr. FLOOD. Take a look at page 181. There you refer to studies designed to evaluate the feasibility of defining and evaluating a specific biochemical marker which will facilitate automated screening of human populations for mutagenic effects. Tell us about that.

Dr. RALL. There are a great variety of enzymes; complex proteins, in the blood. In a mutation, which is a change in genetic material, you can get an altered enzyme occurring in the blood.

This specific proposal is to search through the very many enzymes in normal blood, see if there would be a simple automatic way of measuring some of them, and then applying this to a large human population group to see if there are changes.

You could, for instance, do this to those exposed to the atom bomb in Japan who presumably would have had a large dose of radiation to see if there were any genetic effects.

Mr. FLOOD. You say you are going to study the feasibility. In other words, this is not a fait accompli?

Dr. RALL. This is a very difficult and ambitious project. We would like to get a lot more information before we jump in.

BUDGET INCREASE

Mr. MILLER. Mr. Chairman, if I may clarify one point. Your first question indicated that perhaps this Institute seems to be getting a greater increase than other Institutes.

Mr. FLOOD. It is.

Mr. MILLER. I think it is important that the point be made here—that in the Heart Institute, for example, where the appropriation is almost level between 1971 and 1972, they received a $21 million increase above the President's budget in 1971 and are going to spend it.

Our budget request was already submitted to OMB before the congressional action was taken. Then we made the 1972 budget level with 1971 as a final step in the formulation of the President's budget. If you examine the increase from 1970 to 1972, there was perhaps a more significant increase for institutes such as the Heart Institute in that period than there is for an Institute like this one which received only $777,000 increase above the 1971 President's budget, and in 1972 we come along and put in a request for an increase of $5 million.

I think if you look down all the Institutes and compare the 1971 budget request, the 1971 appropriation and 1972 budget request, you will see that this Institute's program is not moving ahead faster than the other Institutes.

Mr. FLOOD. Mr. Michel.

Mr. MICHEL. Mr. Chairman, thank you.

POSSIBLE DUPLICATION BETWEEN GOVERNMENT AGENCIES

Doctor, let me see if I get this all straight as to where this fine line of definition lies between your shop, the Environmental Protection Agency and the Food and Drug Administration in the area of research.

We just heard testimony from Mr. Ruckelshaus and his backup witnesses in the other subcommittee, and they were talking about pesticides and this type of thing. Let's just take that one issue alone.

Where do you stop; where does EPA begin and stop; what does the Food and Drug Administration have to do with it?

Dr. RALL. Our primary focus is on the potential effects on human health, and it is the function of the National Institutes of Health to be concerned with effects on human health.

As I view it, our Institute is primarily concerned with the effect on human health of environmental pollutants from any sector.

Mr. MICHEL. Isn't EPA also concerned with that same thing?

Dr. RALL. EPA—I really can't speak for their charter.

Mr. MICHEL. They don't limit theirs just to animals?

Dr. RALL. They have, of course, an enormous responsibility for regulation, standards, monitoring, some concern over animal health.

Mr. MICHEL. Would they come to you with certain problems and say, "We are not supposed to be doing this research, this is your end of it?" Do you do the research on that?

Dr. RALL. The predecessors of EPA certainly did come to us with specific problems. NTA was exactly such a problem.

Mr. MICHEL. I realize in breaking this up at this particular time, maybe everything hasn't gotten shaken out. But my concern is that there not be a duplication of effort.

I fail to see how there is going to be the kind of coordination there should be with this broken up the way it is.

Dr. BERLINER. While it may be true this hasn't shaken out yet, the way we look at the major differences, the EPA is responsible for standard setting and regulations, whereas NIEHS is responsible for the research upon which judgments with respect to standards and regulations can be based.

Mr. SHRIVER. Do they take your information then?

Dr. RALL. Yes.

LINES OF COMMUNICATION WITH EPA

Mr. SHRIVER. What is the line of communication between the two?

Dr. RALL. One of the major parts of my job in the last few weeks has been to identify the people in Food and Drug Administration and EPA who need the information we will develop so that those people know we can get it for them.

Mr. SHRIVER. You will be working closely with them?

Dr. RALL. Yes. Over the years we have worked very closely with the groups which make up EPA and will continue to do so in the future. One other point I think is important is that we are responsible in essence for research into the health effects of all pollution, for instance, EPA has no jurisdiction over drugs. So interactions between pesticides and drugs—and we know that interactions can be very important—would tend to fall through the cracks. I feel that this is a major part of our Institute's responsibility, the interaction of pesticides and drugs, drugs and other pollutants, and the general problem of multiple sources.

Mr. MICHEL. Mr. Chairman, may we have the paper on this subject, Organizational Placement of NIEHS, made a part of the record.

Mr. FLOOD. Certainly.

(The paper follows:)

ORGANIZATIONAL PLACEMENT OF NIEHS

Over the past 10 years questions have occasionally been raised concerning the organizational location of the basic research component of the Department of Health, Education, and Welfare's environmental health programs. Each time the questions have been resolved in favor of separating that the basic health research component from the organizations primarily responsible for environmental control programs. This concept, which acknowledges the distinction between developmental research and basic research, was reaffirmed in the 1968 reorganization of environmental programs which resulted in the creation of the Environmental Protection Agency (EPA). This action once again recognized the wisdom of maintaining the programs concerned with long-range, basic, host-related research in the National Institutes of Health and the programs concerned with immediately applicable, applied, control-related research in the EPA.

Additional considerations in support of this jugment are:

1. Effective control programs required reliably developed criteria of biological response in order to establish sound standards for enforcement. The acquisition of knowledge of criteria of biological response requires continuous, long-term, singularly dedicated, basic research efforts. NIH has, through years of experience, attained a reputation of supremacy in such efforts. Regularly programs and enforcement of standards based upon the criteria cited above, require similar singularly dedicated efforts.

2. The distinction between basic research and developmental or technological research is an important one. The former often requires extremely long-term, detailed efforts. The latter, by its very nature, requires quick results. Both make use of similar scientific disciplines; both require similar laboratories and similar equipment; both are similarly costly; and both are equally important and in fact essential (in this context) to human health. Consequently, there is very real fiscal wisdom in maintaining the two efforts under separate though coordinated management. This stems from the fact that a single manager would be sorely tempted, during periods of particular stress, to redirect his resoruces from basic research efforts to developmental research efforts where the "payoff" might be both more rapid and, perhaps, more spectacular. In summary, EPA does research to find today's answers for today's problems. NIEHS uses similar resources to find today's answers to potential problems—in the hope of preventing these potentials from becoming tomorrow's problems.

3. A very pragmatic reason for maintaining NIEHS within the NIH rather than in the EPA arises from the way each is perceived by industry. A segment of NIH can obtain the cooperation of vital industries on the basis of interest in elaborating scientific facts far more readily than a program whose most visible responsibility entails control activities. Since the NIH is not primarily involved in regulatory activities, its "image" inspires useful trust—in much the same way that a doctor is more likely to hear confidences than is an insurance agent, although each has a legitimate need for information.

4. Separation between the organization which discovers criteria and the organization which enforces standards serves to assure the integrity of scientific judgment. Recognizing that regulation requires flexibility of judgment in view of economic concerns, it is vital that basic fact-gathering take place in a setting of empirical independence. NIH provides that setting for NIEHS.

5. Experience strongly indicates that basic science flourishes best within the environment of an agency, such as the NIH, which has science as a primary mission, as contrasted with one which is dominated by its control or regulatory mission. Top flight scientists are more readily attracted and retained in such an environment and their research needs get higher priority attention. It is a fact of organizational life that where control or regulatory functions are a major responsibility of an agency, the problems associated with these tend to preempt the attention and interest of the top leadership.

PROBLEMS OF PESTICIDE USAGE

Mr. MICHEL. I heard this morning that a Senator introduced or was preparing to introduce a bill to outlaw the use or interstate shipment of all pesticides—period.

Dr. RALL. I think that would pose a lot of problems.

Mr. MICHEL. I agree with you. I guess I need not ask the question, but would you favor that kind of legislation at this particular time?

Dr. RALL. I don't think there is a scientific basis for that now, no.

Mr. MICHEL. I think in response to the chairman you said the overall term "pesticides" covers a very wide field. You talked about herbicides and rodenticides and pesticides and all of these things we have to have in some areas to provide the food and fiber the country needs to survive, and the world for that matter.

I think we have found in many cases that the big problem with respect to insecticides is application by those who are not adequately prepared for using them. I think we garnered from the hearing with the EPA people they would try to get into this matter very seriously and in depth to determine just what degrees of application there ought to be in any given area. Then there will be, of course, tolerances that will be arrived at and so on.

I am glad to hear you say right off at this particular point we are certainly in no position to summarily say all pesticides are taboo and we ought to do away with them, because we are certainly not in that kind of shape today. Is that right?

Dr. RALL. I would certainly agree. I think your point about the better application, more careful application is an important one. Their proper use could probably make pesticides twice as safe today, just by making sure they are applied the way they are supposed to be.

MERCURY POISONING FROM FISH

Mr. MICHEL. I was going to ask a series of questions with respect to mercury poisoning, but in your earlier exchange with the chairman I think it has been pretty well brought out that what we know to date shows the mercury deposits to be concerned about are those that are accumulated over a period of years, and it generally follows that the larger the fish, the longer it lives. Therefore, that apparently is the reason the FDA singled out swordfish as being bad for human consumption.

Are there any studies that have been made of the number of people who have died because of mercury poisoning from eating too much fish or too much swordfish?

Dr. RALL. In Japan I think 50 died. It was somewhere in the order of 100 people that have been deemed to have been killed. We can supply that.

(The information follows:)

Two separate instances are known—one in Minamata and one in Niigata—both coastal towns in Japan. At Minamata, 121 persons were affected by mercury poisoning from eating contaminated fish and 46 died. In Niigata, 47 persons were affected and 6 died.

INTRAMURAL AND EXTRAMURAL RESEARCH

Mr. MICHEL. Would you say that most of the research you are going to be doing will be in-house or intramural as distinguished from extramural?

Dr. RALL. No. Our budget provides for next year something on the order of 3/5 for research that will be extramural and 2/5 will be intramural.

Mr. MICHEL. Will any of that extramural research be done by contract?

Dr. RALL. No. All of that is grants. In this breakdown I consider grants to be extramural, extramural and grants to be synonymous. We include what will be almost $2 million for contract research as part of our intramural program.

Mr. MICHEL. What you are saying is that 3/5 of your research budget will actually go for grant research, right?

Dr. RALL. That is right.

Mr. MICHEL. And you consider contract to be intramural?

Dr. RALL. This is an NIH concept.

Mr. MICHEL. I think we have more or less felt that intramural research means in-house, what you are able to do in your own shop and what we give you the resources to do. Many times we find, for example, that we don't want to put on a number of additional Federal employees over an extended period of time and it might really, in effect, be cheaper for the Government to contract certain work out so we don't get stuck with 50 or 100 additional employees plus fringe benefits and all of that.

I don't mean to imply by my line of questioning I am opposed to contracts or grants for that matter.

Rephrasing my question to make that kind of distinction, how much of this research can you actually do in-house without the benefit of grants or contracts?

Dr. RALL. $7.3 million is our intramural research budget.

Mr. MICHEL. Is all that carried on at the Triangle in North Carolina?

Dr. RALL. That is right.

PERSONNEL INCREASE

Mr. MICHEL. How many people do you have down there now?

Mr. KINGMAN. As of the end of April we had 202 onboard and it is slightly larger than that right now.

Our authorized strength as of the end of June will be 220. Of the 18 vacancies we had at that point, we have 12 who are committed by name. The balance are the kind of positions that are typically easy to recruit for—clerical and technical support.

Mr. MICHEL. Are there any transfers being made from Cincinnati down there?

Mr. KINGMAN. The Air Pollution Control Office of EPA is still in the process of relocating people from Cincinnati. We have never had staff, with one single exception. We had one scientist in Cincinnati in 1967. No part of our current enterprise was transferred from Cincinnati to North Carolina. We created in North Carolina essentially all of the programs we have developed there.

Mr. MICHEL. You are asking for how many additional positions this year?

Mr. KINGMAN. Twenty-eight.

Mr. MICHEL. In this year's budget you have how many unfilled as of this date?

Mr. KINGMAN. As of this date we have 18.

Mr. MICHEL. Again, are those professional or subprofessional?

Mr. KINGMAN. They are both.

Mr. MICHEL. What if I came back to you and said, "You have 18 positions open. Why do you need 28 more?"

Mr. KINGMAN. In fairness, all we can say is this: When I first joined the Institute in 1967 I was told the one thing we would not have to worry about was adequate laboratory space. At that time we had the next stage of our interim facilities on the horizon. Four years later we are actually going to occupy those facilities.

Our ability to carry out many of the things which we and this subcommittee would like to see, programs in dosimetry, and in noise, are highly dependent on our being able to use these new facilities. I am particularly conscious of the comment you made last year where in Illinois you had a new facility which you had built. You had a beautiful facility and no staff.

My reaction at that time was that that is tragic. I think it would be equally tragic if it were to occur in North Carolina as well.

Mr. MICHEL. What you are asking for here now is to man those laboratories which have been established so you can get the work done?

Mr. KINGMAN. That is right.

Dr. RALL. There is one aspect to the current figures of 18 vacancies I would like to comment on. When it became apparent that I was going to take over, Dr. Kotin and I decided we would not hire new people until I had a chance to get onboard and decide where things belong. This is an unsual dip due to the change in directors.

ORGANIZATION OF THE RESEARCH EFFORT

Mr. MICHEL. How will you break down your research effort along organizational lines? Do you break it down by air, water, and so on? Is there a magic formula you have arrived at?

Dr. RALL. I wish there were but there is not. We break it down by discipline—pharmacology, toxicology, chemistry, and cell biology. I am not entirely happy with this. I think the unique opportunities in this Institute are to get the cell biologist to work with pharmacologists and toxicologists. This is something I will work on this year.

Mr. MICHEL. This is still a shakeout period, I imagine.

Dr. RALL. That is right.

RESEARCH ON SMOKING

Mr. MICHEL. Going back and reviewing a line of questioning of last year, something with respect to research efforts in smoking and health were asked. Do you get involved in this?

Dr. RALL. I have never been personally involved in smoking and health in a research way until I took over this present job 2 or 3 weeks ago. Certainly our Institute is doing some research on smoking and health.

Mr. MICHEL. I don't mean to put you on the spot inasmuch as you came on board so recently, but I think we ought to have something in the record at least updating what information was supplied in the hearing record in response to my question last year.

Dr. RALL. It is my understanding that is available.

(The information follows:)

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

RESEARCH GRANTS—SMOKING AND HEALTH (DIRECTLY RELEVANT)

Investigator and institute	Total 1971 awards	Estimated amount related to smoking and health
R. L. Riley, Johns Hopkins University	$220, 530	$22, 053
J. L. Whittenberger, Harvard School of Public Health	389, 350	38, 935
N. Nelson, New York University Medical Center	959, 940	95, 994
J. L. Kleinerman, St. Lukes Hospital, Cleveland	79, 322	79, 322
F. E. Speizor, Health & Hospitals, Inc., Boston	52, 686	52, 686
Total	1, 701, 828	288, 990

Note: The above list identifies the several investigators whose research is being supported during fiscal year 1971 and the estimated amount related to smoking and health. The Institute is planning to award approximately $310,000 in fiscal year 1972 on smoking and health through its research grant program.

Mrs. REID. Last year Dr. Steinfeld was asked about money being spent to study the effects of tobacco. He commented that he thought that with the amount of money being spent on research on a less hazardous cigarette, that this year there should be a significant increase in terms of research activities.

I wondered whether there has been any such progress since last year?

Dr. RALL. As I understand it, and this is past history, the research activities have been at about the same level with regard to smoking and health. My feeling, without yet pursuing this as carefully as I shall, is that the National Cancer Institute will carry the major burden on smoking.

LEAD-BASED PAINT POISONING PREVENTION ACT

Mr. MICHEL. One final question. You say on page 5 of your testimony that lead is another heavy metal which can be toxic. You go on to say you have been studying this and now understand better the way the body handles lead during and following chronic exposure.

I had something come to my office just today from some people. Whether or not they know what they are talking about is hard to determine. However, they say thousands of children are brain damaged and hundreds die each year of lead poisoning. They are plugging for some additional money. Last year Congress enacted Public Law 91–695, the Lead-Based Paint Poisoning Prevention Act. This was signed by the President in January and, consequently, there is no money in the 1972 budget for this program. There is, however, the possibility of a supplemental perhaps later on to implement this particular piece of legislation.

It is my understanding that some 200 children died last year due to this problem.

The situation is especially severe in ghetto areas, where young children chew on old, peeling, lead-based paint. Do you know if these statistics are accurate?

Dr. BERLINER. I cannot quote statistics so I cannot answer on the frequency of lead poisoning in chldren for this cause. It is a serious hazard for children living in dilapidated housing where the paint

is cracking and never has been replaced with more modern paints which do not contain lead.

It is true that lead poisoning can and does occur among children. I cannot give you a figure off the top of my head regarding the frequency with which it occurs.

Mr. MICHEL. Do you have any comment on whether or not anything is planned to fund this piece of legislation?

Mr. MILLER. Mr. Michel. First of all, if this authority is funded, it will not be funded in this Institute, but in the Health Services and Mental Health Administration.

It would be very difficult to put a supplemental to good use this late in the fiscal year but we do have under active consideration the possibility of a 1972 budget amendment.

There are no specific funds in the 1972 budget now but we are discussing the possibility of a budget amendment with the Office of Management and Budget.

Mr. MICHEL. Has it been determined precisely whose responsibility it would be to administer this law?

Mr. MILLER. It is "HEW's."

Mr. MICHEL. Is there a specific shop?

Mr. MILLER. I am not certain. I think that the responsibility will be located with those activities which did not go to the Environmental Protection Agency and remained in HEW.

Mr. MICHEL. If that determination has not yet been firmed up, it would make little sense to appropriate any money now for a shop we don't even know.

Mr. MILLER. If we use the organizational argument, we might be accused of being slow in coming to a decision, but solely from a budgetary standpoint, it would not make sense to have a supplemental this late in the fiscal year.

Mr. MICHEL. Do you recall what the authorizing level of expenditure was for that act?

Mr. MILLER. The total authorization for both HEW and HUD is $10 million for fiscal year 1971 and $20 million for fiscal year 1972.

Mr. FLOOD. For what purpose would the money be used? What are the provisions of the act which would be taken care of with the money?

Mr. MILLER. I have some vague idea, Mr. Chairman, but I would like an opportunity to provide an insert for the record.

(The information follows:)

LEAD-BASED PAINT POISONING PREVENTION ACT OF 1971—DESCRIPTION OF FUNDED PROVISIONS

TITLE I

Under this title the Department of Health, Education, and Welfare would make grants to local units of government for screening and treating victims of lead-based paint poisoning on a 75%–25% matching basis (Federal share 75% and local government 25%). The authorization is $3,330,000 for fiscal year 1971 and $6,660,000 for fiscal year 1972.

TITLE II

Under title II the Department of Health, Education, and Welfare would make grants to units of local government for programs of detection and elimination of lead-based painted surfaces commonly exposed to children in residential housing. The authorization is $5,000,000 for fiscal year 1971 and $10,000,000 for fiscal year 1972.

TITLE III

Under this title the Department of Housing and Urban Development would carry out a demonstration and research program to determine the nature and extent of the problem of lead-based paint poisoning in the United States. The authorization is $1,670,000 for fiscal year 1971 and $3,340,000 for fiscal year 1972.

ADMINISTRATION'S POSITION ON THE ACT

Mr. MICHEL. I am also reminded that in November of 1970 the Surgeon General issued a policy statement on the medical aspects of lead poisoning in children. At that time the Administration's position before the Senate Subcommittee was one of open opposition to the particular bill, S.3216 which would have authorized appropriation of funds for screening and treatment of children with lead poisoning as well as for encouraging communities to develop local programs to eliminate the hazards of lead-based paint poisoning.

Mr. MILLER. That is true, Mr. Michel. The Administration did oppose the legislation last year.

Mr. FLOOD. How is the plan of attack set forth in the act?

Mr. MILLER. Under the act, HUD is responsible for determining the extent of the problem and HEW is to provide financial assistance to local units of government for programs to eliminate the causes of lead-based paint poisoning.

Mr. MICHEL. That is all I have at this time.

POTENTIAL DUPLICATION IN ENVIRONMENTAL EFFORTS

Mr. PATTEN. Doctor, I am wondering if we are embarking on a lot of duplication with all these agencies doing things related to environmental protection. Every eighth grade child in America now is a great advocate of Earth Day and ecology. I don't believe we have ever had a year like this. Old Lenin would turn over in his grave if he knew they made his birthday Earth Day and the whole world was in the act.

At Rutgers there are 89 pollution projects. Some come from the State Department of Health, I suppose, regarding sewers, polluted water, polluted streams, and so forth. However, there are many other areas involved. They are taking the bacterial count in the rivers and lakes. You are familiar with what they are doing in this field.

The Department of the Interior has a project in my district which had a good-sized budget. One of the projects they worked on was occasioned by the oil slicks. They were carrying on work to separate fuel oil from water. A million gallons of oil goes out into the bay and everybody is scared to death. I saw some of the work they were doing on this problem of how to meet a crisis such as oil slicks.

Other types of projects concerned our rivers, temperatures, lack of oxygen in the water, and the bacteria count. Everybody is talking about raising the standards of disposal plants and raising the standards of our incinerators and raising the standards of our industrial plants.

Do you think we are going in the right direction or are we wasting some money here? It is a little mixed up in my mind. Everybody is crying for action now. You are part of this picture, some $25 million worth.

Dr. RALL. The problem is how we interrelate with the Environmental Protection Agency. This concerns me very much. We have three people on our staff whose main job it is to work with the people at the Environmental Protection Agency in order to carry out liaison. Although the agency is new, it was created out of existing components, so we have at the moment very good liaison with the components of the agency.

Mr. PATTEN. Every law that comes up on the floor seems to have pollution as part of it. The agricultural bill had something regarding pesticides. We had opposing positions taken by various Federal departments on this. One wanted to get rid of "DDT" immediately. The Department of Agriculture said if it was not for "DDT", India would be loaded with malaria and that "DDT" has been very helpful and pesticides have been helpful. There has to be more understanding of these things.

I am on the Military Construction Subcommittee. In every facility in America they are talking about eliminating air and water pollution. Well over $1 billion of new money is in the budget.

You are in an agency which is of great import to every school child in America at this moment. They have projects where teachers ask students to write to their Congressmen regarding pollution, so 40 pupils in one class send me a letter. I think you know that this has been No. 1 in America since last April 22.

You know that there are counterforces. People in industry are scared to death. So many of them are excited about how much we will understand their problem. I hope that the money we spend will be spent efficiently and I hope we will have some good results without needless duplication.

NIEHS ENVIRONMENTAL ROLE

Dr. BERLINER. If I may try to define the difference between what the Institute is concerned with and some of the regulatory agencies that you mentioned. The Water Quality Administration, the Air Pollution Control Administration, the Department of the Interior are all concerned with how pollutants get into the environment, how to keep oil slicks off the water, how to keep mercury out of the output of plants that use it, and so on.

The role of the Institute is to carry on the research which will define what happens when one of these pollutants does get into the atmosphere and what levels we have to be concerned with, at what point it becomes a hazard to man, and to supply the information to the agencies so they can say, "You may not put out more than so much mercury in the effluent from your plant."

EFFICIENCY OF CURRENT GOVERNMENT PROGRAMS

Mr. PATTEN. You sit here with a feeling of confidence that the money being spent in the 50 States under new departments and in the State universities and in private industry is being well spent.

Are you satisfied that there is coordination involved here and we have a real team functioning?

Dr. BERLINER. I am afraid I am not qualified to evaluate what the various agencies are doing with respect to those things which are not

related to health. I think we can say that as far as health effects of environmental agents are concerned, we have a pretty good grasp of how these activities interdigitate and the extent to which they abut each other. I do not think there is serious overlap in health research, which is what we are primarily concerned with.

PRIVATE INVESTMENT IN POLLUTION CONTROL

Mr. PATTEN. Do you have any notion regarding the growth of private capital investing in antipollution measures, equipment, research and the like?

All of a sudden we have loads of people who are experts on pollution. I know that force is being used.

Dr. RALL. I have no figures. I agree with you that everyday you hear something new.

Mr. PATTEN. In the last 5 years the number of people in this business in the private sector has increased phenomenally.

I have nothing further, Mr. Chairman.

Anyway, Doctor, you know our feeling. The people home want better air and cleaner water. You can get reelected if you make a showing on this. That is the name of the game here.

INFORMATION EFFORTS

Mr. SHRIVER. Along the same line, there is a great amount of reporting in the newspapers concerning the possible harmful affects of various substances in the environment. We are all aware of this.

I am concerned that the public has no way of knowing whether these reports are coming from reputable scientists, whether they are based on adequate research. What means do you have to disseminate the information? Is it just to the agencies that you report? What facilities are used in getting out the information?

Dr. RALL. That is an important problem. I pointed out in my opening statement the nitrate problem which we looked into very carefully. It turned out that at the moment it is not a serious problem.

I think that is important, although it does not create a headline.

We at NIEHS write up technical documents, reviews made to inform other scientists. We are considering the possibility of having these rewritten in general terms so that the local newspapers or magazines could use them. This is just under consideration at the moment.

I think this is the sort of thing you are talking about.

Mr. SHRIVER. Somebody in Government should be doing it. It is hard to know whether what we read is true or not and whether it is based on scientific fact.

APPROVED BUT UNFUNDED RESEARCH GRANT APPLICATIONS

You say you have been unable to fund all of the high quality research that was proposed this year?

Dr. RALL. That is right.

Mr. SHRIVER. What percentage of these proposals will you be able to fund?

Dr. RALL. Up to 50 percent of the approved grants.

Mr. SHRIVER. With a proposed increase of $2.4 million for research grants in fiscal 1972, what percentage of the research projects would you be able to support?

Dr. RALL. I am sorry. I misunderstood you. We now fund about one-third. With the proposed increase we will be able to fund about one-half.

LOCATION OF NEW RESEARCH CENTERS

Mr. SHRIVER. Where did you say the new center would be located?

Dr. RALL. I am reluctant to discuss a place which we are just in the process of evaluating.

(Discussion off the record.)

Mr. MICHEL. You were making a point earlier that we currently have six such centers. These are usually established where the people are.

However, we don't buy the argument that because the Nation's Capitol is here, therefore everything has to gravitate here.

If we have to make it clear every year in a hearing, we will continue to make the point that there are other taxpaying sections of the country which contribute to the Government and have valuable resources. As a matter of fact, the Big Ten schools produce more "Ph. D's" and we have a bigger outgo of "Ph. D's" than any other section of the country. We would like to invite people to come out to Illinois and perhaps we can turn this thing around.

The gentleman from Kansas perhaps shares the same view.

Mr. SHRIVER. We can try. It seems they take away from us rather than contribute.

COOPERATION WITH FDA

Mrs. REID. A special welcome, Dr. Rall. I read that you were born in Aurora, Ill., my hometown.

Dr. RALL. That is right.

Mrs. REID. In discussing the possible duplication and overlapping, you mentioned the Food and Drug Administration. I certainly would assume, however, that you do have to have coordination and cooperation with them.

Dr. RALL. Very definitely.

Mrs. REID. And you do have?

Dr. RALL. Yes.

FUNDS FOR FELLOWSHIPS AND TRAINING

Mrs. REID. How much in fellowships and training grants this year for research science?

Dr. RALL. There will be $3 million, and that is going to be constant this year and next year.

TIME LIMITS ON RESEARCH PROJECTS

Mrs. REID. In response to a question which I asked Dr. Kotin last year about whether or not in your particular field you can be definitive, he indicated that it is very difficult because you must have patience and that these projects necessarily do take a period of years, but can

you set any time limit on any of your projects so that you can say that perhaps in 2 years, you would have thus and so to report?

Dr. RALL. If you deal with a specific topic, that is, let's again use this example of nitrate-nitrite, the problem was reports of some germ in European baby foods, some nitrate concentration, and this could be very serious for the baby. Well, this was an easy one because we really just had to study the nitrate and nitrite concentrations in a broad sample of American baby food to see if they were exposed to air, opened, and then let set for a day, whether the nitrite would go up. It did. So we were able to give a nice "This is no serious problem" answer very quickly. But, unfortunately, methyl mercury, for instance, is terribly complex—how does it get into the ocean, how does it get into those big swordfish—and we just don't know the answer. I understand your concern that research seems to go on and on.

Mrs. REID. I think that is all, Doctor. My other questions have been answered during the previous discussion.

Mr. FLOOD. Mr. Conte?

ELIMINATION OF PERSONNEL DEFICIENCIES

Mr. CONTE. In your thorough review of the personnel situation, the facilities, and the programs of the Institute, you must have discovered some shortcomings and deficiencies. What were they and what steps are you taking to eliminate them?

Dr. RALL. You're correct. My review did reveal some shortcomings and deficiencies. However, these shortcomings were the result of what I view as insufficient numbers of scientific personnel to come to grips with the broad range of problems which confront the Institute, rather than inadequacies in present personnel. In addition, I believe that we will have to broaden the definition we have of environmental health if we are to carry out our responsibilities. For example, from our discussion of methyl mercury and swordfish, it must be quite apparent that, in the interest of human health, we should be concerned with the question of how methyl mercury finds its way to swordfish. I plan that the Institute will take this broader view of its mission in the coming years.

PROGRAM LIMITATIONS

Mr. CONTE. What programs have been restrained in their growth as a result of limitations in funding and employment?

Dr. RALL. In developing the programs of the Institute at a time of funding and employment strictures, Dr. Kotin took what I view as the appropriate action. He established an organizational framework and began, within available resources, to fill out that framework. The effect of his efforts is that, in almost every case, we have laboratories which are at least minimally staffed and working on a representative selection of the problems which confront us. But because of the strictures on our growth, we have been unable to move ahead as quickly as we would hope in developing a broad science base for many of the long-term problems which the various control agencies will face in the coming years.

DEVELOPMENT OF COORDINATION WITH EPA

Mr. CONTE. What steps are you taking to establish an effective working relationship with the Environmental Protection Agency?

Dr. RALL. From our earliest days, we have maintained close and effective liaison with the organizations which now comprise the Environmental Protection Agency. With the creation of the Environmental Protection Agency in December of 1970, we continued to meet with the Agency's constituents. In addition, Dr. Kotin met with Mr. Ruckelshaus on a number of occasions in relation to health aspects of environmental problems; for example, NTA. On the 20th of this month, I will be meeting with Dr. Greenfield, Assistant Administrator for Research and Monitoring, EPA, to discuss current research problems and actions we can take to effect even closer liaison in the future.

AD HOC PROBLEM-SOLVING STIMULUS FOR LONG-TERM RESEARCH

Mr. CONTE. Would you provide us with some specific examples of how long-term research has been stimulated at the Institute by ad hoc problem-solving efforts?

Dr. RALL. I think the current problem of methyl mercury is a clear example of ad hoc problem-solving efforts stimulating long-term research although not all the work was done in our laboratories. When methyl mercury was first discovered to be present in fish at highly toxic levels, a number of questions were asked. Some of these related to how the fish had been exposed to the methyl mercury; others related to the manner in which organic mercury is converted into methyl mercury in our water supplies, and the need for precise information regarding the manner in which mercury affects man. In addition, with the discovery of toxic quantities of methyl mercury in swordfish, it became important to learn from what source salt-water fish were being exposed to methyl mercury. Some of these questions could be and had to be answered in a short time; others will form the basis for long-term investigations into basic mechanisms of action. Many of our recently inaugurated studies mentioned in my opening statement will provide some of the answers to these long-term questions.

DETERGENT INDUSTRY'S VOLUNTARY CURB ON NTA

Mr. CONTE. You state that detergent industry representatives have voluntarily modified plans to use NTA. Specifically, how were they modified? Is further testing of NTA going on?

Mr. RALL. Industry is deferring the widespread use of NTA pending the results of investigations which are being carried out by industry as well as Government scientists.

RESULTS OF METHYL MERCURY STUDIES

Mr. CONTE. You mention several projects designed to determine the biological effects of methyl mercury in man. Have any conclusive results emerged from these projects as yet?

Dr. RALL. As I mentioned earlier, we possess a great deal of general information about mercury toxicity. However, it is important that we refine the information we have. Accordingly, the Institute has

embarked upon long-term studies aimed at developing the required information. We would hope to have results from some of this work to report to you next year.

EXPERIMENTS AT ANIMAL-HOLDING FACILITY

Mr. CONTE. What are some of the new range of experiments you anticipate will be conducted in the new animal-holding facility?

Dr. RALL. One of the great needs in our area of responsibility is for a wide range of animal studies involving long-term exposure of animals to low levels of toxic substance singly or in combination. Since our creation in 1966, we have been hampered by inadequate animal space both in terms of amounts and experimental controls. These new facilities will make possible many studies which have been long delayed due to lack of adequate facilities.

UNFUNDED IMPORTANT RESEARCH

Mr. CONTE. What important research projects were you unable to fund this year?

Dr. RALL. Many excellent but unfunded applications in 1971 were ultimately concerned with providing a scientific basis for realistic air pollution control measures. Others would have provided new data on the fundamental mechanisms of heavy metal toxicity, including lead poisoning and its irreparable effects on the human brain. Studies in animals would have yielded additional knowledge of potential pesticide effects on pregnancy and the developing human fetus. Other proposals would have explained the generation, toxicity, and mechanisms of contaminants found in the foodstuffs of man and his domestic animals.

The list of these unfunded research proposals is long. The studies described in them are excellent, and the need for information we might have gained from them is, in many cases, critical to the health of man.

Mr. CONTE. What kinds of research opportunities are you unable to handle in your own laboratory facilities?

Dr. RALL. In general, there are three situations in which we seek outside contractors to carry out research as a direct extension of our intramural program: One, when the research requires specialized facilities or capabilities which we do not possess; two, when the contractor has proprietary interest in information or records which we need for our research; and three, when the problem is of a nature which would require a significant investment of our total research team and would preclude us from carrying out other studies of high priority.

Mr. CONTE. Thank you.

Mr. FLOOD. Thank you, Doctor.

Dr. RALL. Thank you, Mr. Chairman and members of the committee.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation

	1971	1972
Appropriation	$20,620,000	$25,271,000
Real transfers to: (Proposed transfers for increased pay costs)		
"National Library of Medicine"	-442,000	
"St. Elizabeths Hospital"	-27,000	
Comparative transfers to:		
"Health Manpower"	-274,000	---
"Office of the Director"	-22,000	---
Comparative transfer from:		
"Biologics Standards"	135,000	---
Total obligations	19,990,000	25,271,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
169	Research	---	$9,480,000	---	$11,918,000	---	+$2,438,000
173	Fellowships	---	264,000	---	264,000	---	---
175	Training	---	2,843,000	---	2,843,000	---	---
	Direct operations:						
177	Laboratory and clinical research	197	5,530,000	225	7,314,000	+28	+1,784,000
181	Collaborative research and development	---	984,000	---	1,995,000	---	+1,011,000
182	Review and approval of grants	16	493,000	16	524,000	---	+31,000
183	Program direction	22	396,000	22	413,000	---	+17,000
Total obligations		235	19,990,000	263	25,271,000	+28	+5,281,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	235	263	+28
Full-time equivalent of all other positions	12	12	---
Average number of all employees	214	230	+16
Personnel compensation:			
Permanent positions	$2,747,000	$3,126,000	+$379,000
Positions other than permanent	62,000	64,000	+2,000
Other personnel compensation	22,000	40,000	+18,000
Subtotal, personnel compensation	2,831,000	3,230,000	+399,000
Personnel benefits	289,000	327,000	+38,000
Travel and transporation of persons	166,000	217,000	+51,000
Transportation of things	25,000	30,000	+5,000
Rent, communications and utilities	512,000	807,000	+295,000
Printing and reproduction	25,000	33,000	+8,000
Other services	560,000	682,000	+122,000
Project contracts	984,000	1,995,000	+1,011,000
Payment to NIH Management Fund	593,000	721,000	+128,000
Supplies and materials	635,000	927,000	+292,000
Equipment	783,000	1,277,000	+494,000
Grants, subsidies and contributions	12,587,000	15,025,000	+2,438,000
Total obligations by object	19,990,000	25,271,000	+5,281,000

Summary of Changes

1971 estimated obligations	$19,990,000
1972 estimated obligations	25,271,000
Net change	+5,281,000

	Base Pos.	Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase cost	---	---	---	$128,000
2. Annualization of positions authorized in 1971	---	---	---	140,000
3. Within grade pay increases	---	---	---	34,000
4. FTS rate increase	---	---	---	2,000
5. Noncompeting continuation of research grants	---	---	---	757,000
B. Program:				
1. Research grants	---	$9,480,000	---	1,738,000
2. Laboratory and clinical research	197	5,061,000	28	1,400,000
3. Collaborative research and development	---	984,000	---	1,011,000
C. Payment to "National Institutes of Health Management Fund" for centrally furnished services	---	593,000	---	128,000
Total, increases	---	---	28	5,338,000
Decreases:				
A. Program:				
1. Research grants	---	---	---	-3,000
2. General research support grants	---	---	---	-54,000
Total, decreases	---	---	---	-57,000
Total, net change	---	---	28	5,281,000

Explanation of Changes

1. Built-in increases--These increases will provide $128,000 for annualization of the 1971 pay increase cost; $140,000 for the annualization of positions new in 1971; $34,000 for within grade pay increases in 1972; $2,000 for increased cost in 1972 of using the Federal Telecommunications System; and $757,000 to support the increase in noncompeting continuation grant commitments established prior to 1972.

2. Research grants--The requested program increase of $1,738,000 would fund $1,238,000 in additional new and competing renewal grants and $500,000 to initiate a new Environmental Health Sciences Center for a total of 7 centers in 1972. The request also includes a decrease of $54,000 for general research support grant, a program included in each National Institutes of Health appropriation containing research grant projects, but administered separately by the Division of Research Resources, and $3,000 for a non-initiative program decrease.

3. Laboratory and clinical research--The program increase of $1,400,000 and 28 positions would provide continued development of the Institute's intramural program located at the Research Triangle Park, North Carolina. During the last quarter of 1971, an additional 30,000 square feet of space will be ready for occupancy. The additional space with its specialized design will now make possible the initiation of long-delayed high priority programs as well as the more adequate staffing of ongoing programs.

4. Collaborative research and development--An increase of $1,011,000 will finance research support in ongoing programs as well as the initiation of new ones. Some areas of investigation are trace metals toxicology, pesticides, mutagenesis and others.

Authorizing Legislation

Legislation	1972 Authorized	1972 Appropriation requested
Public Health Service Act of 1944, as amended:		
Section 301 -- Research and Investigation, In General	Indefinite	$25,271,000
Title III, Part A--National Institute of Environmental Health Sciences	Indefinite	$25,271,000

PUBLIC HEALTH SERVICE ACT

Title III, General Powers and Duties of Public Health Service, Part A, Research and Investigation. --

"Sec. 301. The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man, including water purification, sewage treatment, and pollution of lakes and streams."

62-645 O - 71 - pt. 3 - 68

Explanation of Transfers

	1971 Estimate	Purpose
Real transfers to:		
National Library of Medicine	-$442,000	Proposed transfer for increased pay costs
St. Elizabeths Hospital	-27,000	
Comparative transfer to:		
Office of the Director	-22,000	Transfer of research contracting function from NIH Management Fund to Office of the Director for establishing the Office of Contracts and Grants.
Health Manpower	-274,000	Transfer of institutional support funds to Health Manpower.
Comparative transfer from:		
Biologics Standards	135,000	To provide an equitable distribution of the Management Fund in 1972.

National Institute of Environmental Health Sciences

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1965	$ 10,920,000	$ 9,380,000	$ 9,730,000	$ 9,380,000
1966	15,933,000	15,933,000	15,983,000	15,983,000
1967	24,312,000	24,298,000	24,298,000	24,298,000
1968	20,615,000	17,289,000	20,615,000	17,289,000
1969	18,099,000	17,541,000	18,099,000	17,820,000
1970	18,328,000	18,328,000	18,328,000	18,328,000
1971	19,843,000	20,620,000	21,620,000	20,620,000
1972	25,271,000			

Justification

National Institute of Environmental Health Sciences

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	235	$3,120,000	263	$3,557,000	+28	+$437,000
Other expenses.....	---	16,870,000	---	21,714,000	---	+4,844,000
Total.....	235	19,990,000	263	25,271,000	+28	+5,281,000

General Statement

Introduction

This will mark the first year that this Institute will have enough research space to permit the establishment of the full range of required laboratory programs although on a limited scale. This will enable exploration of many more of the important questions dealing with the environment. Since the beginning of this Institute in 1966, resources have permitted the initiation of programs in only a few of the many areas which need investigation. The amounts requested for 1972 will permit extention of investigations into the actual and potential effects on human health brought about by a rapidly changing environment. In addition to the intramural research activities, there is an extramural program which includes grants, fellowships, training programs, university-based centers, and research contracts.

Purpose

The National Institute of Environmental Health Sciences was established in response to the need to increase the store of fundamental knowledge and understanding of environmental agents as hazards immediately or ultimately affecting man's health. The results of research are promptly made available to agencies having responsibility for the environmental monitoring, standard setting and control of all of its phases or compartments. The initial approach is to determine the magnitude and significance of the hazard to man's health from long-term exposures to low-level concentrations of chemical, physical, and biological agents in the environment; and second, to elucidate the underlying mechanisms of adverse response with the hope that principles and generalizations will be identified to provide a scientific base for criteria upon which control agencies could set standards for protective and preventive measures.

The direct beneficiaries of the basic knowledge so developed by the Institute are the categorical programs in environmental control, particularly those encompassed by the Environmental Protection Agency -- such as those concerned with air pollution, radiological health, occupational health, environmental sanitation, solid waste management, and food and drugs. Close liaison is maintained with these activities to ensure the inclusion of their requirements in the development and implementation for supporting research in the Institute's program-planning. The American people are the long-range beneficiaries of the Institute's efforts.

Extramural Research and Training

The support of research and training in the environmental sciences through grant-in-aid is an essential component of the national effort to identify, characterize, and ultimately control known and potential hazards in the environment. Training functions continue to develop new and highly-qualified environmental scientists. Fundamental data elicited from studies of environmental hazards and their mechanisms of action provide the basis for new approaches to the resolution of complex and growing problems of environmental contamination. As the fund of knowledge increases and new techniques of monitoring and analysis develop, new bases for realistic control standards may be expected to emerge.

Intramural Research

The National Environmental Health Sciences Center, the intramural program of the National Institute of Environmental Health Sciences, was created for the purpose of investigating at the fundamental level the long-term and subtle effects of environmental agents potentially hazardous to man. These studies are directed to the development of a scientific base for establishing standards and devising remedial measures. This information is a necessary prerequisite to the establishment of generalizations and principles which can be applied to assure protection of exposed populations. The increasing complexity of our environment makes it imperative to view the problems of environmental hazards from the vantage point of total health effects. Complementing experimental laboratory studies, the Center engages in long-term epidemiological studies of populations with unusual environmental experiences or unique morbidity and mortality patterns. In summary, the Center provides a central facility for intramural research and a focal point for a nationwide effort on the total health effects of physical, chemical, and other environmental factors to which the American people are exposed.

The function of the Center is to identify harmful agents in the environment, discover the mechanisms by which they affect an individual's health and develop data on the effects of chronic exposure, thereby providing a scientific base upon which control measures can be developed. The several classes of environmental agents on which research is now being carried out are natural products, metal compounds and chelating agents, reaction products of organic and inorganic compounds, tobacco smoke constituents, polymer dusts, alpha radiation, pesticides and pesticide synergists.

The narrative material which follows provides in greater detail current and planned investigations for support or conduct either through grants or contracts, or in the Institute's own laboratories. The programs of the Institute are discussed here in terms of the mechanisms employed for their support. These programs are viewed and planned as part of a total national program with each component complementary to the others, with all aimed at the understanding of the hazards to health resulting from man's interaction with his environment.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Research projects.....	$5,945,000	$7,937,000	+$1,992,000
Special programs.....	3,535,000	3,981,000	+446,000
Total research grants....	9,480,000	11,918,000	+2,438,000

Introduction

The Institute awards grants to public and private non-profit institutions covering a broad range of research activities in the fields of environmental health. The general purpose of these grant projects is to identify and characterize the sources, modes of entry, and biologic effects of known and suspected noxious agents in the environment. The research varies in scope from studies of toxic mechanisms at the molecular and subcellular levels to epidemiological studies conducted to identify environmental factors in the etiology of human disease. Projects range in magnitude from the circumscribed efforts of individual investigators to broad based integrated program grants employing the expertise of numerous scientists from a variety of scientifc disciplines. Data developed by these research projects will improve our understanding of specific noxious agents as they affect biologic systems and will permit the eventual establishment of realistic control standards; and will provide the basis for predicting the effect of agents newly introduced into the environment. They will provide fundamental knowledge of environmental stressors and their mechanisms of action. New and refined techniques will evolve which will permit and encourage research into fields which are now at the fringes of our capability.

Program Plans for 1971 and 1972

Institute-supported scientists continue to investigate a broad spectrum of known and potential environmental hazards, acting individually and in combination, for their subtle long-range effects on biological function at the fundamental level.

Pesticide studies constitute a large segment of this effort. Much remains to be learned about this broad array of compounds and their specific effects on target and non-target plants and animals. Investigators are identifying sites of action of known pesticides, mechanism of toxicity, changes elicited by their interaction with other chemical and physical agents, and an understanding of the factors controlling their persistence and distribution in the biosphere. These data continue to facilitate the design of new and safer compounds, more efficient in the control of target organisms and less hazardous to human health.

Efforts continue toward the isolation, identification and testing of airborne gases and particulates to determine the toxic effects of chronic low-level exposure to these contaminants. Projects are supported to determine how the molecular and toxic properties of these compounds are altered by interaction with other atmospheric contaminants, by solar radiation, and by weather conditions.

A number of investigators are studying the specific subcellular events leading to pulmonary irritation and disease.

The Institute supports several projects concerned with the toxicity of food contaminants, a number of which have been shown to cause liver cancer in animals. Important among these are the mycotoxins, which are metabolic products of fungi infesting foodstuffs. Cyclamate, saccharin, monosodium glutamate, and other compounds added to foods during their processing and preparation are also under investigation.

Trace amounts of certain metals are essential to health; however, excess amounts of heavy metals are known to disrupt the biologic functions of plants and animals. For certain additional heavy metals no biological need has been demonstrated and these too may be toxic to man. The Institute is supporting several projects to determine the distribution in the environment and the level of exposure of these elements, their metabolism and storage in the body, and the subcellular sites and dynamics of their toxic action.

In addition to the chemical agents under investigation, there is increasing interest in the biological effects of physical stressors in the environment. Research is being supported to measure the effects of ambient temperature and humidity on human heat exchange and temperature regulation. Components of solar radiation are under study for their beneficial and harmful effects on plants and animals. Studies on noise pollution and crowding are being considered to determine the psychophysiologic effects resulting from these urban stresses.

The magnitude of the problem and the demonstrated research opportunities prompt the request for an increase of $1,992.000. This increase will permit the full funding of non-competing grants and an increase of $426,000 and $779,000 in new and competing projects respectively. New projects awarded by the Institute will be in key areas of concern to the Institute, including pesticides, food toxicants, occupational hazards, heavy metals, physical hazards, chemical air pollutants and contaminants of water supply. They will advance the accomplishments of the mission of the Institute, which is focused primarily on determining effects of long-term exposure to low levels of chemical, physical and biological hazards, singly and in combination.

Special Programs

The Institute supports a program of university-based centers designed to concentrate research skills and efforts on the more complex and challenging problems in environmental health. Each of the six currently supported Environmental Health Sciences Centers focuses on areas of primary interest, yet the broad bases on which they operate reflect a concern for the total environment. The interrelationships of these centers greatly enhance their ability to identify and anticipate important problems in environmental health. Among special areas of interest pursued by the centers are: environmental toxicology; biology of natural systems; respiratory disease and aerosol physiology; environmental management; and pesticide biology. Epidemiologic surveys are underway to determine the health hazards of exposure to airborne gases, vapors and dusts. These are being conducted at industrial sites and in the general population. Others are investigating the synergistic effects of ambient temperatures on the toxicity of environmental agents.

In total, these centers serve as a national resource with the Institute serving as a focal point playing a vital coordinating and collaborating role. Each center provides a framework in which a broad spectrum of research can be integrated and brought to bear on problems of environmental health. These centers also provide unique opportunities for graduate training of excellence and advanced in-depth training that is available in few other places.

A most pressing need for the future of environmental health research is the availability of attractive, stable career opportunities. Environmental Health Sciences Centers provide such a setting not only for those already in biomedical research, but also serve to attract promising young investigators into the field. By contrast, in the immediate future, it is unlikely that the traditional pattern of university training will produce a corps of scientists with a primary commitment to environmental health.

Centers cannot effectively embrace more than a few aspects of this broad and complex field. Accordingly, they differ markedly in their orientation and approaches. Individual centers may emphasize areas such as environmental carcinogenesis, natural biological systems, or pesticide biology, but effective utilization of these resources requires the existence of a focus such as the National Environmental Health Sciences Center, that can identify mission-oriented problems, formulate objectives and implement program efforts in a centrally coordinated manner. The Institute provides a problem solving competence in depth to permit evaluation and review, as well as to maintain close working relationships with these external programs. Coordination of the programs of these centers and liaison with them are carried out through a group made up of key Institute staff and the Directors of the individual centers. Semi-annual meetings of this group serve to assure that the individual research projects conducted in these centers are part of a total coordinated national environmental health research program rather than a merely fragmented, although a high quality effort. It is the Institute's position that attainment of the Nation's goals in this important and emerging health area is best assured by this collaborative effort.

An increase of $500,000 is requested to permit the continued development of this program through the initiation of one additional center grant.

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting	63	$4,213,000	67	$4,970,000	+ 4	+$757,000
2. Competing renewals	11	430,000	24	1,209,000	+13	+779,000
3. Supplementals	(4)	15,000	(10)	45,000	(+6)	+30,000
4. New awards	26	1,287,000	34	1,713,000	+8	+426,000
5. Subtotal	100	5,945,000	125	7,937,000	+25	+1,992,000
6. General research support	---	485,000	---	431,000	---	-54,000
7. Environmental Health Sciences Centers	6	3,050,000	7	3,550,000	+1	+500,000
8. Total research grants	106	9,480,000	132	11,918,000	+26	+2,438,000

Research Grants Program Analysis

Fields	1971 Estimate	1972 Estimate	Increase or Decrease
Pesticides	$2,171,000	$2,723,000	+$552,000
Food toxicants	605,000	1,334,000	+729,000
Occupational hazards	398,000	579,000	+181,000
Metals	458,000	665,000	+207,000
Physical factors	471,000	685,000	+214,000
Air pollutants & smoking	860,000	1,086,000	+226,000
Toxicology, general	197,000	372,000	+175,000
Multicategorical	785,000	493,000	-292,000
Subtotal regular program	5,945,000	7,937,000	+1,992,000
General research support grants	485,000	431,000	-54,000
Environmental Health Sciences Centers	3,050,000	3,550,000	+500,000
Total research grants	9,480,000	11,918,000	+2,438,000

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Total Fellowships.....	$264,000	$264,000	---

Introduction

The fellowships program is a highly flexible and efficient means for supporting the research training of individuals whose career development extends from the postdoctoral period through the more advanced stages of scientific attainment. The program is competitive at the national level and provides opportunities for full-time study and research training for the best qualified applicants.

Program Plans for 1971 and 1972

During 1971 funds were provided to increase the number of Research Career Development Awards over the previous year. These provide salary support over a five-to-eight-year period for highly selected young scientists who have completed their basic research training and who have displayed outstanding aptitude for research. The awards afford an opportunity for these promising individuals to become established as independent investigators. The effects of air pollutants on the respiratory system constitutes an important part of this program. Some awardees will continue to investigate mucociliary function and other protective mechanisms in the respiratory tract. Others will study early changes in respiratory tissue to determine pathogenetic mechanisms fundamental to the development of chronic lung disease.

Funds requested for 1972 will provide for 18 awards, one less than in 1971.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting	13	$182,000	13	$210,000	--	+$28,000
2. Competing renewals	--	---	--	---	--	---
3. Supplementals	--	---	--	---	--	---
4. New	6	82,000	5	54,000	-1	-28,000
5. Total Fellowships	19	264,000	18	264,000	-1	0

Fellowships (by type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Predoctoral	--	---	--	---	--	---
2. Postdoctoral	5	$38,000	4	$31,000	-1	-$7,000
3. Special	7	88,000	7	94,000	--	+6,000
4. Development awards	7	138,000	7	139,000	--	+1,000
5. Foreign	--	---	--	---	--	---
6. Total Fellowships	19	264,000	18	264,000	-1	0

Fellowships Program Analysis

Fields	1971 Estimate	1972 Estimate	Increase or Decrease
Pesticides	$45,000	$53,000	+$8,000
Metals	---	10,000	+10,000
Physical Factors	1,000	---	-1,000
Air Pollutants & Smoking	157,000	176,000	+19,000
Toxicology, general	31,000	24,000	-7,000
Multicategorical	30,000	1,000	-29,000
Total	264,000	264,000	0

Training Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Training Grants.....	$2,843,000	$2,843,000	---

Introduction

Graduate research training grants are made to institutions to improve and to enlarge the pool of qualified scientists who can engage in research on environmental health. These grants also open competitive opportunities for institutions to strengthen their capabilities for research training in subject areas related to the mission of this Institute.

Program Plans for 1971 and 1972

The funds requested will provide for noncompeting requirements and will allow for the competitive renewal of a substantial number of active programs. Several of these programs emphasize the fundamental aspects of pathobiology and toxicology, including cytogenetic effects in the human. For example, the goal of one program is to train physicians in the strategy and techniques of research in pathobiology, clinical-pathological correlations, and epidemiology of environmental diseases. Another program provides training leading to a Ph.D. in experimental pathology. This training is based upon the premise that medical training is not a prerequisite to the conduct of research in this area of macromolecular pathology. It is anticipated that graduates will be prepared to undertake research projects which are related to environmental health and encompass the tools, techniques, and basic knowledge of pathobiology. One other is devoted to the elucidation of the effects of environmental factors on genetic function and structure as they relate to humans. The goal is the development of geneticists competent to study at the chromosomal level the changes and variability, both physiological and morphological, which result from exposure to environmental agents.

The funds requested for new awards should be sufficient to support new applications which are relevant to the mission of the Institute.

Distribution of Training Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Noncompeting.....	32	$1,812,000	22	$1,904,000	-10	+$92,000
2. Competing renewals.....	5	600,000	8	674,000	+3	+74,000
3. Supplementals.....	(1)	25,000	(2)	35,000	+(1)	+10,000
4. New.....	4	396,000	3	210,000	-1	-186,000
5. Scientific evaluation.....	1	10,000	1	20,000		+10,000
6. Total.....	42	2,843,000	34	2,843,000	-8	0

Training Grants (by Program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Graduate.....	41	$2,833,000	33	$2,823,000	-8	-$10,000
2. Scientific evaluation.....	1	10,000	1	20,000	--	+10,000
3. Total training grants.....	42	2,843,000	34	2,843,000	-8	0

Laboratory and Clinical Research

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	197	$2,524,000	225	$2,920,000	+28	+$396,000
Other expenses.....	---	3,006,000	---	4,394,000	---	+1,388,000
Total.....	197	5,530,000	225	7,314,000	+28	+1,784,000

Introduction

All of the intramural research units of the National Institute of Environmental Health Sciences, with the exception of the Occupational Studies Group, are located at the National Environmental Health Sciences Center in Research Triangle Park, North Carolina. The Center serves as the focal point of a nationwide collaborative effort for research in environmental health problems.

The interdependence of disciplines and the assured scientific exchange inherent in the problem-solving approach has been a recognized need in the biological sciences. The use of this approach facilitates the full utilization of data from the Center's own research efforts, university-based centers, and the scientific community.

It is the function of the Center to identify harmful agents in the environment, discover the mechanisms by which they affect an individual's health, and develop understanding of the effects of long-term, low-level exposure, thereby providing a scientific base upon which standards can be developed and control measures established.

The classes of environmental agents for which research programs are now underway are the natural products, including a study of fungal toxins, certain trace metal compounds and chelating agents, reaction products of organic and inorganic compounds, tobacco smoke constituents, alpha radiation and pesticides and pesticide synergists. Within each of these areas, several components or products have been selected for study based either on observation of adverse effects in laboratory animals exposed to these chemicals or on epidemiological studies suggesting adverse effects on human populations exposed to these agents in the environment.

Inasmuch as a completely contaminant-free environment will remain technologically unfeasible, major emphasis is directed towards identifying threshold levels below which no adverse effects can be demonstrated or observed responses are reversible and non-cumulative. Similarly, the storage of environmental toxins in various tissues of man and animals (body burden) is an important factor requiring further elucidation. Adverse effects associated with storage of substances in specific organs and tissues must be identified and quantified.

In addition to these ongoing studies, other programs are in various stages of development relating to specific hazards of exposure to asbestos, mercury, and beryllium, for example. Some of these may be more universal and general pollutants than was originally thought. A careful study is made of environmental distribution of various heavy metals leading to contact with man as they occur

in the environment, either consumer products or environmental pollutants. This will permit us to be current of new developments which may introduce unanticipated hazards for specific or general population groups. This study of technological trends is directed toward assuring maximum protection at the earliest time possible.

Program Plans in 1971

Toxicologic studies of metabolites produced by fungi growing on fruit, vegetable, or special crops like tobacco are being pursued. The extracts showing toxicity in mice, human tissue culture cells, and bacteria are worked up to isolate the toxic components and to identify them. A new mycotoxin has already been isolated and identified by mycelium of the mold Alternaria tenuis and its toxicity is under further study. This mold is a ubiquitous pest affecting many crops.

Several cell lines have been established in tissue culture which have been used to great advantage in the study of cytotoxicity due to mycotoxins and insecticides as well as for the evaluation of the effects of chlorinated hydrocarbon insecticides on cell replication and subcellular effects on nucleic acid and protein synthesis. These systems have also been utilized to evaluate effects of chelating agents which are likely to present a toxicological problem in the near future. For the evaluation of mutagenic chemicals, tissue culture systems are being used and the mechanism of genetic damage and repair are being explored.

Investigations are underway on malformations resulting from the administration of potentially teratogenic agents to several rodent species with particular emphasis on trace metals, trace metal chelates, and pesticides. Information has been gathered on specific herbicides and their derivatives as required for evaluation and action to be taken by other agencies responsible for the protection of the public. Studies have also been carried out to evaluate interacting factors in the toxicity of environmental agents. The contribution of environmental toxins in modifying teratogenic or other harmful effects are being studied. The mechanism involved depends on the capability of many chemicals and drugs to induce microsomal enzymes which can alter the rate of degradation and elimination of many environmental toxins. Also under study are pesticide synergists which block detoxifying enzyme action and can thus aggrevate the toxicity of pesticides, drugs, hormones, and other compounds of importance.

Analytical chemical studies augment the functional programs of the Center by developing new and improved methods for microquantitation of many environmental toxins. A snythetic chemical laboratory is supplying essential derivatives of environmental toxins to help in their study and identification.

Pathologic studies are concerned with the effect of environmental toxins on the structure and function of many tissues and organs. Studies are carried out at the subcellular, cellular, organ, and intact animal level. Histopathologic evaluation has been extended from the light microscope to the ultra structural level with the help of the electronmicroscope. The Virginia opossum is being developed at the Center as one of the more unusual but highly useful laboratory animals. This marsupial provides a unique biological system by virtue of the migration of the early fetus from uterus to pouch at 13 days gestation. The accessibility of the fetus during the developmental period provides an ideal model for studying fundamental problems of differentiation and organogenesis and allows for the study of environmental agents directly on the developing fetus without interaction with the maternal system. A thorough study is being made of the behavior, reproduction and susceptibility of these animals to various environmental stresses, and techniques are being developed to administer test substances to the fetus without causing any trauma.

The aerotoxicology program is now in the final stages of planning and will be activated at the end of this fiscal year following the completion of the facilities. These new facilities will allow testing of environmental chemicals in order to determine the manner in which they affect organs and tissues following inhalation.

At the time the aerotoxicology program is activated, new modern facilities for animal housing will also be available so that long-range studies involving chronic exposure of animals to environmental toxins can be undertaken. This new facility will considerably enlarge the capability of this Center to adequately house animals for studies of many suspect toxins administered over a long period of time.

Research on the biological effects of physical factors in the environment will initially include ionizing radiation, ultraviolet light, microwaves, and sound. Of a special importance is the dosimetry of non-ionizing radiation fields, that is, a determination of the relationships between field intensities and relevant energy absorption processes and distributions in biological tissues must be related to biological response. Through collaboration with the cell biology program, selected biological tissue and biological end points will be used to compare the relative effectiveness of microwaves, ultraviolet light, x-rays, gamma rays, alpha particles and heat on the basis of quantitative energy absorption measurements and basic interaction mechanisms. Such studies are a first step towards the development of generalized dose-response models having predictive value. The development of novel dose concepts and parametric descriptions which can relate damage mechanisms to physical and biological properties of the insult and the damaged entity is the long-term goal.

Statistical design and analysis of experiments are provided for Institute personnel engaged in laboratory research and human population studies. The purpose of this support is to obtain more significant and relevant results from multifactorial animal and human studies through the use of effective collection of data and subsequent analysis. Based on the theory and techniques of mathematical and analytical statistics and experimental design, this is accomplished by independent and cooperative research studies on the biological effects of environmental agents and their interactions with one another. Statistical services are provided to other agencies in the review of research projects related to environmental health.

The scientific information program provides scientific liaison with categorical environmental health programs to maintain mutual awareness of relevant scientific and technical activities. A system for quick retrieval of information on scientific topics relevant to the Institute's programs is being developed. Reviews of important topics are developed and issued as needed (coal workers pneumoconiosis; nitrates and nitrites, and methemoglobinemia in 1970).

Program Plans in 1972

During 1971 the laboratory space available to the Center will be approximately doubled with the completion of the second phase of interim research facilities. This space, with its specialized design will permit the implementation of new programs. Among the new programs to be implemented are those in: aerotoxicology; the development of special research animal species; investigation of comparative metabolic pathways in man and laboratory animals exposed to chemicals; the effect of exposure to environmental chemicals on early detectable changes in higher cognitive processes in laboratory animals; and the teratologic and genetic effects of exposures to environmental agents. A demography program will provide support and complement these studies through its epidemiology and biostatistics branches, the former facilitating the assessment of laboratory data as applicable to man and the latter providing guidance in experimental design as well as statistical evaluation of the significance of data.

The cell biology program will be expanded to include other toxicants of importance which are not being investigated. Studies on mutagenic effects will be emphasized. Attempts will be made to determine the reactivity of organic and organometallic compounds toward the nuclear genome of mammalian cells in tissue culture and toward isolated DNA from mammalian tissue. The agents selected will be among groups used as insecticides, herbicides, food additives, and various types of industrial chemicals.

As resources become available, additional programs related to subacute toxicology, biochemical pharmacology and physiological pharmacology will be initiated. Present studies on growth and development will be expanded to include studies of the potentially harmful effects of environmental chemicals on prenatal growth, the ability of such chemicals to enter the fetus through the placenta, and postnatal effects of prenatally-administered chemicals.

Chemistry, cell biology, pathology, and pharmacology scientists will collaborate on the development of a biological model system to relate the chemical structure of environmental agents to their ability to interact with various types of Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) cells grown in tissue culture and those in the intact host.

The increase of $1,784,000 includes $1,400,000 and 28 positions for program increases, $93,000 for the annualization of the 1971 pay increase cost, $140,000 for the annualization of new positions received in 1971, $28,000 for cost of within-grade salary advances, $2,000 for FTS rate increase and $121,000 to National Institutes of Health Management Fund for centrally furnished services.

Collaborative Research and Development

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$984,000	---	$1,995,000	---	+$1,011,000
Total	---	984,000		1,995,000		+1,011,000

Introduction

This activity serves the important purpose of supplementing and complementing the Institute's intramural research program. Much of the research to be supported through this activity meets a high priority program need of the Institute but would not normally be proposed or initiated by the investigators. Research in this activity is supported through contracts and performed in collaboration with other Federal agencies, academic institutions and industrial research organizations. The research contract mechanism is employed in those instances where the scientific staff identifies program needs which cannot readily be met through the extramural or intramural programs.

Program Plans in 1971 and 1972

The contract-supported research program is now dealing with the toxicological effects of certain heavy metals, lead and cadmium in particular, with special emphasis on the brain, the liver, and the kidney; the interaction of pesticides and other organic chemicals with cell membranes; the production of mycotoxins by fungi that grow on tobacco; and the health hazards to which uranium miners are exposed. Contract support is also being provided for a study designed to evaluate the feasibility of defining and evaluating a specific biochemical marker which will facilitate automated screening of human population for mutagenic effects.

The increase of $1,011,000 will permit the expansion of on-going programs as well as initiation of new ones in the field of trace metal toxicology, screening of chemical mutagens in appropriate biological systems, evaluation of pesticides chosen to replace the residue forming pesticides and exploration of toxins in natural products. It will also allow the exploration of the hazards of inhalation of particulate matter as well as in the more restricted exposure originating from industrial processes which have been taken over by the hobbyist, the artist and the high school student turned craftsman.

62-645 O - 71 - pt. 3 - 69

Review and Approval of Grants

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	16	$266,000	16	$293,000	---	+$27,000
Other expenses	---	227,000	---	231,000	---	+4,000
Total	16	493,000	16	524,000	---	+31,000

Introduction

This activity, under the Associate Director for Extramural Programs, supports the scientific, administrative, and clerical staffs responsible for the over-all coordination and administration of the Institute's grants and awards program.

Functions for which the staff are responsible include review and evaluation of fellowships, research and training grant applications for presentation to the Advisory Council; liaison with applicants, grantees, advisory bodies, other components of NIH and PHS, and other interested organizations; maintenance of a continuing review of ongoing Fellowships, research and training programs; and the compilation and reporting of scientific and fiscal information relevant to all transactions.

The increase of $31,000 will provide $25,000 for the annualization of the 1971 pay increase cost, $2,000 for mandatory within-grade pay increases and $4,000 to National Institutes of Health Management Fund for centrally furnished services.

Program Direction

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	22	$330,000	22	$344,000	---	+$14,000
Other expenses	---	66,000	---	69,000	---	+3,000
Total	22	396,000	22	413,000	---	+17,000

Introduction

This activity supports the Office of the Director, including the administrative, secretarial, and clerical staff required for the administration, technical direction and coordination of all Institute activities; the review of current and proposed programs; the introduction of new knowledge into currently operating programs; and the provision and supervision of centralized administrative services.

The increase of $17,000 includes $10,000 for the annualization of the 1971 pay increase cost, $4,000 for within-grade pay increases and $3,000 to the National Institutes of Health Management Fund for centrally furnished services.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purpose and Accomplishments

Activity: Research grants (Public Health Service Act, Title III, Part A)

1971			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$9,480,000	Indefinite	---	$11,918,000

Purpose: Research grant funds support activities in the study of environmental health within universities, hospitals, laboratories, and other public or private nonprofit institutions. These grants stimulate new studies in fields where further exploration seems likely to be productive.

Explanation: Most of the projects supported by these funds represent a continuation of ongoing research concerned with the source, mode of entry, and biological effects of noxious agents in man's environment. The projects vary in scope from cellular and subcellular studies of the mechanisms of toxicity to field investigations to identify environmental agents acting as determinants of disease in man. They range in complexity from the small circumscribed activity of the individual researcher to broad-based programs that involve the integrated efforts of investigators from a variety of scientific disciplines. Knowledge derived from these projects will ultimately provide a basis for the setting of standards and the development of control activities.

Accomplishments in 1971: During this year, 26 new projects were initiated in areas of key concern, including pesticides, food toxicants, occupational hazards, heavy metals, physical hazards, chemical air pollutants and contaminants of water supplies. In addition, the Institute provided support for six university-based centers. These centers, each with its own area of special interest, pursue work in the areas of environmental toxicology, respiratory disease and aerosol physiology, pesticide biology and others.

Objectives for 1972: The budget request provides for an increase of approximately 25 research projects. These projects will be focused on those areas of particular concern to the Institute.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purpose and Accomplishments

Activity: Fellowships (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$264,000	Indefinite	---	$264,000

Purpose: The fellowships program is a highly flexible means for supporting the research training of individuals at various stages of career development.

Explanation: These awards provide salary support over a five-to-eight year period for highly selected young scientists who have completed their basic research training and who have displayed outstanding aptitude for research.

Accomplishments in 1971: During 1971, the Institute supported 19 fellowships in the various categories with increased emphasis on the special and research career development awards categories.

Objectives for 1972: The funds requested will provide for 18 awards, one less than in 1971.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purpose and Accomplishments

Activity: Training grants (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$2,843,000	Indefinite	---	$2,843,0000

Purpose: Graduate research training grants are made to educational institutions to improve and to enlarge the supply of qualified scientists who can engage in research on environmental health.

Explanation: The grants are awarded to institutions to strengthen the institutional support of training programs and to provide training opportunities for both part-time and full-time students at the pre- and post-doctoral levels in a wide range of disciplines central to the mission of the Institute.

Accomplishments in 1971: In 1971, there were 42 training programs supported by the Institute to provide training opportunities for 336 trainees.

Objectives for 1972: The estimate for 1972 provides for 34 training programs, eight less than in 1971. This reduction will be in the area of non-competing awards while competing awards will increase.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purpose and Accomplishments

Activity: Laboratory and clinical research (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
197	$5,530,000	Indefinite	225	$7,314,000

Purpose: The intramural research program of the Institute was created for the purpose of investigating at the fundamental level the long-term subtle effects of environmental agents potentially hazardous to man.

Explanation: These studies are directed to the development of a scientific base for use in establishing standards and devising remedial measures. This information is a prerequisite to the establishment of generalizations and principles which can be applied in effort to assure protection of exposed populations.

Accomplishments in 1971: Late this year the Center's laboratory space will be approximately doubled with the completion of the long awaited critically needed second phase of interim research facilities. This space with its specialized design will permit the implementation of long delayed new programs in aerotoxicology, the development of special research animal species, investigation of comparative metabolic pathways in man and laboratory animals exposed to chemicals, and the teratologic and genetic effects of exposures to environmental agents.

Objectives for 1972: All new requested positions are required to activate this new highly sophisticated research space. These positions will enable the Institute to plan and carry out long deferred studies which will provide the scientific basis for the criteria which must be promulgated by the various environmental control agencies.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purpose and Accomplishments

Activity: Collaborative research and development (Public Health Service Act, Title III, Part A)

1971			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$984,000	Indefinite	---	$1,995,000

Purpose: This activity serves the important purpose of supplementing and complementing the Institute's intramural research program. Much of the research to be supported through this activity meets a high priority program need of the Institute but would not normally be proposed or initiated by the investigators.

Explanation: Research in this activity is supported through contracts and performed in collaboration with other Federal agencies, university research centers, and industrial research organizations. The scientific staff identifies areas of concern where a research contract can more effectively provide the linkage or complementary effort needed but not readily available through the extramural or intramural research approach.

Accomplishments in 1971: During 1971 the Institute is continuing its support of contract research relating to a number of areas including the subcellular pathology of heavy metal intoxication; the detection of human somatic mutations, the study of the combined effects of smoking, inhalation uranium ore dust, radon daughters, and diesel oil fumes in hamsters and dogs; and the operation of the beryllium case registry. Additional studies being considered for support in 1971 include the toxicology of fungicides, the immunogenicity of inorganics, and the development of microwave radiation dosimetry techniques.

Objectives for 1972: The Institute will continue its contracts concerned with screening of chemical mutagens in appropriate biological systems, evaluation of pesticides chosen to replace the residue-forming pesticides, and exploration of toxins in natural products. In addition, projects will be supported to explore the hazards of inhalation of particulate matter originating from industrial processes, the equilibrium of trace metals and the toxic effect of air pollutants.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purpose and Accomplishments

Activity: Review and approval of grants (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
16	$493,000	Indefinite	16	$524,000

Purpose: This activity supports the scientific, administrative, and clerical staffs responsible for the over-all coordination, and administration of the Institute's grants program.

Explanation: The extramural staff is responsible for review and evaluation of fellowships, research and training grant applications for presentation to the Advisory Council; liaison with applicants, grantees, advisory bodies, other components of NIH and PHS, and other interested organizations; maintenance of a continuing review of ongoing research and training programs; and the compilation and reporting of scientific and fiscal information relevant to all transactions.

Accomplishments in 1971: During the year, an estimated 190 grants were reviewed for scientific merit and program relevance, and surveillance was maintained over 164 grants. During 1970, the major portion of the grants program was relocated to the Institute headquarters in the Research Triangle Park, North Carolina. Completion of this move will be made during 1971.

Objectives for 1972: Staff activities will continue at the 1970 and 1971 level, with greater emphasis placed on the development of new programs in a wide variety of important areas.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purpose and Accomplishments

Activity: Program direction (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
22	$396,000	Indefinite	22	$413,000

Purpose: This activity supports the Office of the Director of the Institute.

Explanation: The Office of the Director includes the immediate Office of the Director and includes the administrative, secretarial, and clerical staff required for the administration, technical direction, and coordination of all Institute activities; the review of current and proposed programs; the introduction of new knowledge into currently operating programs; and the provision and supervision of centralized administrative services.

Accomplishments in 1971: The Institute's contribution to the growing Federal responsibility for environmental quality is emphasized by the completion and publication in 1970 of the Report of the Task Force on Research Planning in Environmental Health Sciences. This report addresses itself to the broad array of environmental health problems and the potential means for their solution, with particular attention to those of greatest urgency. The report is important because it carries with each of the problems identified suggested means for their solution on the general, specific, short-range and long-range levels. During 1971, the Office of the Director will devote a significant portion of its resources to the establishment of effective and working relations with the newly created Environmental Protection Agency.

Objectives for 1972: The Office of the Director will continue to devote most of its resources to the selection of the research questions which most need investigation and to the planning and direction of the total programs of the Institute.

New Positions Requested
Fiscal Year 1972

	Grade	Number	Annual Salary
Laboratory and Clinical Research			
Scientist	GS-15	1	$24,251
Scientist	GS-14	1	20,815
Scientist	GS-13	2	35,522
Scientist	GS-12	6	90,240
Biological Laboratory Assistant	GS- 7	2	17,164
Biological Laboratory Assistant	GS- 5	3	20,814
Clerical Assistant	GS- 4	1	6,202
Laboratory Assistant	GS- 4	1	6,202
Laboratory Assistant	GS- 3	1	5,524
Biological Aid	GS- 2	10	48,970
Total		28	275,704

MONDAY, MAY 10, 1971.

RESEARCH RESOURCES AND GENERAL RESEARCH SUPPORT GRANTS

WITNESSES

DR. THOMAS G. BOWERY, DIRECTOR
DR. JOHN F. SHERMAN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ROBERT W. BERLINER, DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DAVID L. CHICCHIRICHI, EXECUTIVE OFFICER, DIVISION OF RESEARCH RESOURCES
BERTIL G. BERGQUIST, BUDGET OFFICER, DIVISION OF RESEARCH RESOURCES
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
B. FRANK GARDNER, JR., ACTING ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

Research Resources

Object Classification (in thousands of dollars)

Identification code 09-30-0848-0-1-651		1970 actual	1971 est.	1972 est.
	Personnel compensation:			
11.1	Permanent positions	2,496	1,050	1,092
11.3	Positions other than permanent	10	9	10
11.5	Other personnel compensation	42	28	36
	Total personnel compensation	2,548	1,087	1,138
12.1	Personnel benefits: Civilian employees	269	117	121
21.0	Travel and transportation of persons	131	102	102
22.0	Transportation of things	20	8	8
23.0	Rent, communications, and utilities	195	42	42
24.0	Printing and reproduction	34	44	18
25.0	Other services	3,447	1,566	1,677
26.0	Supplies and materials	86	17	17
31.0	Equipment	530	5	5
41.0	Grants, subsidies, and contributions	59,672	63,288	64,788
99.0	Total obligations	66,932	66,276	67,916

Personnel Summary

Total number of permanent positions	186	84	84
Full-time equivalent of other positions	4	3	4
Average number of all employees	185	82	83
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

Program and Financing (in thousands of dollars)

Identification code 09-30-0848-0-1-651		1970 actual	1971 est.	1972 est.
	Program by activities:			
	1. Research resources:			
	(a) Grants:			
	(1) Research	58,195	62,810	64,310
	(2) Fellowships	106	126	126
	(3) Training	317	352	352
	(b) Direct operations:			
	(1) Collaborative research and development	983	1,385	1,384
	(2) Review and approval	702	956	1,044
	(3) Program direction	514	647	700
	2. Division of computer research and technology	4,240	----------	----------
	Total program costs, funded [1]	65,057	66,276	67,916
	Change in selected resources [2]	1,875	----------	----------
10	Total obligations	66,932	66,276	67,916
	Financing:			
25	Unobligated balance lapsing	107	----------	----------
	Budget authority	**67,039**	**66,276**	**67,916**

Program and Financing (in thousands of dollars)—**Continued**

Identification code 09-30-0848-0-1-651		1970 actual	1971 est.	1972 est.
	Budget authority:			
40	Appropriation	76,658	66,201	67,916
40	Portion withdrawn (Public Law 91-204, sec. 410)	−8,632	----------	----------
41	Transferred to other accounts	−987	----------	----------
43	**Appropriation (adjusted)**	**67,039**	**66,201**	**67,916**
46.10	**Proposed transfer for wage-board increases**	----------	1	----------
46.20	**Proposed transfer for civilian pay act increases**	----------	58	----------
46.30	**Proposed transfer for military pay act increases**	----------	16	----------
	Relation of obligations to outlays:			
71	Obligations incurred, net	66,932	66,276	67,916
72	Obligated balance, start of year	54,855	45,750	42,197
74	Obligated balance, end of year	−45,750	−42,197	−42,536
77	Adjustments in expired accounts	−440	----------	----------
90	Outlays, excluding pay increase supplemental	75,597	69,757	67,574
91.10	Outlays from wage-board supplemental	----------	1	----------
91.20	Outlays from civilian pay act supplemental	----------	55	3
91.30	Outlays from military pay act supplemental	----------	16	----------

[1] Includes capital outlay as follows: 1970, $530 thousand; 1971, $5 thousand; 1972, $5 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $8,625 thousand; 1970, $8,850 thousand; 1971, $8,850 thousand; 1972, $8,850 thousand.

NOTES

Includes $121 thousand in 1972 for activities previously financed from (in thousands of dollars):

	1970	*1971*
Division of Biologics Standards	--	94
National Cancer Institute	--	27
National Institute of Allergy and Infectious Diseases	91	--

Excludes $4,472 thousand in 1971 and $4,535 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970
Division of Biologics Standards	116
National Cancer Institute	684
National Heart and Lung Institute	630
National Institute of Dental Research	281
National Institute of Arthritis and Metabolic Diseases	703
National Institute of Neurological Diseases and Stroke	411
National Institute of Allergy and Infectious Diseases	738
National Institute of General Medical Sciences	117
National Institute of Child Health and Human Development	411
National Eye Institute	107
National Institute of Environmental Health Sciences	162

Excludes $12 thousand in 1972 for activities transferred to: Office of the Director, 1970, $8 thousand; 1971, $10 thousand.

General Research Support Grants

Program and Financing (in thousands of dollars)

Identification code 09-30-3968-0-4-651		1970 actual	1971 est.	1972 est.
	Program by activities:			
10	General research support grants (costs—obligations) (object class 41.0)	57,677	60,700	49,200
	Financing:			
11	Receipts and reimbursements from: Federal funds	−57,677	−60,700	−49,200
	Budget authority			
	Relation of obligations to outlays:			
71	Obligations incurred, net			
72	Obligated balance, start of year	61,776	61,017	62,664
74	Obligated balance, end of year	−61,017	−62,664	−64,380
77	Adjustments in expired accounts	−276		
90	Outlays	483	−1,647	−1,716

INTRODUCTION OF DR. BOWERY AND STAFF

Mr. FLOOD. We continue with the National Institutes of Health and now have "Research resources" and also "General research support grants." The presentation will be made by Dr. Thomas G. Bowery.

Doctor, of course these are two separate headings but closely related, and I gather you will present them both.

Dr. BOWERY. That is correct, sir.

Mr. FLOOD. We have biographical sketches of you and your associates.

(The biographical sketches follow:)

BIOGRAPHICAL SKETCH OF THOMAS G. BOWERY

Position: Director, Division of Research Resources.

Birthplace and date: Bellevue, Pa., December 17, 1921.

Education: B.S., Michigan State University, 1943; M.S., Rutgers University, 1948; Ph.D., Rutgers University, 1951.

Experience: Director, Division of Research Resources, 1969 to present; Acting Director, Division of Research Resources, 1968–1969; Associate Director for Operations, Division of Research Facilities and Resources, National Institutes of Health, 1967–1968; Assistant Chief for Operations, Division of Research Facilities and Resources, NIH, 1965–1967; Extramural Operations and Procedures Office, Office of the Director, NIH, 1964–1965; Special Assistant to the Associate Director for Research Grants, Office of the Director, NIH, 1963–1964.

Grants Associate, Division of Research Grants, NIH, 1962–1963; Research Professor, Department of Entomology, North Carolina State College, Raleigh, N.C., 1959–1962; Research Associate Professor, Department of Chemistry, North Carolina State College, Raleigh, N.C., 1953–1959; Research Assistant Professor, Pesticide Residue Laboratory, Everglades Experiment Station, University of Florida, Belle Glade, Fla., 1951–1952; Research Associate in Chemistry, Office of the State Chemist, New Jersey Agricultural Experiment Station, New Brunswick, N.J., 1948–1951; Research Fellow, Entomology Department, Rutgers University, New Brunswick, N.J., 1946–1948.

Association memberships: American Association for the Advancement of Science; American Chemical Society; and Sigma Xi.

Publications: Author of some 23 publications in seven journals.

BIOGRAPHICAL SKETCH OF DAVID L. CHICCHIRICHI

Position: Executive Officer, Division of Research Resources.

Birthplace and date: Millville, W. Va., December 28, 1933.

Education: B.S., Shepherd College, 1959; Annual Summer Institute for Federal Executives, University of Wisconsin, 1967; Federal Budgetary Procedures: Formulation and Presentation, U.S. Department of Agriculture Graduate School, 1968; The Environment of Federal Operations, Executive Seminar Center, Berkeley, Calif., 1970.

EXPERIENCE

Executive Officer, Division of Research Resources, National Institutes of Health, 1971 to present.

Assistant Executive Officer, National Institute of Child Health and Human Development, NIH, 1968–1971.

Administrative Officer, Office of the Director, National Institute of Child Health and Human Development, NIH, 1965–1968.

Grants Management Specialist, Extramural and Contract Management Branch, National Institute of Child Health and Human Development, NIH, 1963–1965.

Administrative Officer, Grants Management Branch, Division of Research Grants, NIH, 1962–1963.

Audit Assistant, Grants Management Branch, Division of Research Grants, NIH, 1961–1962.

Time Inspector, Melpar, Inc., Falls Church, Va., 1959–1961.

BIOGRAPHICAL SKETCH OF BERTIL G. BERGQUIST

Postion: Budget Officer, Division of Research Resources.
Birthplace and date: Pjatteryd, Sweden, March 31, 1922.
Education: B.S., University of Maryland, 1952, Business and Public Administration, Accounting; 1946–1948, Engineering, University of Maryland.
Experience: Budget Officer, Division of Research Resources, National Institutes of Health, 1965 to present; Budget Analyst, Division of Research Facilities and Resources, National Institutes of Health, 1964–1965; Budget Analyst, Bureau of State Services, Public Health Service, DHEW, 1962–1964; Auditor, Division of Internal Audit, Office of the Secretary, DHEW, 1956–1962; Accountant, Division of Audits, General Accounting, 1953–1956; Junior Accountant, Emanual and Pear, Certified Public Accountants, 1952–1953.

Mr. FLOOD. Do you have anybody on board who you think we should know?

Dr. BOWERY. Yes; I have to my left Mr. David Chicchirichi, who is the new executive officer of the division, and Mr. Bergquist, our budget officer, who has been here before.

GENERAL STATEMENT

Mr. FLOOD. Now, you have a prepared statement on both of these items. How do you wish to proceed, Doctor?

Dr. BOWERY. I would like to read this into the record, sir.

Mr. FLOOD. Very well; we will do that.

DIVISION OF RESEARCH RESOURCES

Dr. BOWERY. Mr. Chairman and members of the committee:

In September 1970, in keeping with the expressed intent of this committee, the Division of Research Resources was reorganized out of the Bureau of Health Manpower Education and was established as a free-standing research Division of the NIH. We feel that this status will provide a clearer picture of the Division's programs of support of research resources and general research support and how they complement and undergird much of the research project grant support of the categorical institutes.

Mr. FLOOD. I would like to say for the committee that we appreciate your reaction to these suggestions so promptly.

Dr. BOWERY. We try to react quickly.

Mr. FLOOD. That doesn't always happen around here, but you did.

Dr. BOWERY. The mission of the Division of Research Resources (DRR), in support of the categorical activities of the NIH is: (1) To establish and sustain those resources essential to the advancement of biomedical research and research training leading to the improvement of the health of the Nation; (2) to assist in the maintenance of the autonomy and individuality of academic institutions; and (3) to support innovative biomedical research programs developed primarily through the initiative of the grantee institution in areas of the health sciences where the provision of the research resource provides the

critical mass for successful investigations. In our effort to fulfill this mission, DRR has mounted four basic programs.

Mr. FLOOD. What do you mean by biomedical research? What does the term "biomedical" mean?

Dr. BOWERY. It involves the linkage of the study of the life processes with the actual utilization of this information in a medical context such as in a clinical setting.

BASIC PROGRAMS

1. The general clinical research centers program with objectives to: (a) provide, in both effective form and adequate numbers, the facilities and resources for continuing and expanding the capability of the Nation's clinical investigators to study human disease in a research setting; and (b) extend the capability of medical science to treat and manage disease by applying at the bedside the fundamental biological knowledge acquired in basic research programs.

2. The biotechnology resources program with objectives to: (a) enhance the Nation's biomedical community access to the latest advances in computation, mass spectrometry, and other highly sophisticated technologies originating in the physical sciences; and (b) sponsoring centers of scientific and technological excellence on an institutional, regional, and national basis, by providing tools and capabilities for modern life science research and patient care with efficiency, economy, and effectiveness.

3. The animal resources program with objectives to develop and provide the resources that: (a) upgrade institutional laboratory animal medicine research and care; (b) maintain specialized animal models; and (c) develop the national resource of seven primate research centers that seek to extend studies on primates to the diseases of many by providing sources of healthy primates in the United States and the proper environment needed to undertake such studies.

PROBLEMS IN OBTAINING PRIMATES

Mr. FLOOD. Let me ask you this. In your use of primates for whatever reasons in your programs, do you permit these animals to reproduce?

Dr. BOWERY. We not only permit them; we encourage them.

Mr. FLOOD. Well, what I had in mind was that I heard some time ago we are having a little trouble getting these primates. Of course, that is importing.

Dr. BOWERY. Yes, sir. It involves bringing them in from foreign countries.

Mr. FLOOD. You are having trouble, I gather.

Dr. BOWERY. That is correct. Due to the war in Southeast Asia and the civil unrest that sometimes occurs in South America situations evolve where the foreign governments do not wish to export these animals. Also they have their own conservation problems in these settings.

Mr. FLOOD. Are we being seriously impaired or just impaired?

Dr. BOWERY. I believe we are being impaired. We hope to mount a study in combination with other agencies and the National Academy of Sciences to at least take a look at the South American species to see how serious this problem is.

RESEARCH ON RAT REPRODUCTION

Mr. MICHEL. Mr. Chairman, would you permit a question at this point? It may not be altogether apropos but it reminds me of one I wanted to ask generally of NIH before. I read recently where a scientist had started out with eight pairs of mice and in a confined locality but with proper food, et cetera, they had grown to over 2,000 in number and to such extent that 600 died; then they had lost the urge to reproduce. This was, I thought, a part of a study in population control. Was this funded by NIH, by any chance?

Dr. BERLINER. That is in the National Institute of Mental Health.

Mr. FLOOD. Please continue, Dr. Bowery.

THE GENERAL RESEARCH SUPPORT PROGRAM

4. The general research support program with the objective to provide general support to health professional and university graduate schools and other biomedical research organizations so as to enhance the effectiveness of the research projects underway at these institutions, to redress imbalances in institutional research activities, and at the same time permit the development of institutional objectives along self-articulated lines.

CLINICAL RESOURCE

With these objectives in mind, I would like to briefly discuss how we are adapting these programs to the changes in the broad needs of the categorical programs of the NIH and to close with a few pertinent examples of our interrelationship with some of the new research initiatives of the NIH.

Traditionally, clinical investigations have concentrated on diseases causing mortality and acute illness found in a hospitalized environment. Although this research has been and is vitally important, many chronic and disabling diseases have been studied far less than their prevalence merits. These diseases are especially amenable to study in the ambulatory patient in the outpatient research setting. In order to capitalize on the opportunity for outpatient research, the program is encouraging a partial shift in resources to be devoted to outpatient research studies. It is expected that most centers will operate with combined inpatient-outpatient research in fiscal year 1972.

BIOTECHNOLOGY RESOURCES

An increasingly larger fraction of medical research activities each year is concerned with the molecular bases of disease, and this trend is necessarily accompanied by an evergrowing demand for tools and capabilities such as mass spectrometry, nuclear magnetic resonance, X-ray crystallography, and electron optics, all of which help to provide information at the molecular level. Once identified almost exclusively with life science computer centers, the biotechnology resources program today is a focal point for many types of intricate and expensive technology. By facilitating access to highly specialized instruments and methodologies and their associated expertise, this program is systematically helping to eliminate the barriers between the physical and

biological sciences. The biotechnology resources program has already made substantial progress in meeting some of these needs and expects to direct much of the thrust of its future efforts this way.

ANIMAL RESOURCES

All major medical research and educational institutions require a comprehensive animal resources program. Over half of the biomedical research effort in NIH grant eligible institutions is dependent on the use of animals. Of animals used in these institutions, 68 percent are used for research, 25 percent for educational purposes, and 7 percent for diagnosis, testing, and other purposes. These institutions spend over $50 million per year for the purchase and maintenance of animals. The importance of animal resources is reflected in the fact that over 55 percent of the National Institutes of Health's supported research project grants require the use of animals. In many of these projects, the quality of the animal is becoming a more crucial factor in the experiments. Therefore, we are giving increasing emphasis to: (1) strengthening disease control programs by supporting clinical and diagnostic laboratories devoted to laboratory animal disease; and (2) providing funds for improved management of animal resources.

Categorical institute-sponsored research, employing primates, is receiving increased emphasis. Several institutes have indicated these studies will require a large number of primates, preferably bred and raised under standard conditions and with known medical histories. The seven primate research centers are playing a key role in meeting this need.

GENERAL RESEARCH SUPPORT

Viewed as complementary to project grants, the general research support (GRS) formula-grant program provides funds on a continuing basis to eligible institutions for their flexible and discerning use in their research and research training activities. The program's overall objective has been to advance (or strengthen) the medical and health-related research and research training activities of these institutions. GRS is a necessary element in the total support system through which an institution can forge new directions, innovate programs, support fledgling ideas and the people willing to undertake them. Hopefully, it is the linkage that makes the institution a cohesive health research and research training entity, rather than a set of discrete programs and projects, and enables it to develop an integrated atmosphere for growth in quality.

RESEARCH ON CHILD DEVELOPMENT

Growth during the first quarter of life is generally devoted to accumulating gains in cells, height, weight, and bone maturation. Categorical investigators utilizing general clinical research center facilities have developed a much greater understanding of these four major growth indices. Already this increased comprehension has enabled researchers to correct numerous growth processes that have gone awry. For example, these scientists have induced growth in individuals whose deficiency of pituitary hormones was causing them to suffer an ailment

62-645 O—71—pt. 3——70

known as hypopituitary dwarfism. By the end of 1970, an estimated 2,000 hypopituitary dwarfs had been treated with human growth hormone at General Clinical Research Centers, one of the few facilities in the Nation where the hormone has been available.

Scientists utilizing DRR-supported animal resources are also working actively in the area of child development. A group of specially trained researchers in a primate center have completed a comprehensive study of normal fetal development in monkeys. Fetal tissue taken from macaques, a type of monkey, at six different gestational stages has been intensively studied and analyzed, and complete reports on the development of all major organs and the progress of all growth have been completed. This has set the stage for an attack at the primate centers on the problems of serious infant malformations or developmental defects. A team of primate center scientists is currently studying the effects of drugs, viruses, low blood oxygen level, and different metabolic states on developing monkeys.

CANCER RESEARCH

The division of research resources participates directly and indirectly in the total NIH effort to find a cure for this dread disease. For example, at one of the computer facilities supported by the biotechnology resources program, researchers are attempting to identify the characteristics of patients who are in the "high risk" category for breast cancer. This disease is one of the leading causes of death from cancer in women. Early detection still remains the most effective way to halt this disease. The division-supported computer center is cooperating with 14 other institutions in developing a suitable combination of characteristics that will predict "high risk" women.

Physicians using clinical resources are actively engaged in studying a new approach to the treatment of Hodgkin's disease. This disease is characterized by the malignant enlargement of lymph nodes, and spleen, with fatal spread to other organs of the body. Patients with Hodgkin's disease have an immunologic defect related to thymus gland function. It is theorized that this immunologic incompetence may play a key role in controlling the spread of this malignancy. Seventeen patients with Hodgkin's disease have received human fetal thymus gland transplants and over half have achieved a return to immunologic responsiveness.

Mr. FLOOD. Hodgkin's disease is progressive, isn't it?

Dr. BOWERY. Yes, I believe it is, sir.

Followup of these patients is required to evaluate the value of this treatment for the long-term control of this disease.

The flexibility of general research support assisted an institution in designing a comprehensive program of excellence involving seven different departments in research on the membrane components of cells and tissue. Knowledge of membrane structure and function is essential to an understanding of the cancer process.

HEART DISEASE RESEARCH

A significant portion of the funds allocated to the division are utilized for the conduct of research on the causes and cure of heart disease. For example, during the past year, a team of researchers at

a general clinical research center developed a new, simple noninvasive method of diagnosing diseased arteries. The new process uses the same principle as the familiar stethoscope; instead of listening to heart beats, however, the team electronically listens to and visually displays the sound of blood flowing in the patient's arteries. This new technique when perfected will allow an investigator to conduct research outside of the human body, as opposed to probing into the arteries.

A different approach involves biological and physical scientists at a computer resource. Using relatively innocuous indicator dilution methods in experimental animals and human patients, they are beginning to acquire facts about the nature of blood distribution leading to mathematical modeling and computer simulation. While much remains to be done so far as mathematical analyses and characterizations of cardiovascular phenomena in normal and diseased states are concerned, the efforts of the group in many ways represent a standard for the kinds of multidisciplinary approaches which the solutions of our major health problems will require.

A GRS funded pilot project led to the development of a rechargeable nickel cadmium battery for use as an implantable cardiac pacemaker. This rechargeable pacemaker, one-third the size of conventional models, was cited as one of the 100 most significant new inventions of 1970. Pacemakers utilized prior to this had to be surgically removed every 2 years to be recharged. This pacemaker, however, can be recharged easily and simply through the patient's skin with the patient feeling no pain sensation during the process.

Research advances such as these cited above are the logical outcome of the partnership in the national biomedical research effort carried out by the NIH categorical institutes, the Division of Research, Resources, and nongovernmental research institutions.

FISCAL YEAR 1972 BUDGET

The President's budget for fiscal year 1972 requests $68,069,000 for research resources and $49,200,000 for general research support for a total of $117,269,000, for the programs administered by the division of research resources, an overall decrease of $3,362,000 from the fiscal year 1971 obligations. This level provides an increase of $1 million for the general clinical research centers, and $500,000 for the biotechnology resources. These are offset by the $5 million decrease in the general research support program.

I would be happy to answer any questions the Chairman or the committee may have.

Mr. FLOOD. It is getting late so we will adjourn now until 10 o'clock tomorrow morning and will, of course, have some questions to ask of you, Doctor.

TUESDAY, MAY 11, 1971.

Mr. PATTEN. The subcommittee will come to order.

Dr. Bowery, it is good to have you here this morning. We enjoyed your presentation yesterday.

Dr. BOWERY. Thank you, sir.

Mr. PATTEN. In fact, parts were quite intriguing.

BUDGET FOR GENERAL CLINICAL RESEARCH CENTERS

You have an increase of $1 million budgeted for the General Clinical Research Centers. This is less than a 3 percent increase. On page 196 you say:

"The increase will be utilized to offset the annual rising hospitalization and personnel costs currently estimated at a minimum of 6 percent."

Well, that is quite a trick. You are going to offset increased costs of at least 6 percent with an increase of less than 3 percent in funds. Can your formula be applied to family budgeting also?

Dr. BOWERY. I doubt it, sir. Our current estimate would indicate that the cost increases for this program will be running possibly higher than 6 percent in the ensuing year. This was an attempt to at least stave off some of that rapidly rising inflation by this $1 million increase.

Mr. PATTEN. We get a lot of mail and some public witnesses' testimony each year to the effect that for the amount of money involved this is one of your most important programs.

If you agree, tell us why, and if you disagree we would also like to know why. What is your own professional opinion?

Dr. BOWERY. I would have to agree with the total allocation of funds to the National Institutes of Health. Priorities were set at levels above my operation and they made a determination that this is the most appropriate amount that they could put into this particular program. From their overview perspective this is the correct amount to support the program.

RESEARCH ON MATERNAL DEPRIVATION DWARFISM

Mr. PATTEN. Tell us a little about worthwhile research conducted at these centers. Just as one example, we would like to hear a little more about the research on maternal deprivation dwarfism mentioned on page 203.

Dr. BOWERY. In studies being carried out in the General Clinical Research Centers, this particular one being at the University of Pittsburgh, research work involving the use of this resource by many investigators has shown that children who are deprived of what we would term a reasonable environment, a loving environment, and subjected to adverse reactions can have an effect on their growth system. It can involve the development of symptomatic hypoglycemia, that is, low blood sugar. This indicates that there is a deficient function of some of the steroid hormones involved in establishing the basic patterns for normal growth, and experimentation shows that when children are relieved from a stressful situation the normal flow of hormones tends to recur and the possibility then exists for them to grow out of this depressing situation.

I think we have all known for a long time that placing children in very stressful situations brings about slowness in their development. We are now investigating the basic scientific facts of why this occurs.

ADEQUACY OF THE RESEARCH GRANT INCREASE

Mr. PATTEN. For research grants you are budgeting an increase from $62,810,000 to $64,310,000, or less than a 3-percent increase. This will mean the program level will have to be cut back some, will it not?

Dr. BOWERY. The program will either stand still or we will not be able to fully award all the funds that the peer system has judged to be appropriate based on the scientific merit of these projects. In the normal competitive review cycle that occurs throughout all of NIH's programs, some Division programs will come to a normal termination and will be slowly phased out. Through the use of these two mechanisms we will be able to stay within the allotted funds that are set forth in the President's current appropriation request.

Mr. MILLER. Mr. Chairman, here we come with a set speech. When you are talking about cost of living, essentially you are talking about the continuation costs; and the continuation costs, no matter what percentage they are, are covered in this budget, so what you are talking about is fewer new grants; but we will cover the cost of living of all of the ongoing work, so that there may be fewer new grants than in the previous year although there will be new grants.

Mr. PATTEN. Is there any reason to hold research grants below the current program level other than to make the budget look a little better to the economizers?

Dr. BOWERY. I would defer again to Mr. Miller on that.

Mr. PATTEN. Repeat his answer to the last question.

Mr. MILLER. That is right. You said it correctly.

GOALS OF THE BIOTECHNOLOGY RESOURCES PROGRAM

Mr. PATTEN. Also, for biotechnology resources you are asking for less than enough to cover increased costs. The only difference is that in this instance the justifications frankly say that the small increase will "help" offset the increased cost of these resources. Give us a little more detail about this program and what it seeks to accomplish.

Dr. BOWERY. The program seeks to accomplish a linkage between the physical scientists who have used large tools of investigation, such as mass spectrometry, nuclear magnetic resonance and computers, with the biosciences, the life sciences. There is a need for interaction between the application of these specialized tools which look very closely at the molecular level and study on certain diseases that occur because of improper configuration of the molecules. This is especially needed in such areas as lipid metabolism. We now have the opportunity through biotechnology resources to establish in universities a linkage between physical scientists and bioscientists and to evolve two sets of opportunities. The first is one in which we carry out research on the state of the art of the technology involved, and to assist these university centers at the forefront by ensuring that they are looking at the technology in relationship to biomedical research problems.

At the same time, surrounding this hard core of basic research, is a service function in which the technology is used to help out other investigators in other universities, sometimes regionally. There are a few cases, such as the computer center at the University of California at Los Angeles that is involved in the very difficult area of tissue typing for kidney transplant that tends to serve the whole nation. Information as to the potential donors of kidneys; for example, the typing of their blood and tissues, is made available through the rapid and skilled expertise available at the computer center at UCLA to investigators throughout the United States and on some occasions throughout the

world. The resource is bridging a gap between physical sciences and medical sciences. It is carrying out research within the linkage that develops and then applying this to real life problems that are brought to it by other investigators. As I said before, even larger regions are sometimes involved in this activity.

MASS SPECTROMETRY

Mr. PATTEN. You used the expression "mass spectrometry."

Dr. BOWRY. That is right.

Mr. PATTEN. Could you elucidate a bit on that?

Dr. BOWRY. Every compound has a certain mass and when placed in an electrical arc and burned the compound gives off what we call emission spectra, certain lines on a photographic plate that indicate the composition of the material. By matching the emission spectra of known compounds to unknown compounds you can make identifications. This is an important tool when coupled with other technology for making basically what might be called a fingerprint of the compound. If you have a compound and you are not quite sure what it is, you can run it through a mass spectrometer, get the emission lines, match them against the series of knowns, and be able to narrow down, focus and identify the compound.

ENHANCING RESEARCH BY DISSEMINATION OF RESOURCES

Mr. PATTEN. You say you want to enhance the Nation's biomedical community access to the latest advances in automatic computers, and mass spectrometry, and these other sophisticated things. Were you the Department that was going to have a television receiving set in every doctor's office in the country from a central place and if at 4 o'clock they felt like sitting back and watching something up to date, in 15 minutes in his own office he could have it brought home to him?

Dr. BOWERY. No; that is another element of HEW, sir. They are using computers from the standpoint of trying to develop consultation between certain central resources and the doctor's office. Our activity is more at the basic research level. We have a working link with these organizations and pass on our expertise to the organization in HEW that is evolving this type of program. Our "enhancement" is that of trying to establish a broader geographic base. As an example we recently made a grant to Rutgers University for a computer facility that allows people in this region to utilize this new capability. It is very difficult for any one small group of investigators to readily justify a large installation but when we have an entire university, and on occasion more than one university involved, we can put this kind of resource investment in certain geographical areas. We have approximately 36 computer centers around the country, ranging from the east coast to the west coast.

Another example of "enhancement" is the establishment at the University of Colorado at Boulder of a high voltage electron microscope. The "enhancement" comes by establishing a new scientific and geographical focus since some of the expertise that was resident in Harvard University has moved to the Rocky Mountain area. Through the resource mechanisms we are trying to spread some of the capability

from high foci of technology into others who need it but currently do not have it.

The Colorado example, I think, is an opportunity for us to bring this about.

EQUIPMENT GRANT SELECTION METHODS

Mr. PATTEN. You mentioned Rutgers and Boulder. How do you determine which institutions receive this equipment?

Dr. BOWERY. Basically, there are two approaches to this. Institutions on their own initiative will submit applications to us, be reviewed by their scientific peers and brought forth to our National Advisory Research Resources Council, and a final judgment made as to whether a project is meritorious. Then within the limitations of our budget ability we will fund such resources.

The other approach is to utilize the knowledge of our own staff as to where capabilities lie in some of these technology areas. We go out and discuss with prospective applicants the opportunity to create a resource in their own region. Once we have discussed this with them, then they are free to apply or not apply, be processed through the peer review system and, hopefully, final funding.

RECIPIENT CONTRIBUTIONS TO RESOURCE COSTS

Mr. PATTEN. I saw them installing a magnet at Rutgers, bought in Switzerland at $240,000, in the nuclear physics building. They are trying to curve the path of atoms and other particles; bend it and speed up the velocity through magnetic force. Can you imagine $240,000 for a magnet? Now, you are going to build out there probably at Boulder a 1-million-volt electron microscope. How much of the cost is being borne by the university?

Dr. BOWERY. I am not sure of the exact amount, sir. Possibly a part of the cost is being borne by the university in the construction of the building. This was possibly also partially funded from the National Science Foundation. I would judge that half of the cost of the building to house the instrument may be borne by the university.

(The following information was subsequently submitted:)

HIGH VOLTAGE ELECTRON MICROSCOPY RESOURCE IN COLORADO

The University of Colorado has committed a significant amount of its own funds toward the Regional High Voltage Electron Microscopy Resource recently established under the sponsorship of DRR's Biotechnology Resources Branch. The university has already expended over $250,000 in association with the building, space preparation, and other preliminary arrangements and is pledged to expend the equivalent amount or more in personnel and basic utility costs over the next 5 years in support of the resource operations. Thus, over the first 5 years of the resource's life it is expected that the relative distribution of costs will be as follows: University of Colorado a minimum of $500,000 and the DRR, NIH, approximately $1.5 million.

Mr. PATTEN. I believe you have such an electron microscope in Wisconsin now.

Dr. BOWERY. We have one in Wisconsin and we are now in the process of establishing one at the University of Colorado at Boulder, so there will be two in the Nation.

Mr. PATTEN. But the university does bear part of the cost?

Dr. SHERMAN. Yes, and I think there is another consideration here. The whole concept of this division has two related but separate purposes in mind. One, as Dr. Bowery has pointed out, is to use a different access by which to bring the capabilities of a variety of scientific disciplines together on problems where an opportunity exists for that multidisciplinary effect to do more than a single discipline. The other comes out largely in this latest example, namely, the question of economy of scale where, on the one hand, we are attempting either to have an institution which serves a regional purpose to improve its capabilities both in and of itself, and for that region, or the other, where we take advantage of the knowledge in a scientific sense that a particular group at that institution has, and can serve a very broad function for lots of investigators. In such a case it is felt to be more economical to provide a resource at one location rather than, say, three in scattered places around the area.

UTILIZATION OF RESEARCH RESOURCES BY INDUSTRY

Mr. PATTEN. I don't know whether with, say, your 1 million-volt electron microscope you would have industry and a lot of other people in the neighborhood who want to use it sometimes, but I know at some of the new facilities at Rutgers one of the big problems is that in just one instance 88 industries want it part-time. It reminds me of our Naval testing station here on the Potomac, north of us I guess. By law, we had to fix it so that the Merchant Marine and private ship builders could use the testing facilities part of the time. Now the developing nations of the world that don't have a testing facility want to use the Navy testing facility here, and I was just wondering on some of your sophisticated technology whether Wisconsin, Rutgers, and Boulder will have trouble with other people in the community, mostly industry, who will want to use this facility, or don't you anticipate this, in the case of the electron microscope?

Dr. BOWERY. Normally, we no not have problems from industry wanting to use these resources. One of our problems is really trying to encourage other university investigators to come to these resources. Sometimes they are reluctant to utilize such resources, but we point out that we have deliberately established these on a geographical basis and encourage them to use them. As Dr. Sherman said, the economy of scale permits this, and since we are not in a position to foster a large number of these around the Nation, we feel it is an opportunity to bring investigators together. From the standpoint of industry we have had very little problems involved with them seeking out these resources.

Mr. PATTEN. Doctor, I could give you an example of the facilities at the Nuclear Physics Building at Rutgers. Our drug industry and many others want to use the facility sometimes for their own work.

Dr. BOWERY. If there are cooperative activities that would involve the university scientists and industrial scientists in a collaborative venture, we would encourage them.

Mr. PATTEN. The question is, and I thought I was laying a foundation for the question, who determines the scientists who may use such a piece of equipment and what rules and regulations or guidelines are used in making these determinations?

Dr. BOWERY. Basically, we use as a guide that NIH project grant holders are the ones who are most vigorously encouraged to use these facilities and who do use these facilities. Secondly scientists who are engaged in biomedical research but may not be holders of NIH project grants are the second group that would tend to use these facilities, and then on rare occasions if the facility is not totally used by these two groups of investigators, researchers who are studying in the field of biosciences that has some relation to medical activity would be the third cadre of individuals that utilize these resources. Normally the first two make ample use of such resources.

COMPUTER RESOURCES IN THE R. & D. PROGRAM

Mr. PATTEN. What is the difference between your computer resources activities under your biotechnology resources program and your computer resources activities under your collaborative research and development program?

Dr. BOWERY. The collaborative program is a contract program in which we are trying to establish a very—what we might term—interactive system in which using the computer-based apparatus, pharmacologists in various locations can interact and talk through the computer system and, more importantly, visualize on the computerscope the actual molecule that they are discussing. They are actually able to rotate the pictorial representation of the molecule, add or subtract certain carbon atoms and other atoms involved in the molecule. This really permits an interactive situation rather than forcing them to take an idea, go to a library for literature references, study them and then discuss it. The new interactive system allows an opportunity in an online situation to visualize the compound they are dealing with and interact rapidly with their colleagues.

This is in the early stages of a pilot activity. It is a highly specialized program dealing specifically with pharmacology and the interaction of drugs and life processes.

CUTS IN GENERAL RESEARCH SUPPORT GRANTS

Mr. PATTEN. Let's turn last to the General Research Support Grants. You again are proposing to cut back the basic research support grants from $43,423,000 to $40,800,000, a reduction of $2,623,000. You are practically certain this will be restored, aren't you?

Dr. BOWERY. I am not certain. I am hopeful. I think the basic reason for this reduction is the recognition that in the current fiscal constraints there is a need to utilize the funds in what might be termed special

initiatives or highly targeted programs. This, I believe, is how this offset is to be used.

Mr. MILLER. And there is one additional reason, Mr. Chairman. There is a lot of money for institutional support to medical schools in our health manpower budget under existing legislation, and particularly under proposed legislation, and it is felt that the primary source of institutional support should be in health manpower. Now, there is one big gap there which I think we have to be candid about, and that is that there are some recipients of general research support grant funds which do not receive health manpower funds and there it is a matter of choice and priorities, but there is considerable support to institutions in our health manpower proposal.

Dr. SHERMAN. There is also the phasing out of one aspect of the program.

Mr. PATTEN. What was that?

Dr. BOWERY. The total general research support program, includes the general research support grants for research at health professional schools; the biomedical sciences support grants for research at the graduate departments of universities; and a third component known as the health sciences advancement award program. Two million dollars of the total reduction of $5 million is in the latter area since we are in a normal phaseout of this program and will be dropping from the current nine institutions in the program to four in 1972. The $2 million reduction reflects the normal termination of these particular grants.

Mr. PATTEN. With all due respect to Mr. Miller, my next question is: Did the obvious fact that Congress would restore it enter into your decision to apply to this item some of the overall cuts you had to make? I am referring now to the basic research support grants being cut $2,623,000.

Dr. BOWERY. I am not aware that that was involved in the decision. To reiterate, I think the decision was based on the overriding priority of putting money into new initiatives and the point was expressed that institutional support is flowing through the Bureau of Health Manpower, although basically this support is in the educational area, not the research area. I hope that with the fluidity of these funds there will be an opportunity in the new legislation for these schools to use these funds in more than just educational activities.

VALUE OF GENERAL RESEARCH SUPPORT GRANTS

Mr. PATTEN. I want to get your personal opinion on this. Some very responsible people in the academic field think these funds buy more per dollar than about any other funds you spend in NIH. What is your personal professional judgment with regard to that widely held opinion?

Dr. BOWERY. My personal and parochial view as head of this Division is that I would tend to agree with them. Basically, the reason is based on the ability of the institution to spend the funds within the broad guidelines of biomedical research and research training at the time and in the manner they want to spend them. I think Congress in establishing this program a number of years ago recognized that some portion of the total overall biomedical research effort at NIH

should be in a type of program that would allow self-determination by the institutions, and the judgment made at the time of the initiation of the program by Congress was that the program level should approximate 15 percent of the appropriated research grant funds. Historically, the appropriation level for the program has moved upward to about 10 to 10.3 percent. I would agree professionally with the people who make the judgment that these are moneys well spent.

We have recently had a fairly in-depth study of this program and have found that these funds are used in many ways to take advantage of opportunities in the individual institution that are not met by direct Federal project grants. The flexibility and ability to use these funds to meet many emerging needs that are not identified at the time an institution would submit a full-blown application for a research project give great credence to the statement that you have just entered into the record.

Mr. MILLER. Mr. Chairman, also I don't want you to think that this budget, meaning the total budget for HEW, disagrees with that concept, either. I think, as I previously mentioned, we have attempted to group the institutional support in another part of NIH's budget, namely, Health Manpower, and I think we agree it does have a very high priority. Second, I think when the committee considers this item and the possibility of restoring funds they ought to consider as two pieces: one piece, that cut which applies to the general program which is essentially what you are talking about, and second, that cut which applies to the health sciences advancement award program. Where NIH might not feel as strongly that the money should be restored, is a judgment that that program is perhaps one that can be phased out without any great loss, so I think you ought to consider it as two cuts rather than as one.

FUNDS NECESSARY TO MAINTAIN FISCAL YEAR 1971 LEVEL

Mr. PATTEN. Having heard you say that, I am going to ask how much more you would need to maintain the 1971 program level. It looks to me on page 160 as if you are being shortchanged about $5 million even though Mr. Miller says you are going to get help from the Manpower budget and other areas. But your general research support has a decrease of $2,623,000. Your health sciences advancement award has a $2-million cut. Your biomedical science support shows a $377,000 cut, for a total of $5 million. How much would we have to put in if we would want to maintain the 1971 program level? Let's take first your general research budget, which is $43,423,000 cut to $40,800,000. You can take care of this in the record.

Dr. BOWERY. I would be glad to insert something into the record that responds to the amount of funds that would be necessary to maintain the same level of operation.

(The information follows:)

A total of $55,212,000 would be required in 1972 in order to maintain the 1971 program level, an increase of $6,012,000 over the amount requested in the President's budget and $1,012,000 over the amount available in 1971. As indicated in the following table, the increase reflects an average cost-of-living increase of 6 percent for the general research support program and biomedical sciences support grants offset by a program decrease of $2 million for the health sciences advancement awards which are being phased out.

	1971 estimated obligations	1972 President's budget	Amount required in 1972 to maintain 1971 program level	Difference 1972 1971 estimate and revised 1972 estimate	President's and revised 1972 estimate
General research support program	$43,423,000	$40,800,000	$46,028,000	+$2,605,000	+$5,228,000
Biomedical sciences support	6,777,000	6,400,000	7,184,000	+407,000	+784,000
Health sciences advancement awards	4,000,000	2,000,000	2,000,000	−2,000,000	0
Total	54,200,000	49,200,000	55,212,000	+1,012,000	+6,012,000

Dr. SHERMAN. Mr. Chairman, may I add one comment here on this?

Mr. PATTEN. Yes.

Dr. SHERMAN. Your question about the difference between having funds in one pocket or another is an important one. We feel that the success of the NIH program, in the aggregate, has been due to the fact that the Congress has enabled us to have a diversity of support mechanisms rather than putting all of our money into one or two mechanisms, or, from the investigator's point of view, putting all of our "begs in one ask-it," as one of them has said. Different purposes are best served by different mechanisms. We still feel that this general research support program is basically a very important one—just as important as our training grant program, our research grant program, and the other support devices.

DISTRIBUTION OF FUNDS NECESSARY TO MAINTAIN 1971 LEVEL

Mr. PATTEN. Also furnish for the record where you would have to get the funds to restore this program to the 1971 program level.

(The information follows:)

The following table reflects the amounts to be added to the appropriations of the institutes contributing funds for the general research support grants in order to support this program at the 1971 level plus a 6 percent cost-of-living increase.

National Cancer Institute	$777,000
National Heart and Lung Institute	1,058,000
National Institute of Dental Health	132,000
National Institute of Arthritis and Metabolic Disease	1,058,000
National Institute of Neurological Disease and Stroke	655,000
National Institute of Allergy and Infectious Disease	655,000
National Institute of General Medical Sciences	908,000
National Institute of Child Health and Human Development	505,000
National Eye Institute	204,000
National Institute of Environmental Health Sciences	60,000
Total	$6,012,000

HEALTH SCIENCES ADVANCEMENT AWARDS

Dr. BOWERY. I would say, specifically replying to the $2 million in the health sciences advancement award, that since a number of the current programs are coming to their normal termination at the end of 5 years of activity, that the $2 million requested will be sufficient to carry the four remaining grants for the balance of fiscal 1972. However, I recognize that your question is dealing mainly in areas other than the health sciences advancement award program.

Mr. PATTEN. Well, the gentleman who sits here on my left, Mr. Smith, was not particularly enthusiastic about this item. He and other members of the committee had their doubts about this program from the beginning, but NIH officials were enthusiastic about it. Now it looks to us as if you are cutting this in half. I heard what you said, but it will be up to us then, to complete the record so we can answer the critics.

Dr. BOWERY. I understand, sir.

Mr. PATTEN. You said you would not necessarily cut back the program, that you have sufficient funds to the end of fiscal 1972; right?

Dr. BOWERY. Right.

Mr. PATTEN. And you don't consider that cutting the award program?

Dr. BOWERY. Well, in this particular program we have not encouraged any new applications and we are in the process of bringing to a normal termination 11 programs that had been established, all of which had received 5-year nonrenewable awards. I am just stating that we will not have nine programs continuing on in 1972. We will only have four.

Mr. PATTEN. What we will have to answer to members of the committee is "Why phase it out?"

Dr. BOWERY. I think that was a judgment made by the administration and confirmed by a recent statement by Dr. Edward David of the OST indicating that the judgment had been made that programs aimed at advancing the quality of institutions and in the increased production of health science researchers were ones that would be slowly phased out. Programs of institutional support that were maintaining the basic existing quality, however, would remain supported. The HSAA was a program that was initiated during the time when there was a national feeling that additional centers of excellence should be established around the Nation. Although this is still a valid goal, I believe that constraints upon the institutions and upon the budgetary framework indicate that we are not in a position at this time to continue or expand a program of devceloping additional centers of excellence. There are pressing needs in existing centers to maintain their own stability and their own reasonable level of productivity.

Mr. PATTEN. Mr. Shriver?

ROLE OF VETERINARIANS IN HEALTH RESEARCH

Mr. SHRIVER. Skilled veterinarians are of increasing importance in the development and maintenance of adequate animal resources. Would you please provide for the record a brief account of the role of veterinarians in the overall health research field?

(The information follows:)

Skilled veterinarians are of great importance in the development and maintenance of adequate animal resources. Currently about 750 veterinarians are engaged in the care of laboratory animals. Knowledge of the health status of laboratory animals is essential to their usefulness in research. The possibility that disease may erroneously affect the outcome of a research project must be eliminated. Knowledge of the health of the animal is important in production of laboratory animals, selection of animals for research, management of animals while research is in progress, and in the interpretation of results.

Veterinarians are making significant contributions to the overall health research field. This is illustrated by the fact that approximately 60 veterinarians are involved in medical research in the Public Health Service.[1] Schools of veterinary medicine are awarded approximately $12 million annually by the Department of Health, Education, and Welfare for animal research related to improving human health. Altogether approximately 1,000 veterinarians are engaged in research of all types.[2] The veterinarian's training makes him well qualified to conduct many types of basic medical research. During his professional training the veterinary student spends more time on sciences basic to medicine such as physiology than does the student of human medicine.[2]

A good summary of the contributions of veterinarians to the overall health research field is contained in the booklet "Veterinary Medicine—Its Requirements and Responsibilities in Relation to the Public Health."[3] Portions of it are excerpted here as follows:

"Since the time of Pasteur, veterinary medical scientists have made significant contributions to biomedical science. Smith, Kilborne and Curtice's recognition that an arthropod (a tick) could serve as a vector of an infectious disease, Texas fever, was a highly important medical milestone as was Ramon's success in producing an effective immunizing agent against a toxin. Karl F. Meyer's work on botulism was hailed by medicine and the canning industry as a major accomplishment against this highly fatal food-borne disease. Commonly used fracture splints (Stader) and hip prostheses (Gorman), as well as spinal anesthesia (Benesch) were first developed by veterinarians for use in the treatment of animals, and now are commonplace procedures in human medicine. Today's widespread use of oral polio vaccines follows a 15-year period during which oral vaccines proved effective in animals. Current research in animals on the viral transmission of cancer, connective tissue diseases, inherited liver disorders, congenital musclar dystrophies, and unique infectious diseases such as the 'slow viruses' and organ transplantation are beginning to yield significant results. Hundreds of similar contributions by veterinary medicine to medical science have been made.

"Veterinary medicine occupies a particularly advantageous position among the sciences in its opportunity to make contributions to medical science. For every disease of people a similar and sometimes identical disease exists in some animal species. Many of these 'animal disease models' are better suited for studies on the disease than are corresponding diseases in man himself. Nearly every member of the veterinary medical profession, whether he is engaged in regulatory veterinary medicine, private practice, or in research, constantly encounters disease conditions in animals of which an understanding may contribute to biomedical science and the welfare of mankind.

"Many of the most important diseases of people for which completely effective means of control are not yet available also occur in animals. Vital experimental procedures which rule out the use of man may be undertaken jointly by physicians and veterinarians using these animals as experimental models. In this context, several animal diseases are receiving increased attention as research subjects. Leukemias and Hodgkins-type tumors occur frequently in domestic animals; they are similar in most respects to their human counterparts. Other forms of cancer common in animals, particularly cats, provide excellent opportunities for investigating these diseases, with a view toward solving the human leukemia riddle. Numerous respiratory diseases in animals are very similar to important human respiratory diseases. Pulmonary emphysema of the horse is an almost exact counterpart, while infectious pneumonic processes in swine, cattle, sheep, and dogs are similar to important diseases in people.

"Degenerative nervous disorders similar to multiple sclerosis in man are respresented in several animal species. Several collagen or immunogenic diseases, particularly in dogs, horses, mink, and mice, provide counterparts to human ailments, such as rheumatoid arthritis, collagen associated kidney disease, lupus, and certain forms of anemia. Arteriosclerosis occurs naturally in swine, pigeons, cattle, and dogs, and dissecting aortic aneuryms occurs widely in turkeys. Important advances in the understanding of cardiovascular disease has resulted from studies on these models.

---

[1] Reinhard, K. R., "Role of the Veterinarian in Medical and Public Health Research." Cornell Veterinarian, vol. LV, pp. 139–153, 1965.

[2] Gay, W. I., "Opportunities for the Veterinary Scientist in Medical Research." Journal American Veterinary Medical Association, vol. 153, pp. 1033–1039, 1968.

[3] The Joint Committee on Education, Veterinary Medicine. American Veterinary Medical Association and Association of American Veterinary Medical Colleges, Inc., 1971.

"The broad training offered in veterinary medicine, encompassing several animal species, provides a good background for studies in the field of comparative medicine. Full utilization of veterinarians in human health oriented research teams could shorten materially the search for answers to many enigmatic diseases.

"Most medical schools and many hospitals engage veterinarians in teaching and research programs to provide additional strength in comparative medicine. There is a shortage of skilled veterinary scientists to man these programs."

REDUCTION IN GENERAL RESEARCH SUPPORT GRANTS

Mr. SHRIVER. You make a rather convincing argument in behalf of general research support grants, but you are proposing a $5 million reduction in these grants for fiscal year 1972. Would you justify this cutback further?

Dr. BOWERY. Within the general research support grants program, $2 million of the $5 million reduction reflects the gradual phaseout of the health science advancement award program. These awards were made to 11 institutions for a period of 5 years of nonrenewable support. Only four of these programs will still be operating within their 5 years of committed support during fiscal year 1972. The $2 million budgeted for these four will allow for adequate support of their programs. No new awards are being made in this program.

The remaining $3 million reduction will come from the general research support grants and the biomedical sciences support grant program. Although, as I have discussed before, we feel strongly that the recipient institutions have very wisely and efficiently utilized these flexible funds in self-determining their own emphasis and directon of research activities, it has been considered that within the present fiscal constraints these programs had lesser priority in meeting research objectives than did other programs of a more directed nature.

Mr. SHRIVER. That is all.

Mr. PATTEN. Mrs. Reid?

OUTPATIENT RESEARCH STUDIES

Mrs. REID. Would you expand on your statement that the clinical resources program is encouraging a partial shift in resources to be devoted to outpatient research studies? Where is this being done—and what are the major illnesses of the patients that are studied?

Dr. BOWERY. Since mid-1970· the centers have been encouraged to utilize a portion of existing personnel, space, and hospital funds to create specialized facilities to study ambulatory research patients. Research programs for the study of ambulatory patients are underway at 30 of the 80 active centers. We anticipate a continuation of this trend in fiscal year 1972. Outpatient studies being undertaken include long-term follow up of patients with high blood pressure on a variety of treatment programs, genetic studies relating to metabolic disorders that involve large numbers of research subjects and their relatives; and drug evaluation which require long-term observation of patients receiving a variety of therapeutic agents. Examples of the latter include the study of patients receiving L-dopa for Parkinsonism, phosphate supplements for bone disorders, and special drugs for lower blood fats.

PRIMATE RESEARCH CENTERS

Mrs. REID. Please list the seven primate research centers for the record and comment on what type of animals—other than primates—are found to be the most useful for research, educational purposes, diagnosis, and testing?

(The list follows:)

Oregon Primate Research Center, University of Oregon, Beaverton, Oreg.
Delta Primate Research Center, Tulane University, Covington, La.
Washington Primate Research Center, University of Washington, Seattle, Wash.
Wisconsin Primate Research Center, University of Wisconsin, Madison, Wis.
Yerkes Primate Research Center, Emory University, Atlanta, Ga.
New England Primate Research Center, Harvard University, Southborough, Mass.
National Center for Primate Biology, University of California, Davis, Calif.

NONPRIMATES USED IN HEALTH RESEARCH

Dr. BOWERY. Literally hundreds of different species and strains of animals are used in research, education, diagnosis and testing. I would like to enter into the record a list of type and number of the ones most commonly used for these purposes.

Mrs. REID. Yes.

(The information follows:)

List of animals by type and number most commonly used during 1969 for research, education, diagnosis and testing.[1]

Mice	36,000,000
Rats	12,000,000
Chickens	1,700,000
Frogs	1,600,000
Guinea Pigs	869,000
Hamsters	848,000
Rabbits	577,000
Dogs	372,000
Cats	163,000
Swine	83,000
Primates	68,000
Sheep	36,000
Cattle	30,000
Total all vertebrates	56,000,000

[1] National Academy of Sciences, Institute of Laboratory Animal Resources. ILAR News, Vol. XIV, No. 1, pp. 1–vi, October 1970.

Dr. BOWERY. Mice and rats are the most commonly used species because they are inexpensive, easy to care for, and are suitable for many purposes. Of course, numbers used cannot always be equated to importance. Frequently much valuable information can be obtained from a small group of animals such as primates while other experiments require large numbers of the smaller, inexpensive animals. The point is that each experiment or test has certain requirements that make a specific animal or group of animals best for it. A few examples from animal colonies supported by the animal resources branch of the division of research resources will illustrate this point. Inbred guinea pigs are uniquely suited for certain types of immunological research. Dogs with naturally occurring hemophilia are extremely valuable for research attempting to determine the site of production of the anti-hemophilic factor. Rats with a naturally occurring obesity are impor-

tant animals for certain studies on fat metabolism. Armadillos always have four identical quadruplets, therefore, are useful in studying the relative importance of genetics and early environmental influences on development. These are just a few examples of specific animal models that are most important for specific types of research.

GENERAL RESEARCH SUPPORT GRANT PROGRAM

Mrs. REID. What type of activities are most generally financed by the general research support formula-grant program? How is your program coordinated with the other institutes which base their grants on a categorical basis?

Dr. BOWERY. The general research support grant and the biomedical sciences support grant funds support the following general activities: they allow institutions to build areas of strength in research by developing central research resources, and by supporting research staff and their research activities; they enable institutions to stabilize their development of research programs; they provide institutions the opportunity to meet emerging opportunities in research; they encourage institutions to foster early recognition and support scientific talent; they enable institutions to redress imbalances in their ongoing programs; and most importantly they enhance the role and initiative of institutions in determining the direction and thrust of their programs.

General research support programs complement and strengthen the research activities supported by the NIH categorical institutes. Many projects currently supported by research grants received funding at their inception through GRS funds. The use of these funds is at the discretion of the recipient institution—the institution makes the determination as to which research areas need additional support.

Mrs. REID. What sort of application procedure have you established to assure that only the most worthwhile studies are carried out?

Dr. BOWERY. There are no formal application procedures established by the NIH for the individual projects or activities which are supported through the general research support formula grant programs. However, there are two basic factors working to insure the worthwhile expenditure of these funds. First, the general level of quality involvement in biomedical research that is occurring within each applicant institution is implicitedly considered each year by the Division since the award is based by formula on the amount of research grant support each institution currently is receiving from the NIH categorical Institutes. Institutions must have a minimum of $100,000 of active NIH-NIMH research project grants to be eligible for GRS support. Second, internal advisory committees are established by the grantee institutions to review requests for GRS funds. These committees are frequently composed of individuals within the institution who serve or have served on national review committees and advisory councils. They advise the institutional program director on the quality of the proposed activities and the appropriateness of supporting them. Reports indicate that most institutions receive requests which exceed available funds, a condition which virtually assures the funding of only the most meritorious projects. This is borne out by the substantial number of publications resulting from GRS support which appear in reputable scientific journals.

62-645 O—71—pt. 3——71

Thus, in addition to the general external review made by the Division and its National Advisory Council as to institutional eligibility there is a specific internal review conducted by the institutions themselves as to the quality of each individual project or activity they wish to fund from their GRS allocation.

Mrs. Reid. As a general rule have you found that General Research Support Grants have been more or less efficient than specific grants?

Dr. Bowery. Since, to a large extent, General Research Support Grants provide funds for the younger investigator, the investigator who needs a small amount of support while he is obtaining base-line data prior to submitting a grant application to the NIH, we feel these funds are being very efficiently used. The institution by making a decision to support this investigator through its GRS Award is telling us in effect that they are confident that his research is a good investment. We do feel that the individual project grant for a specifically defined categorically oriented study which is reviewed by the traditional NIH Study Section mechanism is undoubtedly the most efficient means of supporting the established investigator.

Mrs. Reid. Is your Division doing any research regarding the development of artificial organs?

Dr. Bowery. None of our Clinical Research Centers are currently carrying out research on artificial organs in the popular sense, that is, the implanting of machines or devices to carry out normal organ function.

RESEARCH ON KIDNEY DISEASES

Mrs. Reid. Is your Division doing any research regarding kidney diseases?

Dr. Bowery. Investigation in the field of kidney disease continues to be a major interest among a number of Clinical Centers. Of the first 200 kidney transplants done in this country, 75 percent were evaluated in Clinical Research Centers. The Clinical Centers have played a major role in the development of the artificial kidney machine for maintaining patients with renal failure. Investigators using the Clinical Centers have demonstrated that these machines can maintain patients without kidney function for extended periods of time. Clinical Center research covers the entire spectrum of kidney problems including the causes and treatment of infections of the kidney, the relationship of high blood pressure to kidney disease, the causes of kidney stone formation, and the treatment and causes of immune diseases of the kidney.

RESEARCH RELATED TO NARCOTIC ADDICTION

Mrs. Reid. Has any research been carried out in your centers relating to narcotic addiction?

Dr. Bowery. A number of clinical centers are actively involved in studies of various drugs and their abuse. Research on heroin addiction initiated at the Rockefeller Clinical Center led to the development of the use of methadone in treating such addiction. Clinical research centers have assisted in the development of a system for routine urine monitoring on patients to detect narcotic drugs such as barbiturates, tranquilizers, and amphetamines. Other clinical centers are actively involved in studying other drug abuse problems, including the psychological and physiologic effects of increasing doses of amphetamines

and research in the metabolism and effects of marihuana. Increases in narcotics addiction and drug abuse problems will continue to stimulate more extensive research efforts in order to gain a better understanding of the metabolism, effects, and treatment for drug abuse problems. Thus, these DRR supported resources are serving many investigators working in this field.

Mrs. REID. Thank you.

Mr. PATTEN. Mr. Conte?

MAINTAINING AUTONOMY AND INDIVIDUALITY OF ACADEMIC INSTITUTIONS

Mr. CONTE. What activities is the DRR engaged in to fulfill its function of assisting in the maintenance of the autonomy and individuality of academic institutions?

Dr. BOWERY. The general research support grant and the biomedical sciences support grant are the chief instruments of support that the Division uses to assist academic institutions in maintaining their autonomy and individuality. These grants, provided on a formula basis, are flexible funds which the recipient institution can utilize for their self-determined research and research training needs. Typically, these funds are used in such ways as: Enabling an institution to purchase research equipment which will be used by several investigators none of whom could justify the cost on his own research grant; allowing an investigator to quickly follow-up a research lead by providing him with the necessary supplies; to enable a staff member to visit another institution to learn a new research technique; to provide research training on a short-term basis to promising medical or graduate students. Additionally, at institutions where we have established resources; general clinical research centers, primate centers, computer centers, the institution plays a major role in setting standards for the investigators that utilize these resources in carrying out their research. Of course, decisions as to the ultimate mix of users are made on the basis of scientific merit in relationship to the mission of each resource.

CORRECTION OF IMBALANCES IN RESEARCH ACTIVITIES

Mr. CONTE. Would you provide us with some examples of the kinds of imbalances in institutional research activities that the General Research Support program is designed to correct?

Dr. BOWERY. The General Research Support Grant and the Biomedical Sciences Support Grant allow institutions to quickly redress the kinds of imbalances that are likely to develop where relatively large amounts of research support are available chiefly to prominent, well-established investigators. The institution by utilizing GRS funds, can provide research opportunities for the younger, less-experienced investigator and enable him to carry out pilot studies and obtain baseline data and thereby qualify him for competing for research grant funds of his own. Using GRS money an institution can initiate the upgrading of neglected areas through the purchase of modern equipment and the recruitment of new research personnel. These funds are also valuable in the stabilization of high quality, on-going research which may be floundering through under-funding.

Mr. CONTE. From what programs are resources going to be partially shifted in the Clinical Resources program?

Dr. BOWERY. The shift in resources is internal within the program. In mid-1970 centers were given the option of utilizing a portion of existing personnel, space, and hospitalization funds to create specialized facilities to study ambulatory research patients. To date 30 of 80 active centers have developed research programs for the study of ambulatory patients. Full scale development of outpatient research facilities has been limited by the need to preserve existing inpatient programs.

MANAGEMENT OF ANIMAL RESOURCES

Mr. CONTE. What are some of the problems involved in the proper management of animal resources?

Dr. BOWERY. A number of the problems are involved in the management of animal resources. They can be grouped under four broad headings—first, the lack of adequately trained professional personnel for disease control programs and inadequately trained animal care technicians; second, the lack of specialized facilities for animal surgery, radiology, disease diagnosis and other special requirements; third, the lack of basic information on the environmental requirements of some laboratory animals and on the prevention and control of some laboratory animal diseases; and fourth, the periodic under utilization and, therefore, uneconomical utilization of animal cages, facilities, equipment and personnel due to fluctuations in number of animals required during the course of research. The animal Research Program of the Division is helping institutions overcome these problems by supporting training of professional specialist in laboratory animal science and medicine, and developing training materials and prototype training programs for institutions to use in training their animal care technicians.

We are also supporting research to determine environmental requirements and supporting diagnostic laboratories to aid in the control of laboratory animal disease. In addition, we award resource grants to assist institutions in upgrading their animal facilities through the purchase of cages, cagewashers, other basic animal care equipment and building renovations. This mechanism is a most effective way of improving animal research facilities since it provides for careful scientific and administrative peer review of the entire institution's needs and plans for equipment, renovation, personnel, etc. Such review can insure that these activities are well delineated and appropriate to the institution's requirements, while avoiding needless and expense duplication of cages and equipment.

It is expected that the need to deal more effectively with the problems that I have mentioned will become more acute because of the recent passage of the Animal Welfare Act of 1970. This law requires that Federal standards be established for the care, management, and treatment of animals used in research, education, testing, exhibition or intended for sale as pets. It is anticipated that a number of research institutions will have to spend significant sums of money to improve management, purchase large modern cages, and renovate facilities to meet standards of the Act. Many research institutions are making progress in overcoming their animal resource management problems by centralized institutional management of animal resources rather than management by individual investigators. The research

resource award mechanism of the Division is especially suited in helping to solve these problems.

CORRECTION OF HYPOPITUITARY DWARFISM

Mr. CONTE. By how much can human growth be stimulated in patients with hypopituitary dwarfism?

Dr. BOWERY. If treatment with human growth hormone is instituted at an early age, a child with hypopituitary dwarfism will experience essentially normal growth and development. Proper and complete treatment is dependent upon two factors, sufficient human growth hormone being available and early diagnosis and treatment.

In spite of an available treatment, many children with hypopituitary dwarfism must go untreated because of an insufficient supply of human growth horome. Physicians must rely on growth hormone extractions from cadaver sources which are tedious and costly. However, medical researchers may be close to providing a new approach for treatment for a number of children with growth failure. The investigators at a number of Clinical Centers are working to identify a growth horome "releasing factor." This "releasing factor," unlike growth hormone itself is a small molecule and, when identified, it is probable that it can be artifically synthesized, thus providing a new and more accessible method for treatment of a number of children with growth failure.

DIAGNOSING DISEASED ARTERIES

Mr. CONTE. How long is it anticipated before the new method of diagnosing diseased arteries will be perfected?

Dr. BOWERY. This method has progressed to a degree that it is anticipated that it will be applicable in the diagnosis of several valvular diseases of the heart within 1 to 2 years. This technique of on-line computer processing of the sound produced by blood flow should be able to determine the degree of valvular obstruction comparable to that obtained with catheterization of the heart. The specific time that it will take for the application of the process to the diagnosis of coronary artery obstruction is not predictable at this time.

NEW BATTERY FOR CARDIAC PACEMAKERS

Mr. CONTE. Is the new rechargeable nickel cadmium battery generally available for use as a cardiac pacemaker or is more work on it needed?

Dr. BOWERY. The Permanent Rechargeable Cardiac Pacemaker was developed by Dr. Kenneth B. Lewis under partial support of the General Research Support Grant to the Johns Hopkins University School of Medicine. Dr. Lewis is carrying out clinical evaluation studies in animals at present and it is reported that tests in humans will begin within 1 year if adequate research funding is available. This project was developed as a collaborative project between biomedical scientists at the Hokpins School of Medicine and physical scientists at the Hopkins Applied Physics Laboratory.

Mr. CONTE. That is all, Mr. Chairman.

Mr. PATTEN. It is a pleasure to have listened to you, Dr. Bowery.

Dr. BOWERY. Thank you, Mr. Chairman.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Research Resources

Amounts Available for Obligation

	1971	1972
Appropriation	$66,201,000	$68,069,000
Real transfers from:		
"National Institute of Arthritis and Metabolic Diseases" (Proposed transfer for increased pay costs)	75,000	---
"National Institute of General Medical Sciences" (Proposed transfer for increased pay costs)	44,000	---
Comparative transfer to:		
"Office of the Director"	-10,000	---
Comparative transfers from:		
"Biologics Standards"	94,000	---
"National Cancer Institute"	27,000	---
Total obligations	66,431,000	68,069,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Grants:						
202	Research		$62,810,000		$64,310,000		+$1,500,000
	General clinical research centers		(38,004,000)		(39,004,000)		(+1,000,000)
	Scientific evaluation		(215,000)		(215,000)		---
	Biotechnology resources		(9,617,000)		(10,117,000)		(+500,000)
	Animal resources		(14,974,000)		(14,974,000)		---
212	Fellowships		126,000		126,000		---
213	Training		352,000		352,000		---
	Direct operations:						
214	Collaborative research and development	2	1,386,000	2	1,391,000	--	+5,000
214	Review and approval	52	1,055,000	52	1,153,000	--	+98,000
215	Program direction	30	702,000	30	737,000	--	+35,000
	Total obligations	84	66,431,000	84	68,069,000	--	+1,638,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	84	84	---
Full-time equivalent of all other positions	3	4	+1
Average number of all employees	82	83	+1
Personnel compensation:			
Permanent positions	$1,085,000	$1,165,000	+$80,000
Positions other than permanent	11,000	64,000	+53,000
Other personnel compensation	28,000	36,000	+8,000
Subtotal, personnel compensation	1,124,000	1,265,000	+141,000
Personnel benefits	120,000	128,000	+8,000
Travel and transportation of personnel	102,000	102,000	---
Transportation of things	8,000	8,000	---
Rent, communications, and utilities	42,000	42,000	---
Printing and reproduction	44,000	18,000	-26,000
Other services:			
Project contracts	1,205,000	1,255,000	+50,000
Payment to NIH Management Fund	221,000	239,000	+18,000
Other	255,000	202,000	-53,000
Supplies and materials	17,000	17,000	---
Equipment	5,000	5,000	---
Grants, subsidies, and contributions	63,288,000	64,788,000	+1,500,000
Total obligations by object	66,431,000	68,069,000	+1,638,000

Summary of Changes

1971 estimated obligations	$66,431,000
1972 estimated obligations	68,069,000
Net change	+1,638,000

	Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Increases				
A. Built-in				
1. Annualization of 1971 pay increase costs	---	---	---	+$98,000
2. Within-grade pay increase	---	---	---	+11,000
3. FTS rate increase	---	---	---	+6,000
4. One extra day of pay	---	---	---	+5,000
Total built-in increases	---	---	---	+120,000
B. Program				
1. Research grants				
a. General clinical research centers	---	$38,004,000	---	+1,000,000
b. Biotechnology resources	---	9,617,000	---	+500,000
Total program increases	---	---	---	+1,500,000
C. Payment to "NIH management fund" for centrally furnished services	---	221,000	---	+18,000
Total increases	---	---	---	+1,638,000

Explanation of Changes

Built-in--The built-in increases will provide $98,000 for annualization of 1971 pay increase costs, $11,000 for within-grade pay pay increase in 1972, $6,000 for increased cost in 1972 of using the Federal Telecommunications System and $5,000 for one extra day of pay in 1972.

Research grants--The program increase of $1,000,000 for General Clinical Research Centers will provide for continuing operations of existing centers. The increase will be utilized to offset the annual rising hospitalization and personnel costs currently estimated at a minimum of six percent.

The increase of $500,000 for Biotechnology Resources will help offset the increased cost of these resources and allow for a limited increase in the scope of projects supported in selected areas such as electron microscopy.

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1971 House Report	
1. The creation of a separate division to administer these research resource and general research support programs has considerable merit. However, the committee sees no logical reason for placing this new division in the Bureau of Health Professions, Education, and Manpower Training. Moreover, this organizational misalinement distorts NIH budget presentations which in other respects, draw a rather clear distinction between its research and its health manpower programs. The committee endorses the proposal, now being considered, to include the Division of Research Resources among the research components of NIH. (page 31 of House Report)	1. On September 18, 1970, the Division of Research Resources was reorganized out of the Bureau of Health Professions Education and Manpower Training and was established as a free standing research Division of the NIH. Its budget tables and justification will therefore be included with the other research components of the NIH and afford the committee a clearer presentation of these research activities.
1971 Senate Report	
1. The Division, though solely concerned with the support of research resources, is at present organizationally part of the Bureau of Health Professions Education and Manpower Training. The Committee believes that the interests of all concerned would best be served by realigning the Division of Research Resources with the other research components of NIH. (page 53 of Senate Report)	1. The action taken is the same as the action taken for the House Report.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation requested
Public Health Service Act Section 301--Research and Investigation, in general.....	Indefinite	$68,069,000

PUBLIC HEALTH SERVICE ACT

Title III -- General Powers and Duties of Public Health Service

PART A -- RESEARCH AND INVESTIGATION

In General

"Sec. 301. The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man, including water purification, sewage treatment, and pollution of lakes and streams. In carrying out the foregoing the Surgeon General is authorized to--.....

(c) Establish and maintain research fellowships in the Service with such stipends and allowances, including traveling and subsistence expenses, as he may deem necessary to procure the assistance of the most brilliant and promising research fellows from the United States and abroad;

(d) Make grants-in-aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for such research or research training projects as are recommended by the National Advisory Health Council....."

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer from:		
National Institute of Arthritis and Metabolic Diseases	$75,000	Proposed transfer for increased pay costs.
National Institute of General Medical Sciences	44,000	Proposed transfer for increased pay costs.
Comparative transfer to:		
Office of the Director	-10,000	Transfer of research contracting functions from NIH Management Fund to Office of the Director for establishing the Office of Contracts and Grants.
Comparative transfer from:		
National Cancer Institute	27,000	To provide an equitable distribution of the Management Fund in 1972.
Biologics Standards	94,000	To provide an equitable distribution of the Management Fund in 1972.

Research Resources

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$95,341,000	$119,275,000	$140,000,000	$127,637,000
1963	147,826,000	155,826,000	161,826,000	159,826,000
1964	164,674,000	163,869,000	164,674,000	163,869,000
1965	163,715,000	162,959,000	164,759,000	164,759,000
1966[1]	58,719,000	59,969,000	60,469,000	60,469,000
1967	67,821,000	68,534,000	68,534,000	68,534,000
1968	81,141,000	81,141,000	81,141,000	81,141,000
1969	87,500,000	82,719,000	94,823,000	84,809,000
1970	69,698,000	73,658,000	79,658,000	76,658,000
1971[2]	63,701,000	66,201,000	66,801,000	66,201,000
1972	68,069,000			

1/ Excludes the "National Institutes of General Medical Sciences" established as a separate appropriation in 1966.
2/ Excludes the Division of Computer Research and Technology incorporated into the "National Institutes of Health Management Fund" in 1971.

Justification

Research Resources

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	84	$1,244,000	84	$1,393,000	--	+$149,000
Other expenses	--	65,187,000	--	66,676,000	--	+1,489,000
Total	84	66,431,000	--	68,069,000	--	+1,638,000

Background:

Both the Senate and House Committees on Appropriations endorsed the proposal to include the Division of Research Resources among the research components of the National Institutes of Health. A reorganization to effect just this action was carried out on September 18, 1970. Under this realignment the Division of Research Resources was established as a free-standing research Division of the National Institutes of Health. The Division's budget will now be included in the research portion of the overall NIH budget presentation. Organizationally DRR's status as a research Division of the NIH should enable it to better fulfill its broad based mission of supporting the core resources of institutions involved in biomedical research.

General Statement

The National Institutes of Health in support of the national goal of improving and sustaining the health and well-being of the American people, has as an objective the advancement of the Nation's capability for the maintenance of health and for the diagnosis, treatment and the prevention of diseases through the production of new knowledge and professional manpower. It has pursued this, in the main, through the development and maintenance of a strong academic base for the health sciences to provide a broad institutional framework for health research, education and service.

The objectives of the Division of Research Resources in support of this broad NIH mission are (1) to establish and sustain, primarily in academic institutions but also in certain nonacademic research organizations, those resources essential to the advancement of biomedical research and research training leading to the improvement of the health of the Nation; and (2) to assist in the maintenance of the autonomy and individuality of academic institutions in the face of categorical organization of Federal health agencies through flexible general research support funds. This latter program is discussed in General Research Support Grants.

Research Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
General clinical research centers	$38,004,000	$39,004,000	+$1,000,000
Scientific evaluation	215,000	215,000	---
Biotechnology resources	9,617,000	10,117,000	+500,000
Animal resources	14,974,000	14,974,000	---
Total research grants	62,810,000	64,310,000	+1,500,000

General Clinical Research Centers

General Clinical Research Centers are physically discrete research hospital units located in university-affiliated hospitals. The units provide essential bed space, necessary equipment, controlled conditions, and trained personnel for clinical research in every area of medical science. Thus, the General Clinical Research Centers program makes available, in effective form and adequate number, those facilities and resources required by the Nation's scientists to conduct accurate and detailed clinical investigation. Each Center serves as a focal resource for inquiry, examination, and education in an effort to improve the quality of medical care and to enable collaborating groups of investigators from all medical disciplines to study abnormal physiology in virtually all categories of human disease.

The application of fundamental biological knowledge to the care of the clinically ill patient is essential in the fight against human disease. The Clinical Research Centers function as a critical interface at which laboratory discoveries can be translated expeditiously and efficiently into improved mechanisms of patient care. Through a communication network which includes university hospital physicians, physicians primarily with direct patient care, and medical journals, the medical advances emanating from these Centers are brought to bear on the practice of medicine in the 580,000 beds in the 3,700 hospitals across the country that provide most of the inpatient care for acute illness in the United States.

In fiscal year 1970, the Program supported 904 research beds which were distributed through university hospitals containing more than 53,700 beds. More than 2,600 investigators utilized these Centers in the conduct of 3,800 research projects covering virtually all aspects of human disease. Training in clinical medicine was provided to 7,400 individuals. Studies conducted at the Centers included research in cancer therapy, transplantation, population control, growth and development, mental retardation, heart disease, and high blood pressure. The range of clinical research activity is further demonstrated in the following compilation of a few of the many research accomplishments of General Clinical Research Centers during the past year.

High blood pressure: The Clinical Research Center at the University of Colorado is conducting clinical studies on a new drug to combat high blood pressure, minoxydyle. Almost 50 percent of all deaths in the United States are the result of diseases of the blood vessels. Of these, a significant number are due to high blood pressure (hypertension) which, if untreated or poorly controlled, will lead to progressive blood vessel damage and may result in time in cerebral stroke or coronary occlusion (heart attack). Although drugs for the treatment of high blood pressure have been available to medical practitioners for over a decade, none of these have been entirely satisfactory, in part because of the severe side effects they can produce. Unlike other antihypertensive agents, minoxydyle functions by producing directly a relaxation of the constricted blood vessels responsible for increased blood pressure. To date, it seems to be without many of the side effects which complicate the use of other drugs. When carried to completion, these studies will define the therapeutic potential of this powerful new antihypertensive agent

and from them may develop new and hitherto impossible approaches to therapy.

At the Clinical Research Center at the University of Southern California, a new x-ray technique has been developed which may lead to early diagnosis and treatment of one of the treatable forms of high blood pressure. It has been estimated that among adult Caucasians with high blood pressure, ten percent suffer from a form due to excessive secretion by the adrenal glands of the hormone aldosterone. This hormone is normally present in the human body and is essential in the maintenance of normal blood pressure. In the patient with aldosterone-related high blood pressure, excessive aldosterone secretion most commonly originates from nonmalignant tumors in one of the adrenal glands. Surgical removal of such tumors results in a complete cure. Until now, it has been essential to subject the patient to extensive surgery in order that direct visual exploration of the abdominal cavity might be conducted to discover all such aldosterone-producing tumors. The new x-ray technique, by allowing the tumors to be located directly prior to surgery, will allow a much more simple operation to be performed. The surgeon may go directly and quickly to the site of the tumor and remove it, thereby greatly reducing the morbidity and mortality which has in the past been associated with this operation.

Emotional deprivation and disease: Children who are not given sufficient love and emotional satisfaction frequently develop disabling clinical problems. Scientists at the Children's Hospital, Pittsburgh, Clinical Research Center have recently studied several of these neglected children who have developed symtomatic hypoglycemia (a pathologically low, often life-threatening level of blood sugar). Investigation of these children led to the documentation of deficient function of the adrenal cortex, the gland responsible for the production of cortisone, a steriod hormone very important in the maintenance of normal blood sugar. The low blood sugar symptoms disappeared rapidly following improvement in the home environment of these children.

One of the most important and exciting observations in the field of pediatrics in the last ten years has been the documentation of the harmful effect of emotional deprivation on both physical and psychological growth of the child. The syndrome of maternal deprivation dwarfism is well documented. The probable mechanism of this condition is emotional neglect or adverse emotional environment, producing psychological stress which in turn leads to inhibition of release of hormones essential in the normal growth of humans. Upon removing such children from the adverse environment, rapid physical growth occurs and improvement in intellectual functioning follows.

As "Idiopathic hypoglycemia" (low blood sugar of unknown origin) is a significant problem within the pediatric age group, this documentation of the relationship between emotional deprivation and hypoglycemia mediated by adrenal cortical insufficiency is of great significance in the diagnosis and treatment of a large number of children, the cause of whose disorder heretofore has probably been undetected.

Pulmonary Emboli: The General Clinical Research Center at Temple University Hospital, Philadelphia, is currently involved in a new therapy for pulmonary emboli. Blood clots which form in veins in the legs and which break away to pass in the blood streams and lodge in the lungs (pulmonary emboli) account for profound illness and even death in many Americans each year. For a number of years, scientists have searched for a chemical agent with the capacity to dissolve the clots after they have lodged in the lungs in order that the circulation might be restored. This Center is currently involved in a study on the action of the chemical enzyme, streptokinase, produced in the laboratory by bacteria, which has recently become available in sufficiently pure form to be used on patients. This study is not yet complete, but preliminary data indicate that this agent will be significantly more useful in preventing the death of patients from pulmonary emboli than is any treatment currently available.

Obesity: In the Clinical Research Center at Rockefeller University, studies of fat cells and their metabolism have been conducted in children with marked obesity.

One current theory of obesity holds that the number of fat cells developed in the body earlier in life remains constant throughout adult life and that the greater the number of fat cells a person contains the greater is his liklihood ob becoming and remaining obese in adulthood. In significant numbers of the obese children studied in the Center, although total body fat decreased on a controlled weight reduction program, significant decreases in the numbers of fat cells were not found. As a result of these studies, patients less than six years of age are being preferentially admitted for weight reduction, as they are the only grossly obese patients in whom adult patterns and numbers of fat cells have not yet developed and in whom weight loss may be more permanent. Such studies are of significance in that if it can be documented that the development of fat cells in childhood is a response to the types and volume of food eaten by the child at an early age, preventive nutritional measures may be developed by which such cellular patterns, and thereby the difficulties of obesity which are currently present in the adult population in most affluent nations, may be prevented.

Organ transplantation: The field of organ transplantation has been greatly advanced by the research done in this field in Clinical Research Centers. The majority of the transplantation studies performed in Clinical Research Centers have involved kidney transplantation. Recently, the Clinical Research Centers have undertaken exciting studies on the transplantation of other organs.

At the University of Arkansas, scientists have developed a technique of transplanting very small pieces of skin (micrographs). Using this technique, they have evaluated the rejection of these skin grafts and how this rejection may be altered by chemical treatment of the graft prior to its implantation. The ultimate goal of such a study is to develop the potential for permanent skin transplantation in patients suffering from extensive burns. By treating the grafts, the survival time of the graft has been greatly lengthened. This method is far superior to treating the recipient with systemic drugs which lower his body's resistance to infection.

Scientists at the Clinical Research Center at Roswell Park have been transplanting human fetal thymus glands into patients with Hodgkin's disease, a progressive malignant disease of the lymph nodes, spleen, liver and other organs. It is known that patients with Hodgkin's disease have a defect in the immunologic--or defense--system of the body. By transplanting fetal thymic tissue, which is known to be the origin of the body's immunologic system, scientists hope to control this deadly disease.

Many cases of blindness are due to disease or of injury to the cornea--the transparent membrane covering the eye. At the University of Florida Clinical Research Center scientists have restored sight to these people by corneal transplantation. A technique has been developed in which corneas removed after death may be preserved indefinitely for future transplantation. The development of this storage technique has been of extreme importance in supplying a constant source of tissue for transplantation.

Program Plans in 1971 and 1972:

The $39,004,000 requested for fiscal year 1972, an increase of $1,000,000 over the fiscal year 1971 budget level, will allow the Program to conduct its activities at close to present operating levels. New Program guidelines will allow investigators more flexibility in the ability to diversify their activities to include research on ambulatory patients. The increased funds will be utilized to offset the annual rising hospitalization and personnel costs currently estimated to a minimum of six percent.

Scientific Evaluation

This activity provides support for the study sections and preliminary review committees used by the Division to provide scientific merit review of grant applications. These study sections and committees, composed of outstanding authorities in the various field of medical research, are responsible for the scientific peer evaluation of all research grant applications. Their findings and recommendations with the grant applications are forwarded to the National Advisory Research Resources Council.

Biotechnology Resources

In November 1970 the Special Research Resources Program was renamed the Biotechnology Resources Program in order to more specifically convey the true character of its activities.

The goals of the Biotechnology Resources Program are to improve the Nation's health and health research by (1) making available to the biomedical community highly sophisticated instruments and methodologies and their associated expertise for use in modern health research, education, and patient care and (2) sponsoring centers of scientific and technological excellence which can take the lead in the discovery and development of the new health research and patient care methodologies originating in the physical sciences. While the support of life science computer resources was the main thrust of the program when it was established in 1962, the Program has diversified since then to include many of the new advanced technologies such as high resolution mass spectrometry, nuclear magnetic resonance spectrometry, and high voltage electron microscopy that are pertinent to the biomedical area.

In F.Y. 1971 the program anticipates funding 35 Biomedical Computer Resources, eight Biochemical Instrumentation Resources, three Biological Materials Preparation Resources, and one High Voltage Electron Microscopy Resource. Typically these resources: (a) provide service to biomedical scientists who need access to the instrumentation and the technical expertise of the resource for the conduct of their research projects--these specific projects are funded primarily by the categorical institutes of NIH, (b) conduct research and development within the resource directed toward the improvement and extension of resource capabilities as they relate to human health, and (c) train biomedical scientists in the capabilities of the resource, especially as applied to biomedical research and patient care. This mode of operation allows the most efficient and effective utilization of the resource. In particular, it allows the scientific community access to these complicated and costly research tools and associated skills that could not be justified or fully utilized on an individual basis.

In fiscal year 1970, more than 1,867 health scientists utilized the computer resources. Investigations in these resources spanned a range of activities from the storage and retrieval of clinical information and statistical data reduction to the automatic diagnosis of heart disease and the on-line monitoring of the critically ill. In an analogous fashion, 273 investigators used the Biochemical Instrumentation Resources to elucidate the molecular structure of chemical substances that comprise or interact with living organisms. These investigations aid in the study and diagnosis of various human disorders that are known to have a molecular origin. In addition approximately 19,000 biological preparations normally unavailable from commercial sources were provided by the Biological Materials Preparation Resources for use in biomedical research.

Computer Resources

Computer resources serve a wider range of programs of the NIH categorical institutes than do any of the other resource types. There remains today almost no biomedical area which has not had some productive encounter with computer technology, and the Biotechnology Resources Program has been primarily responsible for

this. Moreover, as the complexity of health care and health research rises, the frequency and scope with which computer technology is applied to the health sciences will certainly increase. Examples of the activities that have found the computer to be an invaluable and indispensable tool include the following.

Drug information program: The hospital patient today receives on the average eight potent drugs during his stay. The possibility that the combination of two or more of these drugs is incompatible and toxic to the patient is high, particularly when it is realized that physicians have some 4,000 different drugs from which to choose when prescribing medicine for their patients.

This potential hazard is being systematically eliminated in the Stanford Medical School Hospital Center. Here a computer system is being developed to monitor all drugs prescribed for individual patients and detect all drug combinationa that might result in adverse interactions. If such a combination is identified, the nursing staff and physician are notified before the drugs are administered to the patient. The physician, aware of the potential hazard, may choose to administer the drug combination and watch the patient carefully or with the aid of the computer select a combination of drugs more compatible and nontoxic to the patient.

The Stanford Medical Center believes this program will not only eliminate many undesirable drug reactions occurring in patients subjected to multiple drug therapy but also help in the promotion of a rational and rigorous approach to drug therapy and lead to the development of a common data base which will be useful in both clinical research and patient care.

Cardiovascular diseases: The Mayo Foundation Computer Facility has added another dimension to the study of cardiovascular disease in intact animal and man. With the combination of roentgen videometry (an extension of x-ray methods) and computer techniques, the Center has developed a system which generates dynamic three-dimensional television images of the ventricular cavities of the heart during individual cardiac cycles. Changes of shape and volume of the cavity can be followed and related to simultaneous changes in blood pressure and blood flow. Stop action, slow motion, and real-time replay of the images are possible. The roentgen videometry computer assembly provides a degree of power for studying cardiovascular dynamics in heart disease which has been unattainable heretofore and does it without subjecting the animal or human subject to serious discomfort or risk.

Blood disorders: A research advance in the study of blood disorders and other related diseases has been made by the UCLA Computer Center. This resource has developed a mathematical model which enables researchers studying the hematopoietic (blood-cell producing) system to design and analyze their experiments quantitatively with the aid of the computer. Using simulation techniques, various versions of the model can be constructed and the resulting behavior determined by monitoring the course of the computation with the aid of the on-line TV-like display. Various feedback mechanisms, the oxygen carrying capacity of the red blood cells, and the response of the hematopoietic system when challenges are placed upon it are some of the characteristics that are being examined using this technique. Studies such as these will play an important part in the identification of the causes of and treatment for many types of anemia and other blood diseases.

Cancer research: The design of drugs selectively toxic to cancer tumor cells (e.g., human leukemias) is highly dependent on the knowledge of the growth behavior of these cells and upon the differences that exist in the cell division cycle of normal and tumor cells. Investigations currently under way using the computer resource at the University of Pennsylvania are aimed at understanding these differences and obtaining detailed information on cell growth cycles. By studying the incorporation of radio-labelled compounds into various types of tissues over time as cells proliferate, information on cell growth is assembled by the investigators into a series of complex oscillating curves. Then, with the help of the computer,

they calculate from these curves the relative distribution of the cells in the population among the various stages of growth and division as well as other parameters that describe the cell cycle. These derived results have important implications not only in analyzing tumor cell growth and in understanding the underlying bases for abnormal growth of cancer cells, but also in determining how and when to administer selected drugs such that they kill the maximum number of tumor cells without severely imparing an unacceptably large number of normal ones.

Biochemical Instrumentation Resources

As more and more human diseases are shown to have a molecular basis, and as diagnosis and treatment of disease become increasingly dependent upon the identification of certain chemical substances in the body fluids, the needs for highly sophisticated techniques to study biological molecules continue to grow. In response to these needs, the Biotechnology Resources Program sponsors Biochemical Instrumentation Resources, involving especially high resolution mass spectrometry and high resolution nuclear magnetic resonance spectroscopy, two of the most powerful techniques known for elucidating the molecular structure of chemical substances that comprise or interact with living organisms. Examples of these studies done in these resources are given in the following.

Population Research: The role prostoglandins play in the control of human reproduction is under investigation at the University of Pittsburgh Mass Spectrometry Facility. These hormones are believed to play a role in the induction of normal labor and preliminary studies indicate they may be used to successfully evacuate the uterus and therefore are believed to play a role in labor and the process of giving birth. Using a gas chromatograph-mass spectrometer system, this Facility developed a method to identify nanogram (one billionth of a gram) quantities of prostoglandin in human tissue. With this method it will be possible to monitor physiological levels of these hormones in human blood and other tissues rapidly and quantitatively, a feat not heretofore possible. Such measurements may be useful in the management of spontaneous abortions and in an understanding of the role of these ubiquitous agents in male infertility.

Drug abuse: Physicians today are being faced with an increasing number of patients suffering from an overdose of drugs. The escalating number of drugs in use makes the task of diagnosing these patients even more complicated. Patients in coma present a critical problem to the physician because early treatment is imperative if the patient is to survive. In patients suffering from drug overdose, therapy is best administered when the drug ingested is known. It is therefore mandatory that the physician have available to him techniques which provide rapid and unambiguous identification of drugs present in the human body.

The Massachusetts Institute of Technology Center, in collaboration with Beth Israel Hospital, has used a mass spectrometer coupled to a gas chromatograph and a computer to identify drugs present in the human body. By analyzing blood, urine and other body fluids of patients suffering from drug overdose, the Center is able to positively identify the ingested drug in a matter of hours, and thus allow rapid therapy. The Center has successfully used this technique in a number of cases where drug identification methods used formerly proved insufficient. This work has stimulated similar attempts in other settings throughout the Nation such as the Mass Spectrometry Center for the Research Triangle Region, the Battelle Memorial Institute, and Arthur D. Little, Inc., and may lead to the development of exportable versions of this system that can become available within any major hospital setting.

Mental retardation: Some of the more significant advances toward preventing mental retardation has been made from the knowledge about inborn errors of metabolism. The error often consists of a missing or deficient enzyme system which impairs the delicately balanced breakdown and utilization of body chemicals necessary for normal development. Phenylketonuria and galactosemia are examples of such metabolid disorders. Research at the Michigan State University Mass Spectrometry Facility is

aimed at identifying other metabolic disorders, particularly those that relate to lipid metabolism. Lipids isolated from skin cell cultures and from blood of mentally retarded children suspected of having defects in lipid metabolism are being examined for structural irregularities. The Facility's gas chromatograph-mass spectrometer system has proved uniquely applicable for this study, since only micrograms of lipids are available for analysis. The information on the structure of the various lipid metabolites gained from this work will aid in the indentification of metabolic errors and in the design of the treatment for these disorders.

Biological Materials Preparation Resources

These resources provide scientists with otherwise unobtainable biological materials such as enzymes, nucleic acids, and various subcellular organelles and whole living micro-organisms such as viruses, bacteria, and human cell lines. In addition, the resources develop new chemical and engineering methodologies for upgrading the efficiency and capabilities of the resource. Much of the work aimed at studying the basic life processes such as DNA synthesis and related processes in biochemical genetics is highly dependent on resources of this type. Also studies that require large quantities of purified biological materials are dependent on these resources. The testing of various enzymes for possible antitumor action falls in this class. For example, the isolation of a specific enzyme known to inhibit growth in some tumor lines from a specified bacterium is being done for Yale University by the New England Enzyme Center. Through a large-scale fermentation process the Center was able to produce sufficient quantities of the enzyme so that Yale investigators will be able to test the effects of this enzyme on various mouse tumor lines. These studies may eventually lead to the design and production of new antitumor drugs.

Electron Microscopy Resources

The Country's first one million volt electron microscope dedicated to biomedical research is being installed at the University of Wisconsin with funds awarded by the Biotechnology Resources Program. Completion of the microscope is expected in F.Y. 1972. One of the major endeavors of the resource will be the study of chemosomal fine structure and its relation to heredity and inherited disease in the human. This new facility will enable scientists to obtain information on the detailed structure of living material not available before. It represents an important emerging technology now becoming available to life scientists.

Program Plans in 1971 and 1972

The proposed budget for the Biotechnology Resources Program is $10,117,000, an increase of $500,000 over F.Y. 1971. The funds for F.Y. 1972 are expected to support 46 resources. The projects to be supported are in the areas of on-line computer development, mass spectrometry, nuclear magnetic resonance, high voltage electron microscopy and other techniques concerned with the characterization of molecular structure and function of its relationship to human disease. The increase of $500,000 will help offset the increased costs of providing these sophisticated resources. Additionally, it will allow for a limited increase in the scope of projects supported in selected areas of biotechnology such as electron microscopy.

Animal Resources

The goal of the Animal Resource Program is to develop and provide resources with which the biomedical scientist can develop knowledge for prevention and control of disease in man through experimentation with living systems. The importance of animal resources in reflected in the fact that 57 percent of National Institutes of Health supported research project grants require the use of animals. Animal experiments have been crucial in developing the vast majority of health care advances of which several examples are heart surgery; cardiac pacemakers; vaccines

against viral diseases; drugs to control diabetes, tuberculosis, malaria, and many other diseases; and modern understanding of nutrition. In many of these projects the availability and quality of an appropriate animal model is a critical factor in the experiment. The objective of providing quality animal resources is being met through(1) the Primate Research Centers Program, a specialized national resource that seeks to extend studies on primates to the diseases of man by providing sources of healthy primates in the United States and the proper environment in which to undertake such studies; (2) the Laboratory Animal Medicine Program that supports development of animal model resources and improvement of institutional animal resource programs, and (3) training and fellowship programs to provide an adequate number of specialists for research and service in laboratory animal science and medicine.

Primate Research Centers

The objective of the Primate Research Centers Program is to provide a unique research environment where scientists from many disciplines can conduct biomedical and behavioral research using the nonhuman primate as the experimental animal. This is accomplished by providing grant support for the operation of the seven centers, established in the early 1960's with Federal funds. Conservatively, the current investment in land, buildings, capital equipment and animals in each center is valued at $5,000,000 or a total of $35,000,000.

The nonhuman primate is biologically and behaviorally closer to man than any other animal, and is affected, sometimes uniquely, with many diseases similar to man. Therefore, the possibility of successfully applying information gained from nonhuman primates to man is higher than that obtainable with any other animal. The seven primate research centers collectively have one of the largest and most varied collections of nonhuman primates found anywhere in the world. Currently, some 7,700 animals representing 57 species are available in the centers for use in research by more than 100 center staff scientists and some 200 collaborative scientists from many institutions. Some of the important research areas where nonhuman primates are effectively and increasingly being utilized are: the effects of malnutrition on childhood development, reproductive physiology and population control, alcohol addiction, mental health and mental retardation and a number of others in the biological and behavioral sciences.

The following are examples of studies conducted at several of the primate centers:

Alcoholism: For the first time, an animal model of alcohol-induced physical dependence has been experimentally produced in man's close biological relative--the chimpanzee. Preliminary results indicate that 8-10 consecutive weeks of relatively high alcohol consumption can produce mild to severe withdrawal symptoms when alcohol intake is abruptly terminated. Work during the coming months will be devoted to determining what factors are critical in producing and treating this condition which may effect an estimated 2-3 million persons in the United States each year.

Effects of Infant Malnutrition on Brain Development: A new research program has been initiated at one center designed to determine how protein deprivation during the critical early stages of growth affects the development of the central nervous system and the psychological behavior of children. Preliminary results indicate that infant monkeys maintained on a low protein diet for the first year of life do not compete favorably with well-nourished peers. This multidisciplinary effort will attempt to relate the effects of early nutritional deprivation on behavior to specific chemical, biochemical, and structural changes in the growing brain and should lead to an understanding of how malnutrition affects these changes.

Hookworm Disease: The hookwork still remains an important cause of morbidity in the tropics and is considered one of the important retarding influences on community development. Many aspects of hookworm disease have been difficult to study in the laboratory due to the lack of a good experimental system. Recent studies have shown that certain primates can be infected with the human hookworm and that

the parasite behaves in primates essentially as it does in man. Therefore, laboratory studies using monkeys and apes as experimental models will assist in developing a better understanding of hookworm disease, and the significance of the hookworm in the production of anemia.

Fertility Control: Reproductive biology studies are being undertaken in five of the seven centers and extensive programs in population control are underway at two centers. Recent studies have produced three interesting findings--(a) the administration of low doses of progesterone over a short interval to female rhesus monkeys will inhibit ovulation by preventing the release of pituitary ovulating hormone; (b) the administration of testicular homogenate to mature male chimpanzees and rhesus monkeys results in testicular degeneration, and (c) impregnation of silastic intrauterine devices with progestin will significantly reduce the rate of explusion when these devices are placed into the uterine cavity of various female mammals. These and other studies are leading to a better understanding of human reproductive biology and techniques for controlling population.

Program Plans in 1971 and 1972

The $10,500,000 requested in 1971 and 1972 will support the operation of the seven primate research centers.

Laboratory Animal Medicine and Vivarial Sciences

The objective of the Laboratory Animal Medicine and Vivarial Sciences Program is to significantly improve the capability of institutional animal resources to serve medical research and education programs. This mission is accomplished through grants for support of special animal colonies that are of unusual nature and special value for certain types of research; disease diagnosis and control; research related to improving animal health and care; studies directed to enhancing the usefulness of animal models for research; and general improvement of management and accommodations for institutional animal resources.

Laboratory Animal Disease Diagnosis and Control: An important facet of research utilizing experimental animals is assurance that the animals are in an optimal state of health. This basic goal is dependent upon the ability to recognize and evaluate intercurrent laboratory animal diseases. Diagnostic resources are currently supported at 19 institutions where they underpin over $80,000,000 invested in research projects utilizing animals. The resource laboratories have not only served as the basic support for the animal health program, but have provided new information on disease processes and the cause of laboratory animal diseases. A further spinoff has been the elucidation of new laboratory animal models of human disease. Examples of these activities include detailed studies of a devastating disease outbreak in laboratory stocks of sparrows caused by canary pox virus; the diagnosis and control of bacterial pneumonia in monkeys used for the study of malaria; the recognition of naturally occurring malignant lymphoma as a complication in a drug evaluation project utilizing mice; and the diagnosis of diabetes in the South African hamster thereby identifying a valuable animal model to study this disease.

Animal Welfare: This Program has contributed significantly to animal welfare through disease control programs and historically has assisted a number of institutions in meeting the standards of the Laboratory Animal Welfare Ace of 1966 (P.L. 89-544). With the enactment of the much broader Animal Welfare Act of 1970, there will be an increased requirement for larger and more comfortable animal cages, renovations, cagewashers and sanitizing equipment, and better trained professional and technical personnel to meet the standards promulgated under the act. We know from information obtained through a comprehensive survey of animal facilities and resources that many institutions will be required to expend significant sums of money to meet the standards likely to be promulgated under the 1970 Act. These institutions can request financial assistance from the Animal Resource Program for those purposes related to the quality care of animals used for biomedical research.

Special Animal Colonies: An important area of this Program relates to the support of a number of special colonies which have proven to be quite valuable in human health related research. In most cases, animals from such colonies are available to qualified researchers from other institutions upon request. A case in point is the provision of over 1,200 highly inbred rabbits (representing 14 strains and 14 specific genotypes) to 84 investigators during the past several years from one colony supported by this Program. This particular colony provided genetic models for study of glaucoma, spina bifida, anemia, ataxia, and epilepsy. Examples of other special animal colonies highly useful in research include obesity-prone rats, leukemia cattle, germfree rats and mice used in air pollution research, and inbred guinea pigs of special usefulness in immunology research.

Institutional Primate Colonies: Six institutional primate resources will be supported under this program. Nonhuman primates are maintained in specialized facilities under optimal conditions of animal care and medical supervision where they are made available for multi-disciplinary types of biomedical research. The resource grant also contributes to the economy of research using primates by providing a framework for the multiple or sequential use of these expensive animals. These resources are currently being utilized in over 140 discrete projects, including the areas of reproductive physiology and fetal development, neonatal asphyxia, hepatitis and organ transplantation.

Primate Supply and Breeding: Because of the ever-dwindling availability of certain species of nonhuman primates from their native habitat sources, there is a critical need to assure a future supply of such animals for many biomedical research areas. A study will be initiated to identify those species of nonhuman primates of relevance to biomedical research which are in greatest danger of depletion for accession from native sources. Further, studies will be required to clearly demonstrate the feasibility of commercial domestic breeding and rearing of selected species.

New Animal Research Models: Studies continue to be supported to establish anatomic, biochemical, behavioral and physiological baselines on colonies of animal species which have exhibited the potential of developing into valuable research and educational resources. Such data has significantly advanced the use of miniature swine as a research model in a number of investigative areas, including alcholism, nutrition, microbiology, dentistry, reproductive biology, lipid metabolism, genetics, physiology and social behavior. Adaptation and characterization studies on new species of artic wild rodents (e.g., lemmings) may enhance their usefulness in studies of physiological adaptation, hibernation, energy metabolism, cold acclimatization and middle ear infections. Squirrel monkeys have been established as an important model for study of atherosclerosis. As a result, studies are underway to determine the genetic control of blood cholesterol and the effects of regular exercise (jogging) on development of atherosclerosis and coronary artery disease.

Program Plans in 1971 and 1972

The $4,474,000 requested for 1971 and 1972 will support approximately 64 animal resource projects. Thirty-one of these projects in 1971 and 26 in 1972 are for support of special colonies or development of animal disease models. Thirty-three of the projects in 1971 and 38 in 1972 are for improvement of efficiency and effectiveness of institutional animal programs through disease diagnosis and control, better scientific management, improved physical accomodations, and research related to improved methods of animal care, environmental control, and disease control.

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
Total fellowships.....	$126,000	$126,000	---

The increasing sophistication of animal resources for health-related research requires personnel with highly specialized training. It is the purpose of the Fellowship program to provide this training. The goal of the program is to provide an adequate number of specialists for research and service in laboratory animal science and medicine. The Division anticipates that people with demonstrated ability in laboratory animal medicine will be given fellowships in special areas such as surgery, anesthesiology, pathology, virology, primatology, biochemistry, etc.

Program Plans in 1971 and 1972

The $126,000 available in 1971 will provide support for 14 fellowships at the postdoctoral level. The $126,000 requested for 1972 will provide continued support for seven existing fellowships and seven new fellowships.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Continuations:						
a. Noncompeting.....	7	$71,000	7	$70,000	--	-$1,000
b. Competing.....	1	13,000	--	---	-1	-13,000
2. New.....	6	42,000	7	56,000	+1	+14,000
3. Total fellowships.....	14	126,000	14	126,000	--	---

Fellowships (by type of program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Postdoctoral.....	9	$74,000	10	$84,000	+1	-$10,000
2. Special.....	5	52,000	4	42,000	-1	-10,000
3. Total fellowships.....	14	126,000	14	126,000	--	---

Fellowships Program Analysis

Program Area	1971 Estimate	1972 Estimate	Increase or Decrease
1. Resource Animal Biochemistry...	$5,000	$10,000	+$5,000
2. Resource Animal Comparative Pathology.....	73,000	46,000	-27,000
3. Laboratory Animal Science.....	48,000	40,000	-8,000
4. Resource Animal Parasitology...	---	10,000	+10,000
5. Resource Animal Microbiology...	---	20,000	+20,000
6. Total fellowships.....	126,000	126,000	---

Training Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
Total training grants.....	$352,000	$352,000	---

Training grants are awarded to academic institutions to provide postdoctoral training in laboratory animal medicine. The training is intended to prepare individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through superior knowledge of laboratory animal biology and understanding of research methods. In addition, the trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team. Twenty-six trainees are currently enrolled in nine training programs. The usual training period is two to three years.

Forty-six trainees have completed training since the inception of training grants in laboratory animal medicine. Twenty-six of these are employed by medical schools and fifteen by other academic, research, or governmental organizations. The majority (27) are functioning as directors or staff members of a vivarium, sixteen are engaged in research or are obtaining additional training, and three are engaged in public health and other activities. Although the number of graduates is relatively small, they have filled vitally needed leadership roles in the field of laboratory animal medicine. The rapid progress in developing strong central animal resource programs and in expanding the "state of the art" may be attributed in large part to the influence of these highly trained individuals. A further accomplishment realized from this Program is that it is serving as a catalyst to develop special courses at the undergraduate level in schools of veterinary medicine.

Program Plans in 1971 and 1972

The $352,000 requested for 1972 will provide continued support to eight training programs in the field of laboratory animal medicine. While this will represent a decrease from nine to eight active programs, it is estimated that approximately the same number of trainees (30) will be supported. This is possible since most of the current programs have many approved, but unfunded, trainee positions.

Distribution of Training Grants

Graduate	1971 Estimate No.	1971 Estimate Amount	1972 Estimate No.	1972 Estimate Amount	Increase or Decrease No.	Increase or Decrease Amount
1. Continuations:						
a. Noncompeting.....	9	$352,000	5	$202,000	-4	-$150,000
b. Competing.....	--	---	3	150,000	+3	+150,000
2. New.....	--	---	--	---	--	---
3. Total training grants.....	9	352,000	8	352,000	-1	---

Collaborative Research and Development

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	2	$27,000	2	$28,000	--	+$1,000
Other expenses	--	1,359,000	--	1,363,000	--	+4,000
Total	2	1,386,000	2	1,391,000	--	+5,000

This activity supports research in collaboration with Federal and non-Federal institutions through contracts.

Program Plans in 1971 and 1972

The funds available in 1972 will continue to be used to support research contracts in the areas of chemical/biological information-handling systems and the regular research resource programs of the Division. Emphasis will continue to be placed on the development and evaluation of computer-based tools with which the design and testing of new drugs might be facilitated and with which our store of basic knowledge about chemical substances and their biological effects can be increased. The goal here is a single computer-based research resource which can be shared by geographically separate scientists and which can augment their individual cognitive and logistical capabilities for perusing analyzing, interpreting, and communicating laboratory and clinical data. In addition, special evaluation and development contracts are supported in the other regular resource programs of the Division.

The increase of $5,000 will provide funds for the annualization of 1971 pay increase costs.

Review and Approval of Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	52	$743,000	52	$856,000	--	+$113,000
Other expenses	--	312,000	--	297,000	--	-15,000
Total	52	1,055,000	52	1,153,000	--	+98,000

This activity supports the scientific and administrative staff of the Division's Special Research Grant Programs and General Research Support Programs. This includes program planning and development; and review and evaluation of grant applications for presentation to the National Advisory Research Resources Council. Other duties of this activity include liaison with applicants, grantees, other components of the NIH and DHEW, and advisory bodies, and interested organizations.

The increase of $98,000 includes $77,000 for annualization of 1971 pay increase costs, $7,000 within-grade increases, $11,000 for payment to the "National Institutes of Health management fund" for centrally furnished services, and $3,000 for one extra day of pay.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	30	$474,000	30	$509,000	--	+$35,000
Other expenses	--	228,000	--	228,000	--	---
Total	30	702,000	30	737,000	--	+35,000

This activity is responsible for the overall direction, administration, planning, evaluation and data analysis of the several grants-in-aid programs of the Division of Research Resources

The increase of $35,000 includes $16,000 for annualization of 1971 pay increase costs, $4,000 within-grade pay increases, $6,000 for increased Federal Telecommunicati System charges, $2,000 for one extra day of pay and $7,000 for payment to the "National Institutes of Health management fund" for centrally furnished services.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: General Clinical Research Centers (Public Health Service Act, Title III, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$38,004,000	Indefinite	--	$39,004,000

Purpose: In 1959, Congress recommended the establishment of the General Clinical Research Centers Program as a result of its recognition of the need and desire to create centralized facilities to provide highly integrated research opportunities and services to large numbers of investigatory and research groups around the nation. The program which grew from the broad Congressional mandate has a number of discrete but highly integrated objectives: (1) to provide facilities and personnel sufficient to establish throughout the Nation the optimal environment for human clinical investigation; (2) to promote the rapid application of laboratory and basic science research advances to the immediate care of the clinically diseased individual; and (3) to increase the total body of knowledge of the etiology, natural history, therapy and prevention of human disease.

Explanation: Federal grants are made to fund the cost of establishing and operating clinical centers which are physically discrete research hospital units usually located in university-affiliated hospitals. They provide the essential bed space for clinical research, the laboratory equipment necessary for such research, and are staffed by personnel trained in clinical research techniques. Investigators trained in all areas of medical science utilize these centers. Research in major disease areas include renal disease, cardiovascular diseases, infectious diseases, allergy and immunology, dermatology, cancer, and diseases contributing to high infant mortality rates.

Accomplishments in 1971: In 1971, 80 centers received support. Studies conducted at the centers emphasized population control, cancer therapy, transplantation research, and drug treatment of Parkinson's Disease.

Objectives for 1972: The estimate for 1972 will provide continuing operation for approximately 80 centers. The $1,000,000 increase will allow the activities to be maintained at close to present operating levels with some diversification to facilitate research on ambulatory patients.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Biotechnology Resources (Public Health Service Act, Title III, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$9,617,000	Indefinite	--	$10,117,000

Purpose: The Biotechnology Resources program provides the Nation's life scientists with sophisticated technologies for research, education, and patient care by facilitating access to highly specialized instruments and methodologies and their associated expertise.

Explanation: Grants are made to institutions to conduct a wide variety of health-related research within a university, research institution or region with emphasis on computation, mass spectrometry, nuclear magnetic resonance spectroscopy, high voltage electron microscopy and biological materials preparation. The biotechnology resource is characterized by three component activities: (a) the rendering of services to biomedical scientists whose specific research projects are funded by the categorical institutes of the NIH; these services include access to both instrumentation and expert consultative and other technical assistance, (b) the pursuit of research and development directed toward upgrading existing resource capabilities and the state of the technology as it relates to human disease, and (c) the providion of a base for the training of biomedical scientists in the appreciation and use of the technology. This mode of support makes it economically feasible to provide biomedical scientists supported by other programs of the NIH with both (a) urgently needed scientific capabilities that could not be justified or fully utilized on an individual basis, and (b) the expertise necessary for the most efficient and effective utilization of such expensive and advanced research tools.

Accomplishments in 1971: In 1971 support was provided to 47 resources: 33 Biomedical Computer Resources, 10 Biomedical Instrumentation Resources, three Biological Materials Preparation Resources, and one High Voltage Electron Microscopy Resource. During 1971, 1,867 investigators utilized the computer, including assistance in the diagnosis of heart disease, monitoring the critically ill, and studies of child development. 273 investigators utilized the Biomedical Instrumentation Resources to elucidate the molecular structure of chemical substances that comprise or interact with living organisms including research on chemotherapeutic agents, antibiotics, and the structure and function of normal and abnormal hemoglobins. 19,093 preparations were requested from the Biological Material Preparation Resource.

Objectives for 1972: During 1972, support will be provided to the 46 existing resources.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Scientific Evaluation (Public Health Service Act, Title III, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$215,000	Indefinite	--	$215,000

Purpose: This activity provides support for the study sections and preliminary review committees used by the Division to provide scientific merit review of grant applications.

Explanation: 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 they forward their recommendations to the National Advisory Research Resources Council.

Accomplishments in 1971: Provides support for the review of grant applications and program plans for the Division's several branches.

Objectives for 1972: The $215,000 requested for 1972 will provide support for review of applications for new and competing grants for General Clinical Research Centers, Biotechnology Resources, Animal Resources and Training grants, and the Chemical Biological Information Handling program.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Animal Resources (Public Health Service Act, Title III, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$14,974,000	Indefinite	--	$14,974,000

Purpose: Animal Resources includes the Laboratory Animal Medicine and Vivarial Sciences program and the Primate Research Centers program. The Laboratory Animal Medicine and Vivarial Sciences program assists institutions in providing animal resources required for medical research and education. The Primate Recearch Center program provides a unique research environment where scientists from many disciplines can conduct biomedical and behavioral research using the nonhuman primate as the experimental animal.

Explanation: Grants for Laboratory Animal Medicine and Vivarial Sciences are made to institutions for special animal colonies, research related to improving animal health and care, disease diagnosis and control, studies directed to enhancing the usefulness of animal models for research, and general improvement of management and accommodations for institutional animal resources. The importance of animal resources is reflected in the fact that over 57 percent of the National Institutes of Health's supported research grants require the use of animals.

The seven Primate Centers established in the early 1960's with Federal funds receive operating support through annual grants. The nonhuman primate is biologically and behaviorally closer to man than any other animal, and is affected, sometimes uniquely, with many diseases similar to man. Therefore, the possibility of successfully applying information gained from nonhuman primates to man is higher than that obtainable with any other animal.

Accomplishments in 1971: In 1971, 71 animal resources received support including seven primate research centers. The Laboratory Animal Medicine and Vivarial Sciences program will provide support for 31 projects for special colonies or development of animal disease models, and 33 projects for improvement of efficiency and effectiveness of institutional animal programs.

Objective for 1972: It is anticipated the program for 1972 will support approximately 71 animal resources.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Fellowships (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$126,000	Indefinite	--	$126,000

Purpose: The increasing sophistication of animal resources for health related research requires personnel with highly specialized training. The purpose of the fellowship program is to provide this training.

Explanation: The goal of the Fellowships program is to provide an adequate number of specialists for research and service in laboratory animal science and medicine. It is anticipated that individuals with demonstrated ability in laboratory animal medicine will be given fellowships in special areas such as surgery, anesthesiology, pathology, virology, primatoloty, biochemistry, etc.

Accomplishments in 1971: There were 14 fellowships awards in 1971, 9 postdoctoral, and five special.

Objectives for 1972: Funds requested for 1972, the same dollar level as in 1971, will support 14 fellowships in 1972, 10 postdoctoral, and four special.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Training (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$352,000	Indefinite	--	$352,000

Purpose: There is a critical need for trained specialists in laboratory animal medicine. The impetus of the Laboratory Animal Welfare Act (P.L. 89-544) and pending legislation to further refine animal care imposes an additional obligation on the Federal government and scientific community to provide adequately trained laboratory animal specialists.

Explanation: Training grants are awarded to academic institutions to provide postdoctoral training in laboratory animal medicine. The training is intended to prepare individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through superior knowledge of laboratory animal biology and understanding of research methods. In addition, trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team.

Accomplishments in 1971: In 1968 the National Academy of Sciences through its Institute of Laboratory Animal Resources conducted a survey which indicated that 374 veterinary specialists in laboratory animal medicine or pathology are employed in animal facilities in Public Health Service grant eligible institutions; an additional 109 are needed presently; and 338 more will be needed by 1973. The fact that a large number of medical schools and research institutions simply cannot find any such specialists is causing staffing problems for ongoing resource programs and all research programs which use animals.

There have been 46 graduates of the nine existing training programs. Twenty-six of these are employed by medical schools and 15 by other academic, research or governmental organizations.

In 1971, nine training grants were funded providing support to approximately 26 trainees at the graduate level.

Objectives for 1972: Funds requested for 1972 will provide the same dollar level as in 1971, and will support eight awards which will result in the training of approximately 30 trainees at the graduate level in the field of laboratory animal medicine.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Collaborative Research and Development (Public Health Service Act, Title III, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
2	$1,386,000	Indefinite	2	$1,391,000

Purpose: To support research in collaboration with Federal and non-Federal institutions through the contract mechanism.

Explanation: Implementation of the collaborative programs are largely through contracts with universities, industrial facilities and other Federal agencies.

Accomplishments in 1971: In 1971, support through research contracts was provided in the areas of chemical/biological information handling, special research resources, and laboratory animal care. Major emphasis was placed on the development and evaluation of computer-based tools with which the design and testing of new drugs might be facilitated and with which our store of basic knowledge about chemical substances and their biological effects can be increased. Developments include computer-driven display systems for studying molecules in two or three dimensions and sophisticated file systems for handling the heterogeneous types of data associated with them. Particular attention is addressed to helping individual scientists manipulate, analyze and communicate data they amass in the course of their research.

Objectives for 1972: Program plans for 1972 will continue to support research contracts in the areas of chemical/biological information handling, and the regular research resource areas.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Review and Approval (Public Health Service Act, Title III, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
52	$1,055,000	Indefinite	52	$1,153,000

Purpose: Provide support for the scientific and administrative staff of the Division's special research grant programs and General Research Support programs.

Explanation: Funds are used for salaries and related cost for staff necessary for the program planning and development, review and evaluation of grant applications for presentation to the National Advisory Research Resources Council and the National Advisory Health Council. Other staff duties include liaison with applicants, grantees, other components of the NIH and DHEW, and advisory bodies, and interested organizations.

Accomplishments in 1971: Administrative review and processing of application and grant awards of the special research grant programs of the Division.

Objectives for 1972: In 1972, this activity will continue to provide the scientific and administrative support required for the review of all of the Division's grants at the same level as 1971.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Program Direction (Public Health Service Act, Title III, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
30	$702,000	Indefinite	30	$737,000

Purpose: This activity provides the overall leadership required for the administration, direction and coordination of the several programs of the Division of Research Resources.

Explanation: Funds are used for salaries and related cost for staff of the immediate Office of the Director, Executive Officer, Administrative Office, Budget Office, Program Analysis Office and Information Office.

Accomplishments in 1971: Overall direction and administration of the Division's programs as well as review of current and proposed operations.

Objectives for 1972: In 1972 this activity will continue to provide the overall direction and administration of the Division's programs at the same level as 1971.

62-645 O - 71 - pt. 3 - 73

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

General Research Support Grants

Amounts Available for Obligation

	1971	1972
Total obligations	54,200,000	49,200,000

Obligations by Activity

Page Ref.		1971 Estimate	1972 Estimate	Increase or Decrease
164	Grants:			
	(a) General research support.	$43,423,000	$40,800,000	-$2,623,000
	(b) Biomedical sciences support	6,777,000	6,400,000	-377,000
	(c) Health sciences advancement awards	4,000,000	2,000,000	-2,000,000
	Total obligations	54,200,000	49,200,000	-5,000,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Grants, subsidies, and contributions (total obligations)	$54,200,000	$49,200,000	-$5,000,000

Summary of Changes

1971 estimated obligations	$54,200,000
1972 estimated obligations	49,200,000
Net change	-5,000,000

	Base	Change from Base
Decreases:		
Program:		
1. General research support	$43,423,000	-$2,623,000
2. Biomedical sciences support	6,777,000	-377,000
3. Health sciences advancement awards	4,000,000	-2,000,000
Total program decreases	---	-5,000,000

Explanation of Changes

Research grants--The program decrease of $5,000,000 will result in reduced awards and support to institutions eligible under the General Research Support and Biomedical Sciences Support programs and reflects the gradual phase out of the Health Sciences Advancement Award program.

The reductions were made on the premise that overall medical research efforts would be best served by programming the limited funds available to those areas of special initiatives.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation requested
Public Health Service Act Section 301(d)--Make....grants-in-aid to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research and research training programs.....	Indefinite	$49,200,000

PUBLIC HEALTH SERVICE ACT

Title III--General Powers and Duties of Public Health Service

Part A--Research and Investigation

Appropriation

Section 301(d). Make----grants-in-aid to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research and research training programs: Provided, that such uniform percentage, not to exceed 15 per centum, as the Surgeon General may determine, of the amounts provided for grants for research or research training projects for any fiscal year through the appropriations for the National Institutes of Health may be transferred from such appropriations to a separate account to be available for such research and research training program grant-in-aid for such fiscal year.

General Research Support Grants

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$14,500,000	$16,000,000	$20,000,000	$20,000,000
1963	30,000,000	30,000,000	30,000,000	30,000,000
1964	30,000,000	30,000,000	30,000,000	30,000,000
1965	40,000,000	40,000,000	45,000,000	45,000,000
1966	45,200,000	45,200,000	50,000,000	45,200,000
1967	51,700,000	51,700,000	51,700,000	51,700,000
1968	61,700,000	61,700,000	75,000,000	61,700,000
1969	60,700,000	60,700,000	60,700,000	60,700,000
1970	60,700,000	60,700,000	65,700,000	60,700,000
1971	45,977,000	60,700,000	60,700,000	60,700,000
1972	49,200,000			

Justification

General Research Support Grants

	1971 Estimate	1972 Estimate	Increase or Decrease
General research support grants.....	$43,423,000	$40,800,000	-$2,623,000
Biomedical sciences support grants.....	6,777,000	6,400,000	-377,000
Health sciences advancement awards.....	4,000,000	2,000,000	-2,000,000
Total.....	54,200,000	49,200,000	-5,000,000

General Statement

Under the aegis of its extramural research programs, the NIH has long recognized and supported the development of institutional research strength. Although primarily concerned with fostering categorical research efforts in its attack on the major health problems of this country, this agency is cognizant that the quality of that research is proportional to the quality of the institutions in which it is performed, for these institutions provide the environment in which the research will be performed, and the milieu in which future faculty and research investigators obtain their education and research training. It is imperative, therefore, that institutions engaged in the education of health professionals and in the conduct of biomedical research, have a vigorous research life. To this end the NIH provides non-categorical research grant funds to eligible institutions for the general support of health-related research and research training. These flexible funds assist the institution in achieving its self-conceived research goals and aspirations by permitting it to establish its own priorities in determining the use of these funds. This approach to institutional funding developed out of the realization that institutions that conducted categorical research in response to national needs, could develop imbalances in their overall research programs, and that little if any local control could be exerted over the direction of growth that might result because of such national programs. Consequently, two grant programs were initiated in an attempt to restore appropriate institutional control over institutional research. These two programs were the General Research Support Grant (GRSG) and Biomedical Sciences Support Grant (BSSG) programs. A third program, the Health Sciences Advancement Award (HSAA) was designed to assist health research institutions to join the ranks of the preeminent.

The hallmark of the programs under the General Research Support authority is that they provide flexible funds, to be used at the discretion of the grantee institutions, in fostering health-related research and research training. The following are a few examples of how this flexibility has resulted in significant research results:

A. Early recognition of research potential through pilot research projects.

1. While supported on a GRSG student research fellowship, a young graduate student, William Oppenheim, of the Georgetown University School of Medicine received a 1970 Borden Award for outstanding biomedical research by an undergraduate.

2. In September of 1970, a rechargeable cardiac pacemaker, developed at Johns Hopkins University School of Medicine, was selected as one of the one hundred top inventions of the year, by a panel of 33 leading scientists, engineers, and research administrators, as part of competition supported by Industrial Research, Inc., publishers of industrial and oceanography magazines.

3. A preliminary model of an "audiodontic device, "that is, a system that provides audio-communication through the teeth, has been built and tested at the University of California, Los Angeles School of Dentistry. Development of miniaturized circuitry for an advanced model is underway.

4. At Washington University in St. Louis, a 5-gram radio transmitter has been developed which is small enough to be surgically implanted into the abdominal cavities of mice. The device transmits an ECG and body temperature signal a distance of 30 feet, and remains active for a month or more, depending on the size of the battery.

B. Stabilization of institutional activities.

1. By supporting key research faculty -

Dr. Seymour Lieberman of Columbia University College of Physicians and Surgeons was supported by GRSG funds. Dr. Lieberman's contributions to the biochemistry of the steroid hormones (which has been partially supported by this grant) have been recognized by his being awarded the highest honor of the American Endocrine Society, the Frederick Conrad Koch Award.

2. By preservation of valuable central research resources -

a. At Louisiana State University Medical Center, GRSG funds enabled the institution to maintain a colony of mice that is a tremendously valuable resource for investigations requiring a genetically refined strain of animals.

b. A similarly important mouse colony was preserved at Harvard Medical school through the use of GRSG funds. The importance of this colony is in the study of models whereby environment and certain agents such as sulfonylureas can alter the steady state levels of blood glucose in experimental animals and man.

3. By obtaining critically needed equipment -

a. State University of New York Downstate Medical Center obtained a liquid scintillation counter that has become a valuable research tool.

b. Michigan State University College of Veterinary Medicine is using its GRSG to equip new, special purpose, interdisciplinary research laboratories in Virology, Comparative Hematology, Anesthesiology, and Comparative Parasitology.

C. Establishment of new research entities.

1. The GRSG played an important role in the organization of the Division of Environmental Medicine in the Department of Community Medicine of the Mt. Sinai School of Medicine. This laboratory has become a major national resource for air pollution studies.

2. A BSSG project at the Massachusetts Institute of Technology involved the establishment of the Biomedical Engineering Laboratory at Boston City Hospital.

3. The University of California at Davis, a more recent HSAA grantee has moved vigorously in its program in comparative medicine which now involves more than 60 professional scientists from five schools and colleges of the University. The HSAA is making possible the interdisciplinary utilization of the unusual animal facilities available at Davis and more than 10 species are being investigated for comparative purposes with the ultimate objective of more accurate extrapolation to the understanding of human disease.

Program Plans in 1971 and 1972

General Research Support Grants: In 1972, GRSG's will be awarded to approximately 333 institutions (schools of medicine, dentistry, public health, pharmacy, veterinary medicine, and nursing, hospitals, non-academic research institutes and state and municipal health departments). Over one-half of the funds will be distributed to schools of medicine. The dollar amount of each award will be derived by applying a formula to the level of appropriate NIH and/or NIMH research project grants received by the grantee institution during the preceding fiscal year.

With few exceptions, GRSG funds may be spent for the direct costs of research and research training at the discretion of the recipient institution. Such costs include salaries, student stipends, research equipment and supplies, and numerous other needs.

Biomedical Sciences Support Grants: This program complements the GRSG program by providing equally flexible funds to non-health professional components of universities. This is fitting, because approximately one-fifth of all NIH and NIMH supported research activity is conducted in components of universities other than health professional schools. Conceptually identical to the GRSG program, the BSSG program will provide approximately 116 institutions with awards during 1972. As in the GRSG program, decisions regarding the expenditure of these funds will be made by the recipient institution, thereby providing the grantee with the greatest latitude possible in developing its research program.

Health Sciences Advancement Awards: To date eleven awards have been made. The academic community has been notified that no new applications will be accepted for review. During F.Y. 1972 four institutional advancement programs will continue to be supported with the funds requested, to meet pre-existing commitments.

Distribution of Funds by Program Area in 1972

The following table illustrates the planned 1971 and 1972 distribution of grants within general research support programs. This is a decrease of $5,000,000 from 1971 to 1972 and reflects reallocations from the General Research Support programs to the higher priority new initiative areas funded elsewhere in the NIH budget.

	1971 Estimate		1972 Estimate	
	No.	Amount	No.	Amount
General Research Support				
Educational Institutions:				
Dentistry	33	$2,041,000	35	$1,958,000
Medical	100	23,275,000	102	21,951,000
Public Health	12	1,520,000	12	1,387,000
Pharmacy	15	695,000	15	612,000
Veterinary Medicine	17	1,476,000	17	1,346,000
Nursing	2	87,000	3	122,000
Noneducational Institutions:				
Hospitals	76	7,729,000	76	7,059,000
Research Institutes and Others	69	6,296,000	71	6,120,000
Health Departments	2	304,000	2	245,000
Subtotal	326	43,423,000	333	40,800,000
Biomedical Sciences Support Grants	112	6,777,000	116	6,400,000
Health Sciences Advancement Awards	9	4,000,000	4	2,000,000
Total	447	54,200,000	453	49,200,000

The following table shows the estimated amounts to be provided by each of the contributing appropriations:

	1971 Estimate	1972 Estimate
National Institutes of Health		
National Cancer Institute	$5,901,000	$5,275,000
National Heart and Lung Institute	8,127,000	7,267,000
National Institute of Dental Research	1,028,000	908,000
National Institute of Arthritis and Metabolic Diseases	8,123,000	7,243,000
National Institute of Neurological Diseases and Stroke	5,027,000	4,481,000
National Institute of Allergy and Infectious Diseases	5,044,000	4,494,000
National Institute of General Medical Sciences	6,978,000	6,218,000
National Institute of Child Health and Human Development	3,909,000	3,475,000
National Eye Institute	1,551,000	1,381,000
National Institute of Environmental Health Sciences	485,000	431,000
Subtotal, NIH	46,173,000	41,173,000
Health Services and Mental Health Administration		
National Institute of Mental Health	8,027,000	8,027,000
Total	54,200,000	49,200,000

NATIONAL INSTITUTES OF HEALTH

General Research Support Grants

Program Purpose and Accomplishments

Activity: General Research Support (Public Health Service Act, Title III, Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$43,423,000	Indefinite	--	$40,800,000

Purpose: The General Research Support Grant program was started in 1962 after the passage of Public Law 86-798. The NIH established this program to give institutions heavily engaged in health-related research greater control over the quality, content, emphasis and direction of their research activities than was possible exclusively under the research project grant system. Within broad defined guidelines, the General Research Support Grant may be spent for direct costs of health research and research training in any way deemed appropriate by the recipient institution.

Explanation: Viewed as complementary to project grants, this formula-grant provides funds on a continuing basis to eligible institutions for their flexible and discerning use in research and research training activities. The dollar amount of each award is derived by a formula which basically reflects the level of National Institutes of Health and National Institute of Mental Health research project grants received by the institution in the preceding fiscal year. Eligible institutions include schools of medicine, dentistry, osteopathy, public health and other types of health professional schools, hospitals, state and local health departments and nonacademic health research organizations. The fundamental rationale of this program is that effective health research requires a strong institutional base as well as direct project support. Funds provided by the General Research Support Grant program have been used for the support of central and shared research resources for meeting emerging opportunities, to explore new and unorthodox ideas, to permit early support of promising scientists, and to utilize funds flexibly to improve and foster present and long-range institutional scientific excellence.

Accomplishments in 1971: In 1971 General Research Support grants provided support to 326 institutions.

Objectives for 1972: The General Research Support program will provide support to approximately 333 institutions in 1972.

NATIONAL INSTITUTES OF HEALTH

General Research Support Grants

Program Purpose and Accomplishments

Activity: Biomedical Sciences Support Grants (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$6,777,000	Indefinite	--	$6,400,000

Purpose: The Biomedical Sciences Support program is conceptually identical to the General Research Support Grants program; major decisions related to the use of these grant funds are left to the institutions, giving them great flexibility with a minimum of direction and control from the Federal agency level. This program, however, provides funds to academic institutions other than health professional schools for support of their health related research and research training activities.

Explanation: The Biomedical Sciences Support Grant program provides complementary support to project grants through a formula grant-basis which reflects the level of NIH-NIMH research project grants received by the institution in the preceding year. Grant policies encourage institutions to meet emerging opportunities, to explore new and unorthodox ideas, to permit early support of promising scientists, and to utilize funds flexibly to improve and foster present and long-range institutional scientific excellence.

Accomplishments in 1971: In 1971 Biomedical Sciences Support grants provided support to 112 institutions.

Objectives for 1972: The Biomedical Sciences Support grants program will provide support to approximately 116 institutions in 1972.

NATIONAL INSTITUTES OF HEALTH

General Research Support Grants

Program Purpose and Accomplishments

Activity: Health Sciences Advancement Awards (Public Health Service Act, Title III, Part A)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$4,000,000	Indefinite	--	$2,000,000

Purpose: This award program is designed to assist academic institutions to strengthen significantly their activities in health sciences by (1) supporting the advancement of new and existing health research and training endeavors where an appropriate institutional base for such advancement exists, and (2) encouraging the development of health science activities in institutions that presently possess considerable strength in related fields of science.

Explanation: Awards are competitive on the basis that applicant institutions must identify and describe a unifying research theme or scientific focus within the specific institutional proposal for which funds are requested. Presently a moratorium is in effect on the acceptance of new applications.

Accomplishments in 1971: In 1971, Health Science Advancement Awards were made to nine institutions.

Objectives for 1972: No new awards are contemplated for 1972. Four institutional advancement programs will continue to be supported with the funds requested to meet pre-existing commitments.

TUESDAY, MAY 11, 1971.

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

WITNESSES

DR. MILO D. LEAVITT, JR., DIRECTOR

DR. JOHN F. SHERMAN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH

GEORGE E. PRESSON, EXECUTIVE OFFICER, JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH

B. FRANK GARDNER, JR., ACTING ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH

CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES
OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 estimate	1972 estimate
Personnel compensation:			
Permanent positions	631	653	666
Positions other than permanent	46	70	70
Other personnel compensation	2	5	5
Total personnel compensation	679	728	741
Personnel benefits: Civilian employees	70	87	89
Travel and transportation of persons	93	193	193
Transportation of things	6	10	10
Rent, communications, and utilities	32	80	81
Printing and reproduction	28	40	40
Other services	506	583	521
Supplies and materials	30	50	50
Equipment	73	98	98
Grants, subsidies, and contributions	1,214	1,767	1,429
Total obligations	2,731	3,636	3,252

PERSONNEL SUMMARY

Total number of permanent positions	49	49	49
Full-time equivalent of other positions	6	8	8
Average number of all employees	52	55	55
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 estimate	1972 estimate
Program by activities:			
1. Grants:			
(a) Research	20	520	520
(b) Fellowships	531	1,077	739
(c) Fogarty scholarships	131	170	170
2. International center	1,552	1,869	1,823
Total program costs, funded [1]	2,234	3,636	3,252
Change in selected resources	497		
Total obligations	2,731	3,636	3,252
Financing:			
Unobligated balance lapsing	44		
Budget authority	2,775	3,636	3,252
Budget authority:			
Appropriation	2,954	3,582	3,252
Portion withdrawn (Public Law 91-204, sec. 410)	−163		
Transferred to other accounts	−16		
Appropriation (adjusted)	2,775	3,582	3,252
Proposed supplemental for civilian pay act increases		48	
Proposed supplemental for military pay act increases		6	
Relation of obligations to outlays:			
Obligations incurred, net	2,731	3,636	3,252
Obligated balance, start of year	372	1,316	2,200
Obligated balance, end of year	−1,316	−2,200	−2,327
Outlays, excluding pay increase supplemental	1,788	2,700	3,123
Outlays from civilian pay act supplemental		46	2
Outlays from military pay act supplemental		6	

[1] Includes capital outlays as follows: 1970, $36 thousand; 1971, $98 thousand; 1972, $98 thousand.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $286 thousand; 1970, $783 thousand; 1971, $783 thousands; 1972, $783 thousand

NOTES

Includes $22 thousand in 1972 for activities previously financed from: National Cancer Institute, 1971, $22 thousand.
Includes $500 thousand in 1971 and $500 thousand in 1972 for activities previously financed from: National Institute of Allergy and Infectious Diseases, 1970, $500 thousand.
Excludes $6 thousand in 1972 for activities transferred to (in thousands of dollars):

	1970	1971
Office of the Director	1	6
National Eye Institute	7	

BIOGRAPHIES OF WITNESSES

Mr. PATTEN. Good morning, Doctor. It is nice to have you with us.

Dr. LEAVITT. Thank you, sir.

Mr. PATTEN. I don't believe you have anyone that the committee doesn't know.

Mr. Reporter, we would like Dr. Leavitt's and Mr. Presson's biographies put in the record at this point.

(The biographical sketches follow:)

NATIONAL INSTITUTES OF HEALTH

BIOGRAPHICAL SKETCH OF MILO DAVID LEAVITT, JR.

Position: Director, John E. Fogarty International Center for Advanced Study in the Health Sciences, NIH.
Birthplace and date: June 24, 1915—Beloit, Wis.
Education:
1933–38 University of Wisconsin, B.A.
1938–40 University of Pennsylvania, M.D.
1945–48 University of Minnesota, M.Sci.
1958–59 Harvard University, M.P.H.

Experience:
1968–present—Director, John E. Fogarty International Center for Advanced Study in the Health Sciences, NIH.
1967–68—Acting Director, Office of Program Planning, NIH.
1967—Deputy Director, Office of Program Planning, NIH.
1966–67—Deputy Assistant Secretary for Science and Population, DHEW.
1966—Science Policy Coordinator, OS–ASH, DHEW.
1962–66—Head, Special International Programs Section, Office of International Research, NIH.
1960–62—Assistant Chief, Perinatal Research Branch, National Institute of Neurological Diseases and Blindness, NIH
1959–1960—Chief, Project Services Branch, Collaborative Research, NINDB, NIH.
1958–1959—Postdoctoral Public Health Trainee, Harvard School of Public Health, Boston, Mass.
1949–1958—Clinical Assistant Professor Medicine, Medical College of Pennsylvania, Philadelphia, Pa.
1945–1949—Fellow, Internal Medicine, Mayo Clinic, Rochester, Minn.
1942–1945—Captain, U.S. Army Medical Corps.
1940–1942—Rotating Internship, Philadelphia General Hospital, Philadelphia, Pa.

Association Memberships:
American Medical Association.
Philadelphia County Medical Society.
Society of the Sigma Xi.
American Disabetes Association.
Association of American Medical Colleges.
New York Academy of Sciences.
American Association for the Advancement of Science.
Industrial Medical Association.
Alumni Association of the Mayo Foundation.
American Heart Association.
American Public Health Association.
American Society for Public Administration.

FOGARTY INTERNATIONAL CENTER

BIOGRAPHICAL SKETCH OF GEORGE E. PRESSON

Position: Executive officer, Fogarty International Center, NIH.
Birthplace and date: June 15, 1912, Weir, Kans.
Education:
1935–1938—Columbus University, Washington, D.C., B.C.S.
1938–1939—Columbus University, Washington, D.C., M.C.S.
1941–1942—George Washington University.

Experience:
1968—Present—Executive officer, Fogarty International Center, NIH (GS–15).
1968–1968—Chief, Conference and Administrative Management Branch, Fogarty International Center, NIH (GS–14).
1963–1968—Head, Management Operations Section, OIR/NIH (GS–14).
1962–1963—Staff Assistant, Office of International Research, NIH (GS–14).
1957–1962—Executive officer, Division of International Health, PHS (GS–13–14).
1951–1957—Administrative officer, Division of International Health, PHS (GS–11–12).
1947–1951—Budget officer, Division of Administrative Management, PHS (GS–9–11).
1943–1947—Unemployed—Illness.
1935–1943—Various positions—Securities Exchange Commission and War Production Board (CAF–2–-CAF–9).

General Statement

Mr. Patten. Doctor, you have a statement. How would you like to proceed?

Dr. Leavitt. With your permission, I would like to read it for the record.

Mr. Patten. Fine.

Dr. Leavitt. Mr. Chairman and members of the committee: The John E. Fogarty International Center for Advanced Study in the Health Sciences is developing its capacities to emphazie and encourage interaction within the medical and scientific community of the world through several on-going programs such as conferences and seminars and the Fogarty Scholars-in-Residence. Among other elements of cooperation and advanced study is an organized program of bilateral cooperation and a newly designed effort to obtain useful scientific information from a variety of foreign countries, including Eastern Europe. In addition to these programs, we are continuing the administration and management of the international postdoctoral fellowship program, the International Visitors Center and the special foreign currency program, where, as a result of the increased allocation of foreign currencies, we have enlarged our research abroad in those selected countries where Public Law 480 funds are available. A new program addition to the Fogarty International Center has been the U.S. contribution to the support of the Gorgas Memorial Laboratory in Panama.

In the conduct of our programs, we make special efforts to assure that all the institutes and divisions at the NIH, as well as other health-related organizations within the Department of HEW, and other Federal, international, and nongovernmental agencies are informed of our activities.

If I may, I would like to address myself specifically to some of the above activities.

Conferences and Seminars at the Center

The Fogarty International Center through its conferences and seminar program provides a forum for the review and discussion of major biomedical issues confronting the Nation. Although the Center itself has developed several basic themes for consideration, emphasis is also placed upon cooperation with the various institutes of the NIH, as well as other Federal and international organizations.

The professional staff of the Center, in consultation with its advisory committee and specialists and consultants from the private sector, plan the conferences, inviting men and women of national and international renown to join in 2- or 3-day working session to examine and analyze major issues which now confront our society.

The presentations, findings, and recommendations of these meetings are published or otherwise made available to all interested individuals and organizations and provides an effective means for appraisal of the problems.

The Center's first international meeting, "Reform of Medical Education and the Effect of Student Unrest," was published in cooperation with the National Academy of Sciences. This meeting demonstrated that the traditions, socioeconomic conditions, and power structure of individual countries largely determine the causes and forms of medical

student demands and the manner in which they are met. A recent review stated that this meeting has:

> Not only given an interested public an opportunity to understand the process of constructive change in medical schools and research institutions, but has also provided a valuable text for the study of medical education in widely different societies.

A second conference in the series on medical education, "The Role of Research in Medical Education" was held in July 1970. At this conference we sought to explore in depth the essential role played by biomedical research in the production of competent physicians. It was concluded that research activity within the medical school improves the ultimate quality of medical care in two ways. First, by training the future doctor in the demanding intellectual climate generated by research, and second, through the application of research results applied to the practice of medicine and public health. There was also general agreement that our medical schools can combine the teaching of scientific medicine, and yet impart a humane and compassionate attitude to the young physician without sacrificing the high quality of medical care the American public has come to expect of the medical profession.

I would like also to mention, Mr. Chairman, that the third conference in our medical education series, "The Impact of New Health Systems on Medical Education" is planned for September 1971.

These are but a few examples of the many conferences, workshops, and seminars which have been held and which are planned for the coming years under the sponsorship of the Center.

When Mr. Fogarty's concept of an international center was described on the floor of the Senate by Senator Hubert Humphrey, he stated:

> 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.

Mr. Chairman, we are, as you are aware, awaiting the final development of the plans for the center envisaged by Mr. Fogarty, by this committee and many others. In the meantime, however, we are utilizing Stone House as the pilot facility. Because we are eager to utilize Stone House on a day-to-day basis, we have assisted a number of NIH Institutes, all of the Fogarty scholars, and several international groups by making our facilities, as well as the competencies of our professional and technical staff, available for planning, organizing, and conducting other international scientific meetings and seminars at NIH.

FOGARTY SCHOLARS-IN-RESIDENCE

The Fogarty scholars-in-residence program provides an opportunity for the assembly of outstanding authorities from the United States and abroad to direct their attention to the exploration of problems within their own disciplines, as well as related fields of interest. Here, removed from the day-to-day incursions upon their time and energies, and provided with the necessary administrative support, the scholars direct their full attention to the exploration of broad and important

problems of science, with acquisition of new knowledge, and the study of the application and consequences of scientific advance upon modern society. New efforts initiated through the development of advanced seminars involving experts from universities, national and international organizations will provide background documents and source material for a variety of echelons within Federal departments and outside of Government.

For example, authorities representing all levels of the health care delivery system are manifesting an increasing interest in preventive medicine beyond humanitarian considerations, the prevention of diseases with a high cost in disability and death is most attractive from the financial and political standpoint.

The state of the art of preventive medicine needs to be delineated in an in-depth survey by epidemiologists, biostatisticians, clinical investigators, basic scientists, sociologists, and economists. The Fogarty International Center has begun an in-depth investigation into this tremendous problem. Our scholars-in-residence and other experts are being invited to participate in working conferences and to conduct surveys to supply information which is crucial for a meaningful attack on these pressing medical problems.

BILATERAL COOPERATION

I referred earlier to an organized program of bilateral cooperation. In 1964, because of the balance-of-payments problem, the NIH support for research abroad was significantly curtailed. A number of foreign governments and international organizations were subsequently urged to offset this reduction in NIH support by increasing their own financial contributions to research. With this change in funding and support, it became necessary to develop improved and increased cooperation and collaboration between NIH staff and their counterparts abroad. We therefore proposed that the past ad hoc cooperation be replaced by an arrangement for more organized cooperation.

This idea gained rapid acceptance and a program of informal intergovernmental agreements for cooperation has been initiated. This type of cooperation will (1) provide improved coordination and utilization of limited manpower, financial and other resources available to the NIH and scientific groups of other countries; (2) give greater value to the United States effort by substituting an effective, financially controlled cooperation which will maintain and enhance research previously dependent upon a considerable NIH investment abroad; (3) assure that both U.S. and foreign scientists and scientific organizations are aware, to the extent considered desirable, of research activities, progress and accomplishments by the entire biomedical community; and (4) encourage, within the framework of existing budgetary limitations, the continued and improved communication between scientists and science administrators of the United States and other countries.

NIH OVERSEAS OFFICES

Last year, we reported that the staff of NIH offices overseas had been reduced to a single professional in each office. We also commented that a one-man organization could not be as efficient or

productive as a fully staffed office. We undertook an analysis and review of these offices, especially to determine if we could achieve a greater utilization of our funds and manpower without jeopardizing the flow of scientific information from abroad to the United States. Upon completion of the review and evaluation by our staff and the director's policy advisory committee, it was concluded that the functions of the offices in Rio de Janeiro, Brazil, Paris, France and Tokyo, Japan should be transferred to Bethesda. Since my last appearance before this committee we have redirected and are strengthening our efforts to meet the NIH needs for information from abroad by encouraging a greater professional participation by NIH institutes and utilizing the specialized skills available within the institutes. The offices in Rio de Janeiro and Paris have been phased out and the office in Tokyo is scheduled to close in October 1971. Because of its unusual effectiveness in the administration of Public Law 480 affairs in India the functions and the position in the New Delhi office will continue.

GORGAS MEMORIAL LABORATORY

The U.S. contribution for the Gorgas Memorial Laboratory was transferred in fiscal 1971 from the appropriation of the National Institute of Allergy and Infectious Diseases to our appropriation.

The Gorgas Memorial Laboratory provides the highest level of scientific and technical support in the following disciplines: virology, parasitology, malariology, serology, bacteriology, pathology, hematology, and medical entomology. The world problems of today have reemphasized the continuing public health importance of malaria, viral infection, intestinal parasites and other diseases common to tropical areas. Situated in a tropical environment 2½ hours flying time from the United States, the Gorgas Memorial Laboratory affords exceptional opportunities for research and clinical training in the diseases and problems unique to tropical environments.

SPECIAL FOREIGN CURRENCY PROGRAM

The Special Foreign Currency Program is an unusual resource, enabling the National Institutes of Health to support biomedical research within its program responsibility and departmental objectives in "excess currency" countries abroad. The NIH program, which is financed with an allocation from an appropriation which will be presented to the committee later in the hearings, is limited to the utilization of resources for research, manpower and translation and dissemination of scientific literature. All projects are of a collaborative nature, and only those subjects which are of mutual interest to the United States as well as to the foreign country are supported under this program.

For these program and activities, the Fogarty International Center is requesting a total of $3,319,000 for 1972, a net decrease of $363,000 below the 1971 level of $3,682,000. I shall be happy to answer any questions of the committee.

FELLOWSHIPS

Mr. PATTEN. Thank you, Doctor. I think this would be one place where you might at least hold the line on fellowships. I see you are cutting back from 122 to 79. This means you plan to make only 44 new

awards. Where do you reach the point where it is better to drop a program entirely, rather than limp along at such a low level?

Dr. LEAVITT. At the level proposed for this coming year, I can maintain a viable program. I think further reductions would seriously impair it. I can't give you a precise level at which it would not be worthwhile continuing the program.

GORGAS MEMORIAL LABORATORY

Mr. PATTEN. I see you are asking for the same amount of funds, $500,000 for the Gorgas Memorial Laboratory. What restrictions are there on the use of these funds?

Dr. LEAVITT. This is the contribution made by the Government to the Gorgas Memorial Laboratory, and it is set by law. It must be used in the support of their research activities. Their total outlay per year exceeds $1 million, so that the $500,000 contribution does go to support their on-going activities. It forms a base support for their research.

Mr. PATTEN. Is there an audit made of the use of the funds?

Dr. LEAVITT. Yes, sir.

Mr. PATTEN. How often?

Mr. PRESSON. Prior to fiscal year 1970, the General Accounting Office conducted an audit every year. After the 1969 audit, the laboratory was informed that the GAO audit would be conducted every other year, the next one to be in fiscal year 1971. The Gorgas Laboratory board of directors felt that an audit should be conducted for fiscal year 1970 and therefore contracted with Price, Waterhouse and Co. for that audit.

Mr. PATTEN. What has the laboratory accomplished in recent years, to indicate that this is a worthwhile investment?

Dr. LEAVITT. They have continued work on infectious diseases. I will be very happy to submit a report beyond that covered in the 82d annual report made to the Congress.

Mr. PATTEN. I think it would be well if you did that.

Dr. LEAVITT. I will be very pleased to submit that information.

(The information follows:)

THE GORGAS MEMORIAL LABORATORY

A RESEARCH AND TRAINING FACILITY IN THE TROPICS

The Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., is a nonprofit international biomedical research and training organization incorporated in 1921 under the laws of the State of Delaware; its charter as registered in the Republic of Panama. The Gorgas Memorial Laboratory, the operating arm of the Institute, is located in the Republic of Panama as a living memorial to Maj. Gen. William Crawford Gorgas. The laobratory was established in 1929 through legislative action of the Congress of the United States and of all the National Assembly of the Republic of Panama.

The affairs of the Corporation are conducted by the President and the Board of Directors, elected by the members of the Corporation at annual meetings, held at the Institute headquarters in Washington, D.C. The board of directors meets annually. In the interim between meetings, its functions are delegated to the executive committee. An advisory group of noted scientists and executives of various professional associations assist in developing the research program. The President, all other officers and members of the board of directors and of the executive committee serve without compensation.

FACILITIES

The laboratories are located on a site contributed in 1929 by the Republic of Panama, adjacent to the Santo Tomas Hospital complex in Panama City. The original building with some 4,400 sq. ft., donated with the site, housed the laboratory activities until 1963. The physical plant was augmented in that year with completion of a modern research laboratory building of 17,600 sq. ft. This building was financed through a special contribution (Public Law 86-617) of $500,000 by the Congress of the United States. A modern insectary of 2,648 sq. ft., containing temperature and humidity control equipment, was dedicated in 1964. This building was financed with $132,388 through the generosity of Mr. James H. Rand. An animal building located at the base site, rented animal facilities and field stations at various sites throughout the Republic of Panama, constitute the balance of the research facilities.

FINANCIAL SUPPORT

The maintenance and operational funds for the Gorgas Memorial Institute and the Gorgas Memorial Laboratory are derived in part from philanthropic donations, research grants and contracts; the most important source of funds, however, is the annual contribution from the Government of the United States.

An Act of Congress approved May 7, 1928, as amended, (45 Stat. 491; 22 U.S.C. 278a), authorized annual appropriations for the maintenance and support of the Laboratory. These authorizations have ranged from $50,000 (1929) to $150,000 (1948), to $250,000 (1959), and to $500,000 (1965).

The 90th Congress through Public Law 90-574 (82 Stat. 1005) authorized an increase of an additional $500,000 in the appropriation for fiscal year 1970.

The U.S. Government in 1955 made the National Institute of Allergy and Infectious Diseases, National Institutes of Health—Health, Education, and Welfare, responsible for presenting and defending the Gorgas Memorial Laboratory budgetary requirements, until 1971 when this responsibility was transferred to the Fogarty International Center.

Research grant funding has been obtained from various sources interested in the study and solution of specific problems. Many of these grants have come from agencies of the U.S. Government, especially the Public Health Service and the Army. The amount of such funding varies from year to year; it has steadily increased since 1963 with the availability of adequate facilities and an expanded staff. Subject funding increased from $135,316 for fiscal year 1962 to $297,733 for fiscal year 1968. Anticipated revenue for fiscal year 1969 from grants and contracts has been estimated at $557,242 of which $139,690 are funded by the Department of the Army. Total revenue from all sources for fiscal year 1969 is estimated at $1,134,927.

PROGRAM MISSION

The location of the Gorgas Memorial Laboratory (GML) in Panama City, at sea level and less than 10° north of the equator, provides an important resource for biomedical research. It is one of the few laboratories located in a near tropical area that possesses modern facilities and a competent well-trained scientific staff. Added to these characteristics is the fact that the Gorgas Memorial Institute is an international organization capable of entering into cooperative arrangements and studies with authorities and investigators in any of the countries of the Western Hemisphere.

Capitalizing on these characteristics, the program mission of the Gorgas Memorial Laboratory has been devoted, in the main, to:

1. Research investigations of human diseases which are major problems in the Panama area and the adjacent countries but do not exist in temperate climates. These investigations include both field and laboratory studies and concentrate on the epidemiologic, ecologic and preventive medicine aspects of the diseases. Over the years fruitful opportunities have existed for studies on malaria, leishmaniasis, trypanosomiasis (Chagas' disease), hydatid disease, and other parasitic conditions such as toxoplasmosis and besnoitiosis.

Located in an "arbovirus area" extensive studies have been conducted on a number of arthropod-borne viruses, and on fevers of unknown origin. More than 75 virus strains have been identified and reagents prepared. The Gorgas Memorial Laboratory is a valuable resource in that it is located in an area where arbovirus

activity exists 12 months of each year, in contrast to similar field studies in the United States that can be done only if and when a seasonal activity occurs.

Supportive of the above investigations are the fundamental taxonomic and other entomologic and zoologic studies conducted on the insects, mammals, birds, and reptiles that play a role as reservoirs or vectors of human diseases. In addition, the activity in systematic biology serves as a reference resource to other investigators.

2. Cooperation with other organizations continues in many disciplines and embraces a variety of studies and investigations. Disease surveillance, disease hazards, and infection experiences have been conducted on Peace Corps volunteers in Panama, and on personnel involved in the new canal site studies. In collaboration with the medical staff and nearby hospitals and with health authorities in other areas, new drugs are tested, new prophylactic methods are studied, and new diagnostic procedures are evaluated.

3. Research facilities for visting scientists are available at the Gorgas Memorial Laboratory for studies compatible with the laboratory mission and the availability of appropriate facilities. A long list of investigators from universities in the United States and other countries, members of research organizations such as the Smithsonian Institution and the Rockefeller Foundation, and scientific staff from the U.S. Army and the U.S. Navy, have conducted studies at the Gorgas Memorial Laboratory. These studies have been funded primarily by the parent organizations of the visiting scientists.

4. Training has been an important activity of the Gorgas Memorial Laboratory. This training program has provided opportunities for many individuals to gain practical experience in the research approach to disease situations found in tropical areas. The Gorgas Memorial Laboratory has contributed to the maintenance in the United States of a cadre of medically trained scientists and physicians experienced in tropical diseases. Many students from medical schools and from schools of public health have spent periods of up to 6 months at the Gorgas Memorial Laboratory. Graduate students from universities and medical personnel from the U.S. Army, the U.S. Navy, the Public Health Service and, currently, from the U.S. Air Force, have been in residence from 1 to 2 years to conduct research studies and gain practical experience in the tropical environment.

PROGRAM PLANS IN 1971 AND 1972

The scope of the present research program can be gained from the following summary:

1. Malaria.-Studies on this disease have expanded as various agencies have come to realize the capacity of the Gorgas Memorial Laboratory for advanced studies on malaria. Currently, the major studies are:

(*a*) *Malaria control through administration of drugs.*—Using a malarious area containing approximately 2,300 persons, pyrimethamine-primaquine was administered biweekly and the pertinent aspects of the project were monitored and studied. During a 2-year period the prevalence rate dropped from 17.4 percent to less than 1 percent. Drug resistance was not identified.

(*b*) *Human malaria in Panama monkeys.*—Studies are in progress on the survival of the human malaria parasites, *P. vivax* and *P. falciparum* in monkeys. Some success has been attained with night monkeys, spider monkeys and marmosets. Besides the zoonotic importance of these findings, this work may lead to the identification of an animal model for the study of human malaria.

(*c*) *Drug resistance.*—A study is being made of an area, at the Pacific end of a proposed new canal route in Colombia, for chloroquine resistance in *P. falciparum* malaria. Evidence of this possibility was discovered in three U.S. servicemen working in the area.

2. Arboviruses.-A broad scale study is being done to determine the arbovirus agents present in Panama; the ecology, the epidemiology, and the health hazard of each virus. These studies include surveillance, transmission studies of Venezuelan equine encephalitis and St. Louis encephalitis, and indepth studies of the biology of Venezuelan equine encephalitis. Vesicular stomatitis virus (Indiana) is being studied and the presence of antibodies in arboreal animals presents new aspects to the ecology of this virus.

3. Trypanosomiasis (Chagas' disease). The studies of Chagas' disease can be grouped under three main headings:

(*a*) Clinical studies;
(*b*) Environmental studies;
(*c*) Vector studies.

In the clinical studies the main thrust is improvement of treatment by careful evaluation of drug therapy and by carefully planned studies of the underlying pathology.

The environmental studies have prevention as their main objective. Here the studies are showing time, place, and circumstances under which the disease occurs and is transmitted and how modifications in the environment may interrupt transmission.

In the vector studies, the bugs that carry trypanosomes are investigated in a search for places in their life cycle where controls can be efficiently applied. Such controls would have as their end value the interruption of transmission to man at least and stopping the natural cycle at best.

4. Leishmaniasis. The ecology of this parasite is poorly known. The Gorgas Memorial Laboratory efforts have been devoted to:

(*a*) Epidemiologic studies in four different localities;
(*b*) Continued search for potential wild animal reservoir hosts;
(*c*) Study on leishmanial infections in sloths;
(*d*) Experimental animal inoculations of leptomonad flagellates isolated from sandflies.

Work done by a visiting scientist confirmed a previous Gorgas Memorial Laboratory finding that serotypes of leishmania parasites exist.

5. Bacterial diseases. A collaborative project with the Institute of Nutrition of Central America and Panama (INCAP) has reviewed the serologic evidence of brucellosis in 31 communities, and relative risks to different population segments. Another study has explored the prevalence in wild animals of enteropathogenic bacteria known to cause diarrhea in man.

6. Echinoccosis. A new type of hydatid disease in man has been found and is under study. The apparent natural cycle involves hydatids in a rodent (agouti), and a tapeworm in large felines (puma and jaguar). Initial experiments show that the domestic cat can be infected. The hazards to man are apparent, and are being studied.

7. Yellow Fever. Since the epidemic of sylvan yellow fever throughout Middle America and as far north as Mexico between 1948 and 1956, the Gorgas Memorial Laboratory has served as a sentinel post for the surveillance of this disease. The last recorded occurrence of yellow fever virus activity was detected by the laboratory in Southern Darien Province in 1966. Fortunately, no human cases occurred. This continual reconnaissance provides a safeguard against the invasion of this disease from South America and guards against a repetition of the extensive outbreak of the above mentioned period, as well as the possible spread of the disease into the continental United States.

Of current and immediate importance are studies of the ecology of proposed sea-level canal routes; particular attention is being given to determine the diseases, vectors, and reservoir hosts present along these routes. Over 160,000 invertebrates and vertebrates have been collected and are being systematically studied for disease pathogens.

Detailed information on these programs can be found in the annual report available from the Institute's headquarters, 2007 Eye St., NW., Washington, D.C.

FUTURE OPPORTUNITIES AND PLANS

Of major interest for the immediate future are proposals for the development of two specific projects for long term development: a regional medical library and a primate center.

1. Regional medical library. Based on initial discussions and collaboration between the Gorgas Memorial Laboratory, the National Institute of Allergy and Infectious Diseases, and the National Library of Medicine, a concept was developed for the establishment at the Gorgas Memorial Laboratory of a regional medical library to serve Central America and Panama. This concept was presented to a meeting of the Ministers of Health of these countries; it was given hearty endorsement and the promise of eventual support. The Government of Panama has promised and has taken steps to deed to the Gorgas Memorial In-

stitute a parcel of land for this project, close to the Gorgas Memorial Laboratory and the Santo Tomas Hospital. This plan will be pursued vigorously.

2. Primate center. The Gorgas Memorial Laboratory is a logical site for the development of a center for the breeding and study of New World primates. Primates are becoming an increasingly valuable laboratory animal in biomedical research and development work. As the current sources of primates in India and Africa becomes diminished and prices of monkeys from these areas increase, a serious attempt must be made to breed monkeys of tropical America for research purposes. A primate center at the Gorgas Memorial Laboratory would contribute significantly to this urgent requirement.

Important to the future of a better understanding of tropical diseases is the systematic expansion of the tremendous research and training capabilities of the Gorgas Memorial Laboratory.

ADDENDUM

The Ministry of Health of Panama has announced that, effective February 1, 1969, all medical residents in the Republic will be required to rotate through the Gorgas Memorial Laboratory, for a 2-month period, to broaden their knowledge of tropical diseases.

In addition, the Minister of Health, José Renán Esquivel, M.D., has appointed Dr. Alberto Bissot, Jr., Director General of Public Health, and Dr. Carl M. Johnson of the Gorgas Memorial Laboratory to organize a 3-year residency program in tropical medicine at the Gorgas Memorial Laboratory. Upon completion, these residents will be recognized specialists in the field of tropical medicine.

The above decisions are part of the new National Plan of Public Health developed by Minister Esquivel.

CONFERENCE ON GENETICS

Mr. PATTEN. Pick out two or three conferences or seminars that have been held at the Center during the last year that you feel were particularly significant, and tell us about them.

Dr. LEAVITT. Yes, sir. Last May we had a workshop on recent genetic advances, ethical problems involved in human genetics, and the early diagnosis of genetic defects. This conference also dealt with a relatively new procedure in the medical field called amniocentesis, in which a large needle is inserted into the pregnant uterus any time after the first 3 months of pregnancy. This procedure is performed on a woman whose offspring is suspected of being abnormal perhaps because of past family history. When this amniotic fluid is drawn off from the uterus, it is spun down in a centrifuge so that the fetal cells may be looked at under a microscope. One can often determine from those cells whether or not the unborn child may be defective.

For example, in the case of women with a family history of mongolism, you may be able to detect mongolism before the child is born. This raises some very interesting questions that involve not only the medical profession, but theologians, legal experts, and a variety of other disciplines. For instance do we abort every woman with a defective child in her uterus? The conferees also raised questions on the reliability of the technique involved. In viewing those cells that are taken from the amniotic fluid, do we have 100-percent assurance that that child is defective. These are the kinds of problems that were discussed for 3 days at our meeting. We could not cover the problem adequately in that 3-day period so we are now organizing an even larger conference that will be held in October of this year as a followup. We will pull together not only physicians and scientists but a variety of other disciplines who would be involved in making such decisions re-

lating to genetics. This is important insofar as scientific advances may profoundly affect our society. Just how far do we go with this?

Mr. PATTEN. Was Dr. Stetten in this?

Dr. LEAVITT. Dr. Stetten was not yet officially on board at NIH at that particular time, but he is now well informed of our interest in medical genetics and, in fact, we are working with the National Institute of General Medical Sciences on these and related problems.

Mr. PATTEN. We had quite a session with him last Friday for a couple of hours. It was really a pleasure. That is up his alley; is that right?

Dr. LEAVITT. Yes, sir.

EARLY TESTING TO DETECT GENETIC DEFECTS

Mr. PATTEN. Somebody else testified about making early tests of the fetus, but they didn't mention mongoloids.

Dr. LEAVITT. One must think of the cost of the mongoloid, not only to his family, but to the State, and the loss to society.

Mr. PATTEN. What were these other areas mentioned that this early testing may detect?

Dr. LEAVITT. Perhaps it was Down's syndrome. Other disorders that may be detected are Klinefelter's syndrome and Turner's syndrome.

Mr. PATTEN. Yes; there were three mentioned. In fact I told a group of women about it Saturday. Could you give us one more illustration of a seminar that was held at the Center?

OTHER SEMINARS AT THE FOGARTY CENTER

Dr. LEAVITT. Yes, sir; we had an international symposium on environmental influence on genetic expression. That volume has recently come off the press and been distributed to members of the committee. This had to do with the critical periods in sexual differentiation in human beings.

Mr. PATTEN. Submit for the record anything further along this line. I think you ought to submit a list of all the seminars and conferences you had, for the sake of the record.

(The information follows:)

COLLOQUIUM ON THE REFORM OF MEDICAL EDUCATION

APRIL 9–11, 1969

Cosponsor: National Academy of Sciences, Board of Medicine.
Editors: Dr. Julius Krevans; Dr. Peter G. Condliffe.
Chairman: Dr. Julius Krevans, Baltimore City Hospitals.

The first conference held at the Fogarty International Center took place April 9–11, 1969. The meeting was cosponsored by the Board on Medicine of the National Academy of Sciences. Twenty-five medical educators, biomedical researchers, and medical students from 10 countries met for 3 days and discussed the reorganization of medical schools in the advanced countries of the world.

The education of physicians is under scrutiny in all countries. Not only is there a worldwide shortage of physicians and other members of the health professions, but there is pressure for a profound change occurring in the aims of medical education. The pressure for reform is perhaps most evident in the student movement. At this first conference of the Fogarty International Center, the nature of pressure on medical schools was examined. To obtain a clearer picture of what is going on, we listened to representatives of countries which have undergone substantial reorganization of their medical schools during the past decade in

order to meet the requirements arising from modernization of their economic and social structures.

The proceedings of this colloquium were published by the National Academy of Sciences, Washington, D.C., in May 1970, under the title "Reform of Medical Education, the Effect of Student Unrest."

Favorable reviews have appeared in Nature, the Journal of the American Medical Association, and other publications. The book has stimulated much discussion and action in America and abroad.

International Symposium on Environmental Influences on Genetic Expression

APRIL 22–25, 1969

Cosponsor: NICHD.
Editors: Dr. Norman Kretchmer; Dr. Dwain Walcher.
Chairman: Dr. Norman Kretchmer, Stanford University.

The second conference at the Fogarty International Center took place between April 22–25, 1969, under cosponsorship of NICHD; 65 participants from 18 countries met to discuss critical periods in sexual differentiation in human beings. The problem was examined by experimental and behavioral scientists from the standpoint of their several disciplines. While sex is determined for nearly all individuals at the moment of conception, confusion in sexual identity can arise during development after conception. This confusion can result in anatomical or physiological abnormalities arising principally from environmental influences that come into play after birth and which operate during childhood.

In the case of prenatal influences, the molecular biological mechanisms were explored. Postnatal influences whether biochemical, physiological, or psychological were discussed by representative scientists from the particular disciplinary point of view. A cross-disciplinary synthesis of the problems was undertaken by special chosen scientists who are interested in human development as a unified field of study. Members of the International Association for the Study of Human Development attended the conference which was also the first scientific meeting of the association.

The results of the conference were published as an FIC–NICHD report by the Government Printing Office in June 1970. This report has assisted physicians, psychologists, and others in the health sciences who must treat patients who have health problems, adjustment problems, or developmental problems arising out of failure in the mechanisms of sexual differentiation.

The 6th Colloquium on Pupillography

MAY 22–23, 1969

Cosponsor: NEI–NINDS.
Chairman: Dr. Henry Wagner.

The Sixth Colloquium on Pupillography was an assembly of invited scientists who work in an area of research having to do with the anatomical, physiological, and pharmacological study of the pupil of the eye. The instrumentation developed for pupillography is a very advanced contribution to biomedical engineering. The exquisitely sensitive mechanisms controlling the iris, respond to many agents including drugs. Diseases such as glaucoma involve the iris and its control mechanisms. The pupil provides an excellent model for the study of servomechanisms in the nervous system.

The speakers were selected by a committee on the basis of a review of their abstracts and their stature in the field. The purpose of this colloquium was to bring scientists up to date on the results of the latest findings in the field, to coordinate further studies, and to reveal the most promising avenues of research.

Conference on the Family in Transition

NOVEMBER 3–6, 1969

Editor: Dr. Harry Kincaid and Editorial Board.
Chairman: Dr. Preston Valien, HEW, Office of Education.

In all societies, past and present, the family is the primary institution within which children are born and reared. As such, the social, economic, and demo-

graphic forces that are reshaping the family throughout the world have profound implications for childbearing patterns—not only for today's population of reproductive age, but also for succeeding generations. The dynamic social processes that determine these transitions in different cultural contexts, the features of family structure that are most affected, and the results of these modifications in terms of the spacing and limitations of births form the subject matter of this conference.

The major aim of this conference was to encourage research on these topics so that we will have a better basis for projecting future childbearing patterns. A stronger research base is needed from which to initiate policies and launch programs that will hasten the transition toward smaller families.

In general, the research papers presented findings on regional or subcultural patterns of change. The discussions placed these findings in a broader cultural context, reviewed the possibilities for related studies elsewhere, and identified important gaps in knowledge.

This conference complemented a second in the field of population problems which was held September 27–October 4, 1970, on "Regulation of Mammalian Reproduction." It dealt with the human part of the problem and sought to clarify the social factors that determine acceptance of different family planning techniques. Without knowledge of these social factors, advances in contraceptive technology are not likely to stabilize the population.

A book was prepared from the conference proceedings which will appear by summer of 1971. The contributors to the conference rewrote their papers in the light of the discussions. The Government Printing Office, Washington, D.C., will issue the book.

Colloquium on the Role of Adenyl Cyclase and 3'5' AMP in Biological Systems

NOVEMBER 17–19, 1969

Editors: Dr. Martin Rodbell; Dr. T. W. Rall; Dr. Peter G. Condliffe.
Chairman: Dr. T. W. Rall, Case Western Reserve School of Medicine.

Ten years ago Prof. Earl W. Sutherland, now at Vanderbilt University, isolated a new compound called cyclic adenosine monophosphate or cyclic AMP. Today this compound turns out to be a key compound in the regulation of cell chemistry. Many important hormones work in the body through the stimulation of cell catalyst which makes cyclic AMP. Besides its significance in endocrinology, cyclic AMP is an important compound in regulating many different biological processes from the growth of molds to the growth of cancer cells. Its discovery and the elucidation of its role has shown that several metabolic diseases may be due to a lack of this compound. This may open the way for successful treatment of some endocrine disorders and other disorders. Discovery of this enzyme and cyclic AMP may also assist applied research on the control of algae and other environmental problems.

The proceedings of this conference are to be published by the Government Printing Office by summer, 1971. It will be one of the most important summaries of on-going work in the area of regulatory biology.

Workshop on Amniocentesis and the Use of Amniotic Fluid

Rapporteurs: Dr. Henry Nadler, Children's Memorial Hospital, Chicago, Ill.; Dr. William Uhlendorf, Division of Biologics Standards, National Institutes of Health, Bethesda, Md.
Chairman: Dr. Peter G. Condliffe, Fogarty International Center, National Institutes of Health, Bethesda, Md.
Number of participants: 17.

This workshop was held in order to examine technical aspects of amniocentesis and the use of amniotic fluid for prenatal diagnosis of genetic defects. The results of the discussions, which lasted 2 days were written up by the rapporteurs and were presented to the participants in the Conference on Ethical Problems in Human Genetics; Early Diagnosis of Genetic Defects in May 1970. The two reports will be included in the proceedings of the full conference.

Workshop on Epidemiology of Cancer for the International Union Against Cancer

MARCH 2–4, 1970

Chairman: Dr. T. O'Connor.
Cosponsor: NCI and FIC.

This workshop is one of the series in which the Fogarty International Center assists international organizations, particularly private and semi-official groups in carrying out studies, seminars, and conducting other activities of importance to the mission of the NIH at the international level. The International Union against Cancer brought together a group of 12 experts to consider specific areas where epidemiology can be useful in assessing the validity of methods for cancer therapy, as well as detecting the causes of different types of cancer. The results of this workshop were later communicated to the International Cancer Congress in Houston, Tex. and were made available to interested scientists and clinicians in the proceedings of the congress.

Discussion of Histidine Biosynthesis

APRIL 10–12, 1970

Chairman: Dr. Bruce Ames, University of California, Berkeley.

The biosynthesis of histidine in bacteria is under control of a linked set of genes which are collectively called the histidine operon. This operon is widely studied as a model for the study of gene action. At the 3 day meeting, 40 scientists discussed the latest work in the field. Four speakers from abroad were invited to bring recent information from their laboratories. Portions of the new material presented have been incorporated into scientific papers published subsequently.

Discussion of New Biochemical Approaches to the Study of Neuronal Function

APRIL 18–19, 1970

Chairman: Dr. Marshall Nirenberg.

The unit of action in the nervous system is the nerve cell or neurone. This unit transmits messages, for example, from the spinal cord to the muscles, from parts of the brain to various parts of the body or from one part of the brain to another. There are literally millions of such action units in the brain. It is believed by some that these fundamental components of the brain can form thousands or millions of cross connections with each other.

Plasticity of the nerve cell means its ability to form new connections with other nerve cells and thus to alter nervous function, brain function, possibly memory, as well as those higher intellectual functions by which we distinguish man from other animals.

It is believed that our new understanding of how large molecules like proteins are made by all cells in the body may help us understand how nerve cells modify their cross connections and behavior. This is one of the most exciting areas of biology to have emerged from the work on the genetic code.

This meeting brought together a highly selected group of men who are leaders in molecular biology. Following their success in deciphering the genetic code and in elucidating how cells make proteins, they are turning their attention and expertise to the basic unit of the nervous system. Understanding of memory, of learning processes, the effects of drugs, the development of the mind—await progress in our knowledge of how the nerve cell works. The discussion afforded these pioneers an opportunity to exchange ideas and to critically examine different experimental approaches to the field.

Conference on Ethical Problems in Human Genetics
Early Diagnosis of Genetic Defects

MAY 18–19, 1970

Editor: Dr. Maureen Harris, Fogarty International Center.
Chairman: Dr. Robert Morrison, Cornell University.

This conference dealt with the methods available for diagnosis and therapy of disease in unborn and newborn children. Findings arising from fundamental research on cultured human cells have recently been applied to the early diagnosis of genetic defects prior to birth. Combined with the technique of "amniocentesis", in which amniotic fluid containing fetal cells is withdrawn from the pregnant mother, these advances enable the trained human geneticist to distinguish normal from abnormal babies within 4 months of conception. Such diseases as Down's Syndrome (Mongolism), can be thus detected by examination of the cultural amniotic cells. Other more serious diseases, even those leading to early death, can also be detected. This striking advance in medical knowledge enables the genetic counsellor to tell anxious parents that their child will be normal or that it will be certainly defective. Early diagnosis will offer therapeutic possibilities for treatment prior to birth to avoid abnormal development of the baby. Such is the case in Rh disease. Some diseases, although not yet detectable in the aminotic fluid cells, can be detected by biochemical tests on the new-born child. For example, early diagnosis of phenylketonuria (PKU) will allow institution of dietetic therapy which will prevent the mental retardation accompanying this disease.

These developments also raise profound ethical problems. Obviously abortion must be considered in cases where the child-to-be is gravely defective and where there is no effective therapy. This meeting dealt with these ethical considerations which must guide the responsible physicians as well as the reliability and safety of the techniques for mother and child. The responsibility of government administrators for administration of public funds to support this work was also considered.

As the results of fundamental genetic research are introduced into medical practice, they will affect increasing numbers of people, offering them positive solutions to mental retardation and other afflictions. This meeting was the first of a series devoted to public considerations in the application of the fruits of fundamental research into health problems.

The proceedings of this conference will be published in 1971 by the Government Printing Office, Washington, D.C.

Round Table Conference on Normal and Abnormal Heart Rhythmicity: Electrical and Mechanical Influences

MAY 20–21, 1970

Cosponsor: National Heart and Lung Institute.
Chairman: Dr. Torsten Teorell, Fogarty International Center Scholar-in-Residence.

A multitude of experimental and clinical observations and theories have given a certain insight into the mechanisms of heart rhythmicity. Yet, many problems remain unsolved, particularly with regard to the possible influence of mechanical factors prevailing in the heart wall (that is, tension, various degrees of filling, influence of blood pressure, thorax pressure, et cetera). Feedback of such mechanical factors on the electrical events have been demonstrated in experiments on isolated heart tissue and in many clinical observations. The purpose of this conference was to review and discuss the "mechano-electrical coupling" from electrophysiological, biophysical, and clinical viewpoints with regard to its possible implications in abnormal activities of the heart.

About 20 investigators from various sectors of physiology and cardiology were invited to participate in the conference. The transactions were informal, mainly leaning on discussions, but a few specialists were asked to present a brief introduction to a few of the "headlines" for the ensuing discussion.

Abstracts of the roundtable discussions were distributed to participants and will be made available to interested research works and clinical investigators.

First Roundtable Discussion on Taxonomic Problems Relating to Malaria Parasites and Allied Organisms

MAY 25–26, 1970

Editor: Dr. P. C. C. Garnham.

Chairman: Dr. P. C. C. Garnham, Fogarty International Center Scholar-in-Residence

This meeting was held in order to consider the relationships between malaria parasites that infect man and those which are found in the animal kingdom and which can sometimes infect other species besides the usual host. While malaria has been greatly reduced in many parts of the world, largely through the use of powerful insecticides such as DDT, there is always a danger remaining from the natural reservoir present in wild animals which live in close proximity to man. Through study of these animal parasites, scientists can understand some of the problems that arise when resistant strains of parasite arise which are not susceptible to control through medication. The discussions assisted Professor Garnham in his studies on the classification of parasites and will be continued at a second roundtable to take place November 22–23, 1971. The results of these roundtables will be published as a report by Professor Garnham in an appropriate scientific journal.

Conference on Reform of Medical Education
II.—Role of Research in the Education of Medical Personnel

JULY 20–21, 1970

Editors: Dr. Arthur Furnia; Dr. Peter G. Condliffe.

Chairman: Dr. Cecil J. Watson, Northwestern Hospital of Minneapolis.

New concepts for the training of physicians are emerging in response to the need for expansion of health manpower. The scientific training of doctors is being reexamined at many medical schools in an effort to shorten the time required to produce a practicing physician. At this meeting the pedagogic role of experimental science and research in the medical school was discussed in detail.

The discussions indicated that good medical training cannot be imparted to students without exposing them to the experimental method. In all curricula that were discussed, a significant role is played by training in research techniques in order to stimulate students to understand their professional activities and to effectively utilize the results of modern biomedical research in their practice.

The proceedings of this second conference will be published in 1971 by the Government Printing Office, Washington, D.C.

Radionuclide Applications in Hematology

SEPTEMBER 8–10, 1970

Chairman: Dr. Nathan Berlin.

Cosponsor: National Cancer Institute.

This workshop was a small meeting of 12 people who belong to an international group which meets regularly to discuss the use of radioisotopes in the study of blood disorders. Institutions in several countries have previously hosted this meeting. In 1970, the Fogarty International Center was approached by Dr. Nathaniel Berlin, Scientific Director of Clinics and Laboratories of the National Cancer Institute, to inquire whether we would host the group and assist them as part of our policy aiding collaboration, and facilitating international exchange of information. The Fogarty International Center provided a place for the meeting and made the necessary administrative arrangements for the group. The results of the workshop, besides leading to specific publications in scientific journals, stimulated further experimental developments. In addition the individual participants, upon returning to their own countries, gave lectures at which the results of the workshop were disseminated to other workers in hematology.

Workshop on Peridontal Disease in Puberty and Adolescence

SEPTEMBER 10–11, 1970

Chairman: Dr. P. N. Baer.
Cosponsor: National Institute of Dental Research.

This workshop was held at the request of the National Dental Institute in order to facilitate their consideration or peridontal disease which is one of the major subjects to which the Department of DHEW is paying special attention. A group of experts was provided with a place to hold their meeting as well as administrative and financial support for their deliberations. The results of the workshop were written up by Dr. Baer, the chairman of the group, and will be made available to other interested research workers in the field.

CONFERENCE ON THE REGULATION OF MAMMALIAN REPRODUCTION

September 27–October 4, 1970

Cosponsor: Center for Population Research, National Institute of Child Health and Human Development.
Editor: Dr. Sheldon Segal.
Chairman: Dr. Seldon Segal, Population Council, Rockefeller University.

This conference reviewed scientific knowledge in reproductive biology. Control of mammalian fertility requires the development of simple and safe methods for contraception together with acceptance of the methods by substantial numbers of people.

Present methods for regulating human fertility leave much to be desired although there has been improvement in the past decade. The development of simpler, safer and acceptable methods depends upon new findings from the experimental biologists. Present knowledge about mammalian reproduction is inadequate for development of new techniques for control of fertility. This conference was held in order to assess the different areas in reproductive biology that underlie contraceptive technology. The conference was divided into eight sessions, each occupying half a day. Running throughout these sessions was the theme of hormonal control of the tissues and organs which are involved in reproduction. A particularly interesting session was one on the pituitary gland where some recent work suggests that at this point newly discovered compounds in the brain control the synthesis of pituitary hormones that regulate sexual function in men and women. These findings suggest that new types of compounds may safely modify normal sexual functions so as to lower fertility without changing daily living patterns.

The conference identified several promising areas of research where there are possibilities for technical development of new techniques in fertility regulation.

The proceedings of the conference will be published by C. C. Thomas Co., Orlando, Fla., in 1971.

Colloquium on Transfer RNA and Carcinogenesis

OCTOBER 5–7, 1970

Editors: Dr. Ernst Borek; Dr. Robert Gallo.
Chairman: Dr. Ernest Borek, University of Colorado Medical Center.
Cosponsor: NCI.

Transfer RNA (tRNA) has a central role in translation of the genetic code and protein synthesis and it has been proposed that cell differentiation may occur through variations in tRNA. Furthermore, abnormal tRNA's have been found in malignant human and animal tissues. There is abundant and exciting work which has appeared in this field in recent years with striking implications for research in cancer as well as for the eventual contral of neoplasia in man. Although one symposium on tRNA has been held (New York 1968), it dealt with tRNA structure and function per se and was generally limited to studies in bacterial systems. This symposium concentrated on tRNA in animal and human cells particularly those studies which were relevant to the functional role of

tNRA in protein synthesis and how this applies to cell differentiation and the cause of cancer.

Proceedings of this colloquium were published in the May 1971 issue of Cancer Research for dissemination to scientists in the field.

Workshops on Environmental Health Problems

1970–71

Cosponsor: National Institute of Environmental Health Sciences.
Organizers: Dr. Douglas H. K. Lee, NIEHS; Dr. Peter G. Condliffe, FIC.

In 1972 the United Nations is sponsoring a conference in Stockholm to consider environmental problems at the international level. In preparation for this conference the various nations are preparing national presentations of their own problems and also of those problems which they feel must be solved by international coordination and agreement.

In preparation for this meeting, the Department of Health, Education, and Welfare will examine the various aspects of environmental problems that fall within its mission. The environmental health sciences are the responsibility of one of the constituent institutes of the National Institutes of Health, the National Institute of Environmental Health Sciences located in the Research Triangle Park, N.C. The Fogarty International Center, which is the principal focus for coordination of NIH international activities, has undertaken to assist NIEHS in its task of scientific preparation for the U.N. conference by holding a series of workshops to examine a number of topics which need attention. These are listed below. They are topics where there is controversy as to the precise effects of known pollutants, uncertainty as to the mechanisms by which they produce their effects or simply a lack of information as to the extent of the problem. Each workshop was attended by about 15 scientists who are experts in their field.

I. Metallic contaminants and human health: October 26–28, 1970

Chairman: Dr. Douglas H. K. Lee, NIEHS.
Editor: Dr. Douglas H. K. Lee, NIEHS.

Metallic contaminants of the environment can cause serious problems. A number of these have been discovered including poisoning of water supplies by arsenic and inhalation of dust or mists containing such metals as beryllium. The extent of these problems and effects of these metals on health were considered at a workshop in October.

II. Environmental factors in respiratory disease: February 1–3, 1971

Chairman: Dr. Douglas H. K. Lee, NIEHS.

A second workshop on environmental factors in respiratory disease was held in 1971. Experts from some of the clinical specialties and from occupational and industrial health professions examined the types of respiratory disease, their extent and the direction in which to encourage research and technological development in order to find practical solutions. Specific examples of respiratory disease induced by industrial and environmental pollution such as asbestosis were discussed. Methods for control were tabulated and some recommendations were made for monitoring populations. The results of the workshop are to be published in the series on environmental health problems as Fogarty International Center documents.

III. Mutagenic effects of environmental contaminants: March 29–31, 1971

Chairman: Dr. James Neel, University of Michigan.
Editors: Dr. Eldon Sutton, University of Texas; Dr. Maureen Harris, Fogarty International Center.

Mutagens abound in today's world. They are substances which can modify the genetic constitution of man and other organisms and whose effects are transmitted to future generations. Environmental contaminants, introduced through human manufacturing and other activities appear to be an increasing problem and may contribute to the increasing load of defective genetic material in populations. Examples are radioactive isotopes from fallout, chemicals produced for agricultural purposes such as herbicides or "weedkillers," viruses produced during the

preparation of vaccines, and many other of the complex products of modern industry. Of the mutagenic effects of common atmospheric pollution from such sources as the automobile, little that is definitive can be said today since no coordinated research on mutagenic effects of these materials has been carried out.

The members of this workshop assessed the burden of genetic disease as seen by the physician and discussed the biochemical mechanisms by which mutations are introduced into the genes.

Practical and feasible methods for detection of potential mutagenic agents have been developed in several research laboratories. The members of the workship considered these and made recommendations for their use in monitoring the mutagenicity of chemicals prior to their introduction into the environment. In addition, systems were discussed for monitoring the human mutation rate so that any change in the mutation rate can be detected.

Publication of the proceedings of this workshop is expected in 1971.

IV. MULTIPLE FACTORS IN THE CAUSATION OF ENVIRONMENTALLY INDUCED DISEASE: JUNE 14–16, 1971

Chairman: Dr. Paul Kotin, Temple University Medical Center, Philadelphia, Pa.
Editor: Dr. Douglas H. K. Lee, NIEHS.

This workshop will consider diseases which have a multifactoral origin or which are suspected of being due to complex environmental factors. This includes many cancers, diseases of the liver such as cirrhosis, arteriosclerotic diseases which cause failure of the circulatory system, many obstructive lung diseases and diseases of the kidneys. Some specific instances of interaction between disease-causing agents such as pesticides, and a host of compounds in the environment which inhibit key metabolic processes will be discussed in detail. Also considered will be environmental factors such as fibers and dust in the atmosphere, compounds which are stored in the body for a long time such as certain radioisotopes as well as compounds like the pesticide DDT and metallic contaminants such as lead and mercury. An assessment will be made of epidemiological approaches to defining these complex situations, as well as experimental models for their study. Methods for prevention and control of diseases of multiple origins will be discussed. This conference is in effect a summary workshop in which the results of the previous three workshops will be dovetailed and an attempt made to summarize the situation. Like the first three workshops on specific areas, this summary workshop will also be published and made available to the delegates at Stockholm in 1972.

SYMPOSIUM ON ORAL SENSATION AND RECEPTION

NOVEMBER 23–25, 1970

Chairman: Dr. J. F. Bosma.
Editor: Dr. J. F. Bosma.
Cosponsor: National Institute of Dental Research.

As part of a series of National Institute of Dental Research activities relating to one of the major objectives in the Secretary of DHEW's program of special areas requiring attention, a symposium was held at the Fogarty International Center on oral sensation and reception. Besides being of importance in dental health, the study of oral sensation and perception is extremely useful to persons interested in the physiology, psychology of development in childhood. Methods for the study of the nervous network surrounding the mouth are related to psychological problems of varying sorts all during development. These were considered in detail at this meeting. Proceedings of the symposium will be published during 1971 and will be made available to the scientific public.

CONFERENCE ON GLYCOPROTEINS WITH HORMONAL ACTIVITY

APRIL 19–21, 1971

Co-Chairmen: Dr. C. H. Li; Dr. Gilbert Ashwell; Dr. Mortimer Lipsett.
Rapporteur: Dr. Peter G. Condliffe.

This conference was called to discuss recent developments which have appeared during the past year in connection with glycoproteins found in the

pituitary gland and in the placenta. Through the work of several laboratories in the United States and abroad, it has been discovered that several of the hormones known to be important in mammalian reproduction, namely the gonadotropins and several other hormones concerned with normal functioning of the thyroid apparently have common chemical features. The realization that these features exist and are shared by apparently dissimilar physiological principles has led several investigators to postulate common mechanisms of action at the biochemical level or cellular level. If this is so, it may be possible to devise ways of intervening in disease states where one or more of these hormones' production and utilization is disturbed. These and other factors were considered at this meeting of 50 scientists drawn from six countries. A portion of the proceedings was presented at the annual Red Cross research conference following the meeting on glycoprotein hormones; a report on the conference is being prepared and will be published in a major general scientific periodical.

Conference on Allosteric Interactions

APRIL 29–MAY 1, 1971

Cochairmen: Dr. Jeffries Wyman Fogarty, Scholar-in-Residence; Dr. John Edsall, Scholar-in-Residence.
Rapporteur: Dr. Jeffries Wyman; Dr. John Edsall.

The subject of these discussions, allosteric interactions is an extremely advanced topic in physical biochemistry which is today of great importance in the regulation of many biological processes. Specifically, it has to do with enzymes and special proteins which upon reacting with particular compounds change their shape and thereby acquire catalytic and other properties of use to the organism or to particular tissues. An example is the case of hemoglobin, the red pigment in the blood cells which carries oxygen and the waste product carbon dioxide. When oxygen is bound by hemoglobin after being absorbed through the lung into the blood stream, the molecule of hemoglobin which is comprised of four subunits, binds the oxygen and in so doing alters its shape and acquires the ability to carry additional molecules of oxygen. Its effective carrying capacity is greatly increased by these "cooperative mechanisms" and it is thus able to increase the carrying capacity of the blood for oxygen depending upon the tension of the gas. When the hemoglobin molecule arrives at the site where it is to give up its oxygen for use in the tissue its shape changes back to the original form and it thereby acquires a great capacity to transport carbon dioxide back to the lungs where it is given up into the atmosphere in exchange for fresh oxygen. Without the cooperative interactions between the subunits of hemoglobin and the allosteric changes in shape of the protein the capacity of blood to carry oxygen great distances through the blood stream to the tissues, would be a fraction of what it actually is. Similar activation of enzymes in the tissues has been found to account for the ability of particular organs to acquire enhanced activity that is needed to metabolize complex foodstuffs and other substances. This conference considered the full range of such problems. The participants upon their return to their laboratories will have a better understanding of the most recent developments in the field, gained first hand from leading experimental scientists involved. They will thus be better able to accomplish work on their own problems as well as instruct their associates and students as to the latest developments without waiting for information to arrive through the usual slow route of publication.

Conference on Prospects in Gene Therapy

MAY 24–26, 1971

Cosponsor: NINDS.
Organizers. Dr. Ernst Freese; Dr. Peter Condliffe.

At present, no genetic disease is curable, although research has developed methods for treating the symptoms of some genetic diseases. For example, the mental retardation associated with phenylketonuria (PKU) can be avoided by keeping the patient on a low phenylalanine diet, but the defect in the enzyme which metabolizes this amino acid cannot yet be corrected. This defect might be corrected either by chemically converting the mutant gene for this enzyme into the normal gene, or by introducing a new, normal gene into the chromosome.

Both have been accomplished in certain micro-organisms, and research efforts are now in progress to effect similar gene therapy in animal cells and eventually in man.

This conference will review known methods for alteration of genes and for introducing new genetic information into cells and will deal with applications of these procedures to clinical disease. In addition, the ethical problems involved in alteration of the genetic constitution of man will be considered.

Workshop on Histocompatibility Tissue Antigens in Man

JULY 5–10, 1971

Cosponsor: World Health Organization.
Editor: Dr. Howard Goodman.
Chairman: Dr. Bernard Amos, Department of Microbiology and Immunology, Duke University Medical Center, Durham, N.C.

An antigen is a large molecule which when it comes in contact with a cell causes that cell to modify itself so as to in future recognize the particular antigen. As a result of this modification and acquired ability to recognize the antigen, the cell may respond in different ways including making special proteins called antibodies if it is a particular type of white blood cell. Recent results from experimental immunology, the science of disease resistance, suggest that all cells possess the ability to recognize antigens, including antigens that are embedded in the surface of other cells from different individuals within the same species. The rejection of foreign tissues by the body is undoubtedly due to the ability of the cell to recognize "foreign-ness" through the antigen on the foreign cell which is called a histocompatibility antigen. The foreign cell in other words does not possess the password and so it is rejected by the host cell or the group of cells it is invading. This system of recognition is universal through the animal kingdom and in vertebrate animals has been made use of to repel invasion by bacteria and other infective agents. The ability of the cells to recognize other cells from the same individual and to detect invasion by other cells or foreign invaders is thus of importance both in resistance to disease and in transplanting organs or tissues from one individual to another.

This workshop will consider the knowledge in this exciting area of advanced research and also the nature of the control exerted by heredity. From work in this field can come better ability to identify high-risk groups in the population who are susceptible to cancer, heart disease, and a number of ailments which afflict an aging population. Once identified in advance of the onset of the disease, preventive measures can be taken through dietary control or other measures.

The results of the workshop will be published as a World Health Organization technical report, issued in four languages. It will thus be available to research workers in immunology, transplantation, cancer, and other fields of biomedicine throughout the world.

Conference on the Reform of Medical Education

III.—Medical Education and Medical Care—A Dynamic Equilibrium

NOVEMBER 1–3, 1971

Chairman: Dr. Philip R. Lee.
Editors: Dr. Peter G. Condliffe and others.
Cosponsor: Bureau of Health Manpower Education.

The conference will be the third in the series sponsored by the Fogarty International Center on problems in medical education. The intention is to examine the relationship between medical schools and the health care systems in advanced countries. Particular attention will be devoted to the United States, the United Kingdom, Scandinavian countries, France, Germany, Australia, and New Zealand. All of these countries have characteristics of their health care system which are analogous to those of the United States and Canada. After a comparative review of existing systems of medical education and systems for the delivery of health care by world authorities on these subjects, the conference will devote attention to factors governing the selection of entrants to medical schools, the social roles played by medical graduates; the different roles played in the health care system pending upon whether or not the system is a unified national

system as in the United Kingdom or a pluralistic system as exists in France and the United States. Selected speakers will discuss these various points. The common problems and features which govern professional education for health care will be summarized by the chairman of the conference, Dr. Philip R. Lee, who is Chancellor at the University of California in San Francisco. The proceedings of the conference will be published and made available to the medical profession and the general public.

Conference on Ethical Issues in Genetic Counseling and the Use of Genetic Knowledge

OCTOBER 10–14, 1971

Organizers: Dr. Peter G. Condliffe; Dr. Daniel Callahan.
Cosponsor: Institute of Society, Ethics and the Life Sciences, Hastings-on-Hudson, N.Y.

Research in genetics has enabled scientists to determine the biochemical basis for genetic disease and to use this knowledge in developing therapeutic means for treating the symptoms of many of them. Through this research, parents will be given the opportunity to know the genetic health of their children before they are born. In an era in which population control is coming to the fore in the U.S., this knowledge may provide the basis for their choosing to abort a genetically defective fetus. There are great legal and ethical implications of such a decision based on knowledge provided by the research scientist. In addition, biochemical tests can now determine, in some cases, whether a person is a carrier of a genetic disease. In this case, carriers can be counseled not to marry, since their chance of producing an affected offspring is greatly increased. Again, there are judgements involved here that are based on the scientist's knowledge, but which transcend his realm.

This conference will be the second in a series on the impact of scientific research on society. (The first conference was Ethical Problems in Human Genetics: Early Diagnosis of Genetic Disease.) The meeting will bring together scientists, lawyers, and theologians to discuss genetic disease and how it affects the population; current methods for prenatal diagnosis of genetic disease and its implications for abortion of the fetus; methods of genetic counseling and the psychological interaction between the physician, the counselor, and the patient; and the establishment of public policy in the use of genetic knowledge.

Conference on Immunization in Tuberculosis

(Progress to date and future trends and research needs)

OCTOBER 26–28, 1971

Cosponsor: National Institute of Allergy and Infectious Diseases, NIH.
General Chairman: Dr. Jesse L. Steinfeld, Surgeon General, USPHS.
Scientific Chairman: Dr. William R. Barclay, American Medical Association.

This conference is being called at the instance of the Surgeon General, USPHS, to review the state of knowledge concerning immunization against tuberculosis. Despite great progress in controlling this disease through use of streptomycin and other chemotherapeutic agents, immunization remains a powerful tool for the same purpose. In much of the world tuberculosis is controlled through the use of vaccines such as BCG. School children in most Western European countries are routinely immunized as a public health measure. In North America, for a variety of reasons, immunization has not been widely used. Because of recent advances in the general area of mycobacterial research, more potent and safer vaccines may beome available in the near future. It is timely, therefore, to review progress in the field by bringing together an international group of experts for the benefit of the United States public health authorities who will ultimately have to make decisions about the use of the new products of research.

Conference on Translation, Its Mechanism and Control

NOVEMBER 8–10, 1971

Cosponsor: National Institute of Child Health and Human Development.

The proteins in all living organisms determine normal growth and development, as well as normal bodily functioning. The study of the biosynthesis of

proteins is one of the most actively progressing areas of research in molecular biology, and many of the molecular events involved are well understood. It has also become clear that these mechanisms are strikingly similar among a wide variety of species and that the process of protein synthesis has certain universal properties. Differences and species specificities have also been observed, and these are particularly interesting.

This conference will try to resolve areas of conflicting evidence from different research laboratories and plan future areas of profitable research, particularly the important processes which regulate protein synthesis. The conference will also try to delineate inconsistencies in nomenclature and develop a uniform system of nomenclature.

Conference on The Biology of Animal Cell Surfaces

MAY 1972

Cosponsor: NIAMD.
Organizer: Dr. Victor Ginsburg.

Cell surfaces have receptor sites for hormones, carry out transport of molecules into and out of the cell, and participate in "cell recognition." The latter is important to phenomena such as tissue formation development, regeneration and the immune response. These subjects constitute largely unknown areas of cell biology, but have intrinsic interest.

The study of cell surfaces may also have immense practical applications:

Cell surfaces have antigens which differ from tissue to tissue and person to person; if the structures of these antigens can be established the following can be done:

(1) If histoincompatibility antigens are known, infusion of haptens would prevent graft rejection without suppressing the immune response.

(2) If tumor antigens are known, high titer antisera could be produced and purified. The antibodies could be used diagnostically or perhaps therapeutically.

This conference will consider the organization of the molecules that make up the animal membrane, the chemical nature of the cells antigens and receptors, and the mediation of cell-cell interactions by surface components.

Conference on Epidemiological Approaches to Mutagenesis and Carcinogenesis

SEPTEMBER 1972

Cochairmen: Dr. Milos Padovan; Dr. Richard Doll.
Cosponsors: International Agency Research on Cancer; National Institute of Environmental Health Sciences.
Editor: To be chosen.

This conference is being called to examine new approaches to the epidemiological study of carcinogenesis. It is widely believed by authorities on cancer that there is an environmental factor in the causation of most cancers. The conference will review present epidemiological knowledge concerning carcinogenesis and the role of endocrinological, nutritional, and immunological factors therein. The conference will bring together experts on laboratory study of these questions as well as experts on field study who deal directly with human populations. By holding this meeting in Yugoslavia, it will be possible through collaboration with the International Agency for Research on Cancer to bring experts not only from the Western world but from Eastern countries as well. In this way many questions can be considered which would not be possible to do if the meeting were held in the United States. The proceedings of this meeting will be published by the International Agency for Research on Cancer which is one of the cosponsors. It is expected that there will be approximately 80 to 100 participants divided between North America and Western Europe, Eastern Europe and the Soviet Union, with representation from Australia, Asia, and Japan.

INTERNATIONAL SYMPOSIUM ON METABOLIC INTERCONVERSIONS

OCTOBER 1972

Chairman: To be chosen.
Cosponsor: National Heart and Lung Institute.

Every year an International Symposium on Metabolic Interconversions of Enzymes is held in a different country. The first such symposium was held in Italy and was financed by the Italian Biochemical Society. The second was held in 1971, in Germany, and was financed by funds from German sources made available to the organizing committee. The Fogarty International Center has agreed to support the Third International Symposium which is on a subject of considerable importance to a number of NIH institutes in carrying out their research mission. Enzymes are large molecules, called proteins, which promote normal chemical reactions in the body, utilization of foodstuffs, and catalyze other necessary functions in all organisms. As such, the study of enzymes, their mechanism of action and the results of the reactions they catalyze are of extreme importance in biology and medicine. Practical applications of enzymology have been found in all branches of medicine both for diagnosis and for treatment of disease. Understanding of enzyme action is essential for improvement of our ability to deal with genetic disease, cancer, and a variety of major public health problems. The proceedings of the meeting will be published and a number of American participants from within and outside the National Institutes of Health will be invited as well as the foreign participants who will bring their expertise to the meeting.

Dr. LEAVITT. I would like to add we work very closely with the Institutes. We worked with the Child Health Institute on that particular conference. We are currently working with the National Institute of Environmental Health Sciences in producing a series of scientific documents that may be used at the U.N. conference in Stockholm in 1972 on the human environment. These are contributions that the Center makes, along with its sister Institutes.

PREVENTIVE MEDICINE

Mr. PATTEN. You mentioned preventive medicine. This, I hope, will be my satellite as a Congressman. Some fellows have antiwar, everybody has a satellite. I would like my satellite to be preventive medicine. Anything you can pass on to me that I can use I would appreciate. As you say, it hasn't been delineated. I think that this is a big thing. You talk about a smear for cancer detection that can save the lives of millions of people, but we don't deliver. There are doctors in my district who want us to make massive efforts using this smear test for early detection of cancer. There is great interest on the part of some, but so many more don't seem to care.

Dr. LEAVITT. Mr. Chairman, preventive medicine has not been a very popular subject, even in my own profession.

Mr. PATTEN. Because as you say it hasn't been delineated. I know this. We have had a TB program ever since I can remember. I have worked on our county tuberculosis program since 1930 and I know going around with X-rays brought results. It is a pleasure to know that my TB hospital is empty. We had 400 patients and a waiting list.

I was in the polio drive in 1933 in my county with President Roosevelt. We had bands in New Brunswick and all over. I came down here to the Sheraton. President Roosevelt came out and gave us a citation. It is a great pleasure and satisfaction to know that nobody died from polio in my State last year. Isn't that terrific? When it

comes to preventive medicine, I look especially at our citizens who don't go to doctors because they don't have the money. You and I know we are talking about the real thing.

PREVENTIVE CARE FOR OLDER CITIZENS

We have a little project in my county where we take the older citizens in our housing projects by bus up to the old TB hospital. We give them free physicals and we give them treatment. We have massage, whirlpool baths, and different things. We actually give them treatment besides diagnosis. If they need an X-ray they get it. The facilities are there. We are thrilled by what we see and what we have accomplished with some of these people. Common things like hearing aids, false teeth, eye glasses, which make them much more comfortable and they can enjoy life more, but this whole field of preventive medicine has not been delineated, and I am thirsty to know more.

Dr. LEAVITT. Yes; it is much less expensive to apply preventive techniques than it is to live without them, waiting until disease develops, and then bearing the high cost of treatment and long-term care.

Mr. PATTEN. I don't think people in general, or Members of Congress, are aware of the importance of preventive medicine. I would like to carry the ball and go with it. If you can give me some help, I would appreciate it.

Dr. LEAVITT. I would be happy to do so.

Mr. PATTEN. You might have thoughts. After all, I am not in the business. I don't live with it all day long, every day, but as you said, it is not properly delineated.

The people in the operation I spoke of would like to expand this program to include all the housing projects in the county. When I tell them to broaden it, they say, "You need money." I was there personally and I can tell you the old people appreciate the attention. One big item is busing people. Just transportation of the older citizens is really a problem.

FOGARTY CENTER BUILDING PLANS

It is a pleasure to look back at the way we have knocked down TB, polio, and other things. This has little to do with your getting your money. Let's talk about the building program. What is the status of the building program?

Dr. LEAVITT. The plans for the new Fogarty International Center building will be completed by early autumn. However, we at this time have no building funds available. It is my understanding that these funds would be included in the 1973 budget.

Mr. PATTEN. You have planning funds.

Dr. LEAVITT. Yes, sir; $500,000 was provided for the planning.

Mr. PATTEN. If you had the money you could go to bids, couldn't you, this fall?

Dr. LEAVITT. Yes, sir.

Mr. PATTEN. Has any estimate been made?

Dr. LEAVITT. The last estimate that I heard was $7 million. That is for a poured concrete structure.

Mr. PATTEN. You know this is behind the schedule anticipated by the committee.

Dr. LEAVITT. Yes, sir.

Mr. PATTEN. Why has it been held back?

Dr. LEAVITT. It has taken us some time to complete the plans. They have been reviewed and changed on a number of occasions, and we have had to obtain several approvals by various commissions before we could submit final plans.

Mr. PATTEN. Mr. Shriver?

AGENCY FOR INTERNATIONAL DEVELOPMENT FUNDS

Mr. SHRIVER. Dr. Leavitt, do any of the foreign participants in your programs also receive funds from the Agency for International Development? In other words, do you have any cooperative agreement with that Agency in connection with international health activities?

Dr. LEAVITT. No; none of the participants in our programs receive funds from the Agency for International Development. Applicants for an international postdoctoral fellowship award are first reviewed by their respective national nominating committee in each of the participating countries. A second review is conducted in the United States by an international fellowships review committee. One item considered in each of these reviews is other funding for the participant. We would not support a candidate with dual funding.

In response to the second part of your question, we do not have any cooperative agreement with the Agency for International Development in connection with international health activities.

CLOSING NIH OVERSEAS OFFICES

Mr. SHRIVER. On page 7 you say some NIH offices overseas are being closed, and that NIH needs for information from abroad will be met by encouraging greater professional participation by the institutes and utilizing the specialized skills available within the institutes. Would you explain this further?

Dr. LEAVITT. Because of the interest of the executive branch in reducing expenditures outside the United States which affect the balance of payments with other nations, the NIH reduced the professional staff in its overseas offices from three to one. Experience since that time has shown that there is no doubt that a single individual in an overseas office with one specialty in science cannot adequately cover the needs of NIH as a whole within the geographic area involved. During fiscal year 1970 this matter was examined in more detail and a decision was made to terminate the overseas offices and utilize the funds and positions within the Fogarty International Center in Bethesda to carry out these functions.

Because of the special situation with regard to Special Foreign Currency in India and Pakistan, it was decided to make an exception to this decision and permit the NIH representative at the American Embassy in New Delhi to remain. Because of the value of this individual to the successful operation of our Special Foreign Currency Program in South Asia, it is planned to continue this office indefinitely.

Information and liaison functions formerly carried out by the NIH

representatives overseas will now be carried out from Bethesda by the Fogarty Center using individuals or teams of specialists who will maintain contact with foreign institutions and make on-the-site assessments on the state of the art in certain areas or disciplines throughout the world. In this way we can draw upon the specialists of the Institutes to provide surveys and reports on specific scientific activities rather than expect one professional to provide reports in many fields of endeavor. To put it bluntly, a report or study on cancer virology in any foreign country would be far more acceptable to the profession than a report on cancer virology by a scientist with a background in biochemistry.

Mr. PATTEN. Mrs. Reid?

FOGARTY SCHOLARS

Mrs. REID. Would you tell us more about the Fogarty scholars, who they are and where they come from.

Dr. LEAVITT. At the present time, we have four scholars-in-residence. They are:

Prof. Isaac Berenblum, professor and head, department of experimental biology, Weizmann Institute of Science, Rehovot, Israel, is currently a Fogarty Scholar-in-Residence. Educated in England, Dr. Berenblum is a graduate of the Medical School, Leeds University. He has served on the faculty at both Leeds University and the University of Oxford; while at Oxford he was in charge of the Cancer Research Center of Britain. Before assuming his present position at the Weizmann Institute in 1950, Professor Berenblum was a visiting scientist at the National Cancer Institute.

Professor Berenblum is recognized as an outstanding authority on experiments in how cancers start in the body and while a Fogarty Scholar-in-Residence will work closely with scientists at the National Cancer Institute. He is currently devoting a portion of his time to writing a book entitled "Carcinogenesis as a Problem in Biology." In addition he is participating in seminars and conferences with colleagues at the NIH.

Professor Berenblum has received several honors and awards for his scientific accomplishments and is a founding member of Israel National Academy of Sciences and Humanities.

Prof. John T. Edsall, of the Biological Laboratories, Harvard University, Cambridge, Mass. was a Fulbright Visiting Lecturer at Cambridge, England in 1952, chairman of the board of tutors at Harvard and president of the International Congress of Biochemistry. He was editor in chief of the Journal of Biological Chemistry 1958–67.

Professor Edsall, a basic scientist of high repute, has been providing a tremendous stimulation in the area of blood chemistry through a series of seminars he has been presenting and also a number of lectures and informal talks. He is a coleader of an international conference on "Allosteric Enzymes." Allosteric enzymes are special, very large protein molecules which are essential to human body functions. One such molecule is hemoglobin which transports oxygen from the lungs to the tissues and returns carbon dioxide. Abnormal functioning of this allosteric protein leads to sickle cell anemia in which the tissues of the body are deprived of oxygen. In addition to his active involve-

ment in these conferences, he has devoted some of his time in completing a second volume of a classic book "Biophysical Chemistry."

Prof. E. Torsten Teorell, professor of physiology and medical biophysics, University of Uppsala, Sweden, is a medical biophysicist of distinction. Dr. Teorell is a member of Royal Swedish Academy of Sciences whose Nobel Institute awards the Nobel prizes. He also is a member of the Swedish Medical Research Council.

During his first period of residence he was effective in stimulating interest in the field of heart arrhythmias (irregular heart beats) with emphasis on the mechanical and electrical stimulation aspects. His concern over the lack of supportive data pertaining to sudden death and his own conviction that a mechanical or electrical failure occurs prompted his bringing together a group of experts in the area for an international conference. These activities were carried out in close cooperation with the Heart and Lung Institute and provided a stimulus to investigators pursuing problems in the heart arrhythmias.

More recently Professor Teorell has focused on an area known as "pharmacokinetics," a field in which there is considerable interest because of widespread use of drugs. In the late thirties he published his views on drug distribution in biological tissues based on theoretical calculations he had made. With the recent emphasis on drug metabolism, it has been found experimentally that much of the laboratory data substantiates some of Professor Teorell's earlier theoretical work. He is currently planning an international conference to be held at the Fogarty Center during fiscal year 1972, with the expectation that the bringing together of experts in this field will greatly enhance our knowledge of drug metabolism.

Prof. Jeffries Wyman, professor of biology, University of Rome, Rome, Italy, is currently a Fogarty scholar in residence. After spending 25 years as a member of the Harvard faculty, Dr. Wyman began a new career in the international arena and was the first science attaché at the U.S. Embassy in Paris. He than served as Director, UNESCO Field Science Cooperation Center for the Middle East, Cairo, before assuming his present position in 1960.

Professor Wyman is a distinguished molecular biologist of world renown, a member of National Academy of Sciences and in 1970 became Secretary-General, European Molecular Biology Organization. He has made significant contributions to the understanding of oxygenation of hemoglobin and continues to be an active laboratory researcher. He collaborated with Professors Monat and Changeaux in France to write a paper on "Allosteric Models" which is considered a classic in its field. Allosteric models are special kinds of proteins in the body such as hemoglobin, which carry oxygen from the lungs to the tissues. While a scholar in residence he will be working closely with another scholar, Prof. John T. Edsall, in both the writing of a book on "Biophysical Chemistry" and the presentation of a conference and seminar series in "Advanced Biochemistry."

PUBLIC LAW 480 FUNDS FOR OVERSEAS OFFICES

Mrs. Reid. Have all of the overseas offices been operated through Public Law 480 funds?

Dr. Leavitt. Some of the expenses of the NIH office in New Delhi are paid with Public Law 480 funds. The salary of the U.S. employee

is, of course, paid with U.S. dollars. None of the expenses of the other offices were paid with Public Law 480 funds.

COORDINATION WITH WHO AND AID

Mrs. Reid. Are there any present plans to place all of the international health and medical activities under the Center eventually?

Dr. Leavitt. I am not aware of any plans to place all of the international health and medical activities under the Center.

Mrs. Reid. Do you coordinate your programs with the World Health Organization and the Health Activities of AID.

Dr. Leavitt. I would say that while we do not formally coordinate our programs with either the World Health Organization or the Agency for International Development, we do maintain active liaison with WHO research programs through the International Health Attaché who is a staff member of the U.S. Mission, Geneva. We also work closely with the PAHO Department of Research Development and Coordination here in Washington. I might add that our interest in WHO was reflected in my appointment earlier this month to serve as an alternate delegate on the U.S. delegation to the 24th World Health Assembly. Current information on AID health programs is made available to the Center through direct contact with the Director, Office of Health, AID, and through weekly reports issued by the Office of International Health, DHEW.

FOUNDATIONS ENGAGING IN CONFERENCE ACTIVITY

Mrs. Reid. In regard to the conferences which you conduct, are there any foundations engaged in similar activities which they are financing?

Dr. Leavitt. There are a number of U.S. foundations which do conduct conferences, some of which may be on health matters. It has been our experience, however, that these are usually a one-time exploration of one facet of the problem.

We do feel that the Center is unique in its approach whereby we are devoting ourselves to the continuing study of the many aspects of health problems.

INTERNATIONAL RESEARCH RESULTS

Mrs. Reid. Can you tell us about any results of research carried on outside the United States in a cooperative venture. Perhaps you could develop this for the record.

Dr. Leavitt. I would be pleased to do so.

(The information requested is furnished below:)

The National Cancer Institute Biometry staff is engaged in international collaborative studies in cancer with Norway, Poland, England, India, Japan, and Colombia. Studies are undertaken on a cooperative basis with scientists of these nations to establish better understanding of the basic epidemiology and demography of malignant disease, and the greater or lesser risk of cancer observed in individuals who move to other nations where the occurrence of cancer is well known. For example, cancer of the stomach is quite prevalent in Japan but not in the United States, and, due to factors not yet completely identified

and studied, when the Japanese individual immigrates to the United States of America, he actually assumes the lower U.S. risk. Studies in Japan and other nations are yielding important data that contribute to better understanding of the factors involved in the initiation and development of cancer occurring in the United States of America. The collaboration of scientists abroad has been extremely helpful and in turn the exchanges of information have aided cancer control programs in the respective countries in which studies are made.

The National Heart and Lung Institute has a continuing project with the researchers at the Hiroshima Atomic Bomb Casualty Commission making use of their cardiovascular examination procedure, but expanding their special measurement techniques in a jointly agreed upon protocol with an NHLI field-based study unit in Hawaii. The objective of this cooperation is to use comparable diagnostic and laboratory and clinical measurements which are applied equally in the Japanese population in the ABCC study and among Japanese men in Honolulu to determine what differences exist in characteristics which may relate to cardiovascular diseases and stroke.

A group of Harvard University medical investigators, headed by Dr. Alexander Leaf, and cooperating with a University of Quito, Ecuador, research team, have discovered what they believe is evidence of a link between low cholesterol levels and the virtual absence of coronary heart disease among the elderly of a remote Andean village. Blood serum cholesterol levels as low as 140 were recorded in the population of Vilcabamba, Ecuador, with average levels among adults ranging between 120 and 165. (According to the American Heart Association, the average cholesterol level for the typical 50-year-old American male is 250.) After extensive cardiovascular studies conducted by the Quito group, only two elderly individuals over 75 years of age in the village of 800 persons showed evidence of atherosclerotic heart disease. Electrocardiographic studies of a similarly elderly population in the United States would show 95 percent with cardiovascular disease. Nutritional surveys disclosed that the Ecuadorian villagers consume an average of 1,700 calories a day, only 153 calories of which is derived from animal fat. The average adult American male consumes 2,400 to 2,600 calories per day, of which 450 to 500 are animal fat, about three times the level in Vilcabamba. These findings are consistent with those reported in many other international studies of the relationship between diet and heart disease. These studies have indicated that a diet low in animal fats is associated with a decreased risk of heart disease, the No. 1 killer of middle-aged American men.

Dr. Kenneth McIntosh, Laboratory of Infectious Diseases, NIAID, who has isolated new viruses from several outbreaks of human respiratory infections in the U.S. has taken a working assignment at the National Institute for Medical Research, Mill Hill, London, England. Similar viruses have been isolated and reported as causing respiratory infection in the United Kingdom. Respiratory virus research in England has made an important contribution to NIAID efforts to identify new etiological viruses, characterize their disease spectrum, develop diagnostic methodology and develop vaccines. Interactions between scientists of the Intramural Program of NIAID and Mill Hill have provided an excellent method of furthering scientific interchange which has been of mutual benefit to both countries.

GM 14896, Professor Jan-Erik Edstrom, Karolinska Institute, Relation of Chromosomal RNA to DNA Fractions. This is an excellent study utilizing the chromosomal puffs in polytene chromosomes of *Chironamus* in a study of the chemical and functional nature of RNA formed during puffing. The information to be gained is extremely important to an understanding of the regulation of the timing of action of particular genes during development. Dr. Edstrom is a unique person due to his background, an innovator in his field, and particularly outstanding. Since it may soon be possible to create and study polytene chromosomes in man, this study is of direct human genetics program interest.

Dr. Makio Murayama, NIAID, is collaborating with Dr. Braunitzer of the Max-Planck Institute for Biochemistry in Munich on the amino acid sequence of hemoglobin from *Ureachis caupo*. Dr. Murayama is also collaborating with clinicians from the University of Ghana Medical School on the use of urea in the treatment of sickle cell anemia crises.

Dr. Taiishi Mishima, a Japanese, worked in cooperation with two Americans,

NEI grantees, to develop a delicate technique to measure tear flow using fluorescin dye. This is significant in some congenital disorders where tear flow is not normal (pre Tay-Sach syndrome).

Dr. Peter J. Fischinger, NCI, is working with Dr. Werner Schafer, Director of the Max-Planck Institut fur Virusforschung in Tubingen, Germany. Dr. Fischinger is especially interested in the biology of sarcoma and leukemia viruses and is joining Dr. Schafer in response to the latter's expression in collaborative studies and the exchange of personnel.

Funds Necessary to Maintain 1971 Level for Research and Training

Mr. Patten. Dr. Sherman, this completes the hearings on the research components of the National Institutes of Health. There are two things that came up time after time during these hearings. One is that the 1972 budget for so many programs is below the 1971 program level. The other is the level and the method of funding fellowship and training programs under the 1972 budget. We want to make sure the record is clear on both of these issues. Mr. Michel asked you to put a table in the record with regard to the first point. We just want to be sure that the table will clearly set forth for each appropriation, and separately for each activity that is set forth in the budget schedules, the additional amount that would be required to maintain the 1971 program level. With regard to the fellowship and training programs, I think we will have to have two sets of figures, one assuming no transfer to the health manpower appropriation and, two, perhaps this should be in parenthesis under the first figures, what the additional amount would be assuming the transfers are made as proposed in the budget.

(The information follows:)

NATIONAL INSTITUTES OF HEALTH—ESTIMATED INCREASES IN 1972 BUDGET REQUEST REQUIRED TO MEET 1971 PROGRAM LEVEL

[In thousands]

Budget activity	DBS	NCI	NHLI	NIDR	NIAMD	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	RR	FIC	OD	Total
Research grants		$5,725	$7,085	$1,018	$5,388	$4,838	$3,363	$5,509	$3,013	$1,245	$569	$3,769	$31		$41,553
Fellowships		678	1,088	330	990	354	460	2,419	360	901	16	8	$413		8,017
Training grants:															
(1) assumes no transfer to BHME		646	1,058	312	904	858	535	2,625	609	180	187	21			7,935
(2) assumes transfer of $23 million to BHME		(501)	(816)	(257)	(689)	(687)	(437)	(2,303)	(545)	(133)	(171)	(21)			(6,560)
Direct operations:															
Laboratory and clinical research		639	494	128	703	297	469		295	138	166				3,329
Collaborative research and development		5,205	1,792	222	834	2,520	665	1,268	892	80	59	81			13,618
Biometry, epidemology and field studies			57	18	171	212			112	9					579
International center													68		68
Biologics standards	$287														287
Training activities								6	2						8
Review and approval of grants		123	123	23	109	134	73	137	89	30	13	35			890
Program direction		46	28	5	23	10	7	27	16	6	3	15		254	440
Total, direct operations	287	6,013	2,494	397	1,840	3,173	1,214	1,438	1,406	263	241	131	68	254	19,219
Estimated increase to meet 1971 program level:															
(1) assumming no transfer	287	13,062	11,725	2,057	9,122	9,223	5,572	11,991	5,388	2,589	1,013	3,929	512	254	76,724
(2) assumming transfer	(287)	(12,917)	(11,483)	(2,002)	(8,907)	(9,052)	(5,474)	(11,669)	(5,324)	(2,542)	(997)	(3,929)	(512)	(254)	(75,349)

Note: Computations provide for 1971 funding level for all activities and reflects currently estimated cost of living increases.

NATIONAL INSTITUTES OF HEALTH ESTIMATED INCREASES IN 1972 BUDGET REQUEST REQUIRED TO MEET 1971 PROGRAM LEVEL

National Library of Medicine

	(*Thousands*)
Grants:	
Medical library assistance	0337
Direct operations:	
Lister Hill National Center for Biomedical Communications	170
Toxicology information	80
Library operations	420
National Medical Audiovisual Center	35
Review and approval of grants	5
Program director	95
Subtotal, direct operations	805
Estimated increase to meet 1971 program level [1]	1,142

[1] Computations reflect estimated cost of living increases for all activities.

RATIONALE FOR CUTBACK IN FELLOWSHIPS AND TRAINING

Mr. PATTEN. On the second point, we should have a good, complete statement regarding the cutback of the fellowship and training programs. It should include statistics comparing 1971 with the 1972 budget, and a narrative setting forth the rationale behind this basic revision, and what you believe the effects will be.

Dr. SHERMAN. Yes, sir, we will provide that for the record.

(The information that was submitted follows:)

COMPARISON OF 1971 APPROPRIATION WITH 1972 BUDGET—FELLOWSHIPS AND TRAINING GRANTS

[In thousands of dollars]

	1971 appropriation	Reserve	Reprograming	1971 comparable level	Change	1972
Fellowships	49,964		−40	49,924	[1] −7,021	42,903
Training grants	116,827	[2] −7,441	−50	109,336		109,336

[1] Includes $5,021,000 program decrease to return to the 1971 requested level and $2,000,000 decrease in National Institute of General Medical Sciences predoctoral program.

[2] Includes $6,641,000 proposed transfer for pay increases and $800,000 reprogramed by the National Heart and Lung Institute.

The fellowship reduction will be spread across 10 appropriations and it is estimated that it will result in a reduction of 219 predoctoral fellowships and of 591 in other types of fellowships. It is estimated that there will be a reduction of 121 training grants between 1971 and 1972 resulting from increased costs. The transfer of $23 million to Health Manpower reflects the decision to transfer the salary portion of the grant and does not affect the number of grants.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

Amounts Available for Obligation

	1971	1972
Appropriation	$3,582,000	$3,319,000
Real transfer from:		
"National Institute of Arthritis and Metabolic Diseases" (proposed transfer for increased pay costs)	54,000	---
"National Institute of Neurological Diseases and Stroke" (proposed transfer for increased pay costs)	30,000	---
Comparative transfer to: "Office of the Director"	-6,000	---
Comparative transfer from: "National Cancer Institute"	22,000	---
Total, obligations	3,682,000	3,319,000

Obligations by activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase Decrease Pos.	Increase Decrease Amount
	Grants:						
235	Research	---	$ 520,000	---	520,000	---	---
236	Fellowships	---	1,077,000	---	739,000	---	-$338,000
237	Fogarty Scholarships	---	170,000	---	170,000	---	---
238	International Center	49	1,915,000	49	1,890,000	---	- 25,000
	Total, obligations	49	3,682,000	49	3,319,000	---	- 363,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	49	49	---
Full-time equivalent of all other positions	8	8	---
Average number of all employees	55	55	---
Personnel compensation:			
Permanent positions	$ 676,000	710,000	+ 34,000
Positions other than permanent	72,000	78,000	+ 6,000
Other personnel compensation	5,000	5,000	---
Subtotal, personnel compensation	753,000	793,000	+ 40,000
Personnel benefits	89,000	93,000	+ 4,000
Travel & transportation of persons	193,000	193,000	---
Transportation of things	10,000	10,000	---
Rent, communications & utilities	80,000	81,000	+ 1,000
Printing and reproduction	40,000	40,000	---
Other services			
Payment to NIH Management Fund.	96,000	101,000	+ 5,000
Other	506,000	427,000	- 79,000
Supplies and materials	50,000	54,000	+ 4,000
Equipment	98,000	98,000	---
Grants, subsidies, and contributions	1,767,000	1,429,000	-338,000
Total obligations by object.	3,682,000	3,319,000	-363,000

Summary of Changes

1971 estimated obligations	$3,682,000
1972 estimated obligations	3,319,000
Net change	-363,000

Increases:	Base Pos.	Base Amount	Change from Base Pos.	Change from Base Amount
A. Built-in				
1. Annualization of 1971 pay increase costs	---	---	---	34,000
2. Extra days pay	---	---	---	4,000
3. Within-grade pay increases	---	---	---	11,000
4. FTS rate increase	---	---	---	1,000
Subtotal	---	---	---	50,000
B. Payments to NIH Management Fund for centrally furnished services	---	96,000	---	5,000
Total, Increases	---	---	---	55,000
Decreases:				
A. Program				
1. Fellowships	---	1,077,000	---	-338,000
2. International Center	---	1,819,000	---	- 80,000
Total, decreases	---	---	---	-418,000
Total, net change	---	---	---	-363,000

Explanation of Changes

Built-in-Increases--These increases will provide: $34,000 for annualization of 1971 pay increase; $4,000 for the extra day of pay; $11,000 for within-grade pay increases in 1972; and $1,000 for increased cost in 1972 of using the Federal Telecommunications system.

Program Decreases--The decrease of $338,000 reflects a reduction of 43 International Postdoctoral Fellowships. The decrease of $80,000 results from reduced program operations in the International Center.

Authorizing Legislation

	1972	
	Authorization	Appropriation Requested
Legislation		
Public Health Service Act		
Title II - Administration Section 207 (g) Service Fellowships		
Title III - General Powers and Duties of Public Health Service		
Part A - Research and Investigation In General (Section 301)		
International Cooperation (Section 308)		
	Indefinite	$3,319,000

PUBLIC HEALTH SERVICE ACT

Title II--Administration

Public Health Service

"Section 207.(g) In accordance with regulations, individual scientists, other than commissioned officers of the Service, may be designated by the Surgeon General to receive fellowships, appointed for duty with the Service without regard to the civil service laws and compensated without regard to the Classification Act of 1923, as amended, may hold their fellowships under conditions prescribed therein, and may be assigned for studies or investigations either in this country or abroad during the terms of their fellowships."

Title III -- General Powers and Duties of Public Health Service

PART A -- RESEARCH AND INVESTIGATION

In General

"Section 301. The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man, including water purification, sewage treatment, and pollution of lakes and streams. In carrying out the foregoing the Surgeon General is authorized to--.....

62-645 O - 71 - pt. 3 - 76

(c) Establish and maintain research fellowships in the Service with such stipends and allowances, including traveling and subsistence expenses, as he may deem necessary to procure the assistance of the most brilliant and promising research fellows from the United States and abroad;

(d) Make grants-in-aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for such research or research training projects as are recommended by the National Advisory Health Council....."

International Cooperation

"Section 308. (b) In carrying out his responsibilities under this section the Surgeon General may --

(1) establish and maintain fellowships in the United States and in participating foreign countries;

(2) make grants to public institutions or agencies and to non-profit private institutions or agencies in the United States and in participating foreign countries for the purpose of establishing and maintaining fellowships;

(5) facilitates the interchange between the United States and participating foreign countries, and among participating foreign countries, of research scientists and experts who are engaged in experiments and programs of research or research training, and in carrying out such purpose may pay per diem compensation, subsistence, and travel for such scientists and experts when away from their places of residence at rates not to exceed those provided in section 5 of the Administrative Expenses Act of 1946 (5 U. S. C. 73b-2) for persons in the Government service employed intermittently."

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer from:		
National Institute of Arthritis and Metabolic Diseases	$54,000	Proposed transfer for increased pay costs.
National Institute of Neurological Diseases and Stroke	30,000	Proposed transfer for increased pay costs.
Comparative transfer to:		
Office of the Director	- 6,000	Transfer of the research contracting functions from NIH Management fund to Office of the Director for establishing the Office of Contracts and Grants.
Comparative transfer from:		
National Cancer Institute	22,000	To provide an equitable distribution of the Management Fund in 1972.

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1968	$500,000	$500,000	$725,000	$500,000
1969	600,000	600,000	600,000	600,000
1970	3,460,000	2,954,000	2,954,000	2,954,000
1971	2,664,000	3,582,000	3,582,000	3,582,000
1972	3,319,000			

Justification

John E. Fogarty International Center for
Advanced Study in the Health Sciences

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	49	$842,000	49	$886,000	---	+ $44,000
Other expenses.....	---	2,840,000	---	2,433,000	---	- 407,000
Total.....	49	3,682,000	49	3,319,000	---	- 363,000

General Statement

The John E. Fogarty International Center for Advanced Study in the Health Sciences is designed to facilitate and expand the continuing effort of the National Institutes of Health and the United States Government to broaden the knowledge base of the biomedical sciences. The Center serves as the focal point for the international activities of the National Institutes of Health and is responsible for the administration of the International Postdoctoral Fellowships Program, The Fogarty Scholars-in-Residence Program, The Conference and Seminars Program, International Visitors Center and the Special Foreign Currency Program (PL 480).

In administering these activities, the Fogarty International Center places its efforts on 1) facilitating the useful exchange of distinguished scientists and scholars as well as promising young scientists; 2) providing an environment, including facilities, which will contribute to the exchange, expansion and evolution of ideas; and 3) promoting international cooperation for the dissemination and sharing of biomedical knowledge both on a bilateral and multilateral basis to supplement and assist that exchange of knowledge by individual scientists and institutions.

The Fogarty International Center is requesting $3,319,000 in 1972, a net decrease of $363,000 below the 1971 estimate of $3,682,000.

Research Grants

Special Programs	1971 Estimate	1972 Estimate	Increase or Decrease
Gorgas Memorial Laboratory	$500,000	$500,000	---
Scientific Evaluation	20,000	20,000	---
Total research grants	$520,000	$520,000	---

Introduction

The Gorgas Memorial Laboratory explores the fundamental biomedical ecology of Panama and the Central American Republics and translates basic research to applicable public health measures. Situated in a tropical environment 2-1/2 hours flying time from the United States, this Laboratory offers exceptional opportunites for research and clinical training in the diseases and problems of the hot, wet tropical environments. Some diseases which are being researched include Chagas' disease, leishmaniasis, malaria, viral infections, intestinal parasites, and infantile diarrhea, all of which constitute a continuing threat to the tropical areas of the world.

Program plans 1971 and 1972

The support of the Gorgas Memorial Laboratory will be funded through the Fogarty International Center. It is anticipated that research on the above mentioned diseases will continue. Scientific and technical support will be provided in the following disciplines: virology, parasitology, malariology, serology, bacteriology, pathology, hematology, and medical entomology. The anticipated advances from this laboratory will assist in diagnosis, treatment, and management of tropical diseases which are rampart in hot climates.

The scientific evaluation grant provides for committee evaluation of the International Postdoctoral Fellowship Program by distinguished U. S. scientists.

Distribution of Research Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
1. Gorgas Memorial Laboratory.....	--	$500,000	--	$500,000	--	---
2. Scientific Evaluation.....	--	20,000	--	20,000	--	---
Total, research grants.....	--	520,000	--	520,000	--	---

Fellowships

	1971 Estimate	1972 Estimate	Increase or Decrease
International Postdoctoral Fellowships.....	$1,077,000	$739,000	-$338,000

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 1971 and 1972

This program will be continued in 43 countries during 1972. 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.

Funds requested in the revised estimate for 1972 will provide for 79 awards compared to 122 in 1971, a decrease of 43. This decrease reflects the priorities in the 1972 President's Budget related to national health programs.

Distribution of Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Continuations						
Noncompeting.....	54	$397,000	35	$299,000	-19	-$98,000
New awards.....	68	680,000	44	440,000	-24	-240,000
Total fellowships.	122	1,077,000	79	739,000	-43	-338,000

Fellowships (By type of Program)

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
International Post-doctoral.....	122	$1,077,000	79	$739,000	-43	-$338,000

Fellowship Program Analysis

	1970 Actual	1971 Estimate	1972 Estimate	Increase or Decrease
International Postdoctoral..	$1,026,595	$1,077,000	$739,000	-$338,000

Fogarty Scholarships

	1971 Estimate	1972 Estimate	Increase or Decrease
Fogarty Scholarships.....	$170,000	$170,000	---

Introduction

The objective of this program is the exploration of current problems confronting society as a result of modern biomedical research, the delineation of problems to come and the synthesis of new approaches for the solution of these problems. The program will also promote fruitful exchange of ideas between distinguished leaders in science, scholars in other disciplines and other creative individuals.

The program selects outstanding scientists and other scholars who focus their attention on broad aspects of important issues raised by the findings of modern biomedical research. While in residence at the Center the scholars are encouraged by group interaction to attack broad problems, the solutions to which require an interdisciplinary approach or whose solution lies beyond the knowledge of a single individual. The program draws the scholars from the international biomedical community, and from among those people who possess special qualifications in science administration, those whose scholarly attainments suggest that they can contribute to the interactions of the group. The scope of this program includes a continuing series of comparative studies and assessments of the trends of international science policy and the organizational structure and management of research and development on an international scale.

The unique environment at the NIH offers an unusual opportunity for scholars to interact with large numbers of intramural staff scientists in discussion--focusing attention on important health problems, holding small conferences, workshops and, on a group basis, assessing the state-of-the-art in many disease areas. It is expected that scholars will provide inspiration to others and delineate important areas of research.

Program Plans in 1971 and 1972

Funds requested for 1972 will provide for 6 awards, the same as in 1971.

International Center

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	49	$842,000	49	$886,000	---	+$44,000
Other expenses.....	---	1,073,000	---	1,004,000	---	- 69,000
Total.....	49	1,915,000	49	1,890,000	---	- 25,000

The John E. Fogarty International Center for Advanced Study in the Health Sciences has made rapid improvement in its advanced study program where emphasis has been placed upon the Conference and Seminars Program and the Fogarty Scholars-in-Residence Program. Other elements of international cooperation and advanced study include an organized program of bilateral cooperation and a redesigned effort to obtain scientific information by utilizing the competences and specialists of the various NIH Institutes.

Through its Conference and Seminars Program, The Fogarty International Center provides a forum for the review and discussion of major biomedical issues confronting the nation. In addition to basic themes developed by the Center, emphasis is placed upon cooperation by and with the various Institutes of the NIH, as well as other federal and international organizations.

Program Plans for 1971 and 1972

Conference and Seminar Program

Objectives of the Conference and Seminar Program are:

To promote advanced study in the health sciences by conducting international conferences, seminars, workshops and training courses within the scope of the NIH mission, i.e., advancement of knowledge for the nation's health.

To identify the legal, ethical, social and economic problems that may arise from new findings of biomedical research.

To advance our understanding and insight into these problems confronting us by holding cross-disciplinary conferences and seminars.

To stimulate research in particular fields by holding training seminars, workshops and courses, drawing on the international and biomedical research community for participants and faculty.

During 1972 the following conferences will be held at the Center:

Workshop on Histocompatability Antigens in Man.

Reform of Medical Education III. The Impact of New Health Systems on Medical Education.

Ethical Problems in Genetic Counseling.

Taxonomy of Malaria Parasites II.

Workshop on Epidemiology of Cancer.

Epidemiological Approaches to Mutagenesis and Carcinogenesis.

Follow-up action based on the conclusions of these conferences and seminars will be sought through NIH Institutes, through collaborative arrangements with other countries, with one of the international agencies with health science programs such as the WHO, or with other U. S. government agencies.

The Fogarty International Center provides the opportunity for scholarly considerations, for informal and unstructured exchange and a facility which will permit and foster daily communication among the professional staff of NIH and distinguished scientific visitors.

Scientific Activities (PL 480 Program)

The Fogarty International Center has the coordinating and policy formulation function and operating responsibility for the NIH Special Foreign Currency Program supported with an allotment of funds from the appropriation "Scientific Activities Overseas" managed by the Office of the International Health, Office of the Secretary, DHEW.

International Visitors Center

The International Visitors Center provides a dignified setting for the reception of visiting American and Foreign scientists; affords an opportunity to visitors for discussion of international biomedical problems with professional staff; and for the establishment of appropriate contacts between such visitors and the Fogarty International Center and NIH staff members.

The request this year for the International Center is $1,890,000, a net decrease of $25,000 from 1971.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Program Purpose and Accomplishments

Activity: Research grants (Public Health Service Act Title III Part A)

1971		1972		
				Budget Estimate
Pos.	Amount	Authorization	Pos.	Amount
---	$520,000	Indefinite	---	$520,000

Purpose: The major portion of this research grant appropriation is to support the work performed by the Gorgas Memorial Laboratory. In addition funds are provided to evaluate International Postdoctoral Fellowship applications.

Explanation: The amount of $500,000 provides a major portion of the resources to fund the programs of the Gorgas Memorial Institute in Panama. The Institute is investigating diseases which are prevelant in tropical areas and to which U. S. citizens in these areas are subject.

Accomplishments in 1971: A $500,000 grant was awarded to support the Gorgas Memorial Institute and the remainder of the funds were awarded to a scientific evaluation committee.

Objectives for 1972: The continuation of these grants for 1972 will be furnished from this appropriation.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Program Purpose and Accomplishments

Activity: Fellowships (Public Health Service Act Title III Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,077,000	Indefinite	---	$739,000

Purpose: 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.

Explanation: The International Postdoctoral Fellowship Program supports Fellows from 43 countries. 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.

Accomplishments in 1971: In 1971, 122 International Postdoctoral Fellowships were awarded.

Objectives for 1972: Seventy-nine International Postdoctoral Fellowships will be awarded.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Program Purpose and Accomplishments

Activity: Fogarty Scholarships (Public Health Service Act Title III Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$170,000	Indefinite	---	$170,000

Purpose: The Fogarty Scholars-in-Residence program, which was initiated in 1969 selects outstanding scientists and other scholars who focus their attention on broad aspects of important issues raised by the findings of modern biomedical research. While in residence at the Center the scholars are encouraged by group interaction to attack broad problems, the solutions to which require an interdisciplinary approach or whose solution lies beyond the knowledge of a single individual.

Explanation: Fogarty Scholars-in-Residence through the unique environment at NIH have an unusual opportunity to interact with large numbers of intramural staff scientists in discussions--focusing attention on important health problems, holding small conferences, workshops, and, on a group basis assessing the state-of-the-art in many disease areas.

Accomplishments in 1971: In 1971, six Fogarty Scholarships were awarded.

Objectives for 1972: Six Fogarty Scholarships will be awarded.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Program Purpose and Accomplishments

Activity: International Center (Public Health Service Act Title III Part A)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
49	$1,915,000	Indefinite	49	$1,890,000

Purpose: The John E. Fogarty International Center for Advanced Study in the Health Sciences is designed to facilitate and expand the continuing effort of the National Institutes of Health and the United States Government to broaden the knowledge base of the biomedical sciences. The Center serves as the focal point for the international activities of the National Institutes of Health. The Center also is responsible for the administration of the International Postdoctoral Fellowships Program, the Scholars-in-Residence Program, the Conference and Seminars Program, the International Visitors Center and the Scientific Activities Program (PL 480).

Explanation: In administering these activities, the Fogarty International Center will focus its efforts on (1) facilitating the useful exchange of distinguished scientists and scholars including promising young scientists; (2) providing an environment, including facilities, which will contribute to the exchange, expansion and evolution of ideas; and (3) promoting international cooperation for the dissemination and sharing of biomedical knowledge both on a bilateral and multilateral basis to supplement and assist that exchange of knowledge by individual scientists and institutions.

Accomplishments in 1971: In addition to operating the grants and fellowships programs mentiond, the International Conference Program held nine conferences and seminars during fiscal year 1971. Administered and operated other programs mentioned above.

Objectives for 1972: We will continue to coordinate, administer and operate these International Programs of the National Institutes of Health.

TUESDAY, MAY 11, 1971.

BUILDINGS AND FACILITIES

WITNESSES

RICHARD L. SEGGEL, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
DR. JOHN F. SHERMAN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM W. PAYNE, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
ROSS HOLIDAY, DIRECTOR, OFFICE OF ENGINEERING SERVICES, NATIONAL INSTITUTES OF HEALTH
JOHN E. SHARKEY, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

BUILDINGS AND FACILITIES

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 estimate	1972 estimate
NATIONAL INSTITUTES OF HEALTH			
Travel and transportation of persons			5
Printing and reproduction		45	50
Other services	−344	1,823	4,695
Supplies and materials	14		10
Equipment	82		
Lands and structures	19	3,200	1,890
Total, National Institutes of Health	−299	5,068	6,650
ALLOCATION TO GENERAL SERVICES ADMINISTRATION			
Travel and transportation of persons	1	2	
Printing and reproduction	4	5	
Other services	451	464	16
Lands and structures		1,176	75
Total, General Services Administration	456	1,647	91
Total obligations	227	6,715	6,741

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

	Costs to this appropriation					Analysis of 1972 financing			
	Total estimate	To June 30, 1969	1970 actual	1971 estimate	1972 estimate	Deduct selected resources and unobligated balance, start of year	Add selected resources and unobligated balance, end of year	Appropriation required, 1972	Appropriation required to complete
Program by activities:									
(1) Research facilities	155,039	18,625	486	1,433	3,565	7,721	6,156	2,000	124,774
(2) Service and administrative facilities	60,552	22,826	2,552	3,688	3,515	3,897	1,707	1,325	26,264
Total program costs, funded	215,591	41,451	3,038	5,121	7,080	11,618	7,863	3,325	151,038
Change in selected resources [1]			−2,811	1,594	−339				
Total obligations			227	6,715	6,741				
Financing:									
Unobligated balance available, start of year			−12,930	−14,373	−7,658				
Unobligated balance transferred from other accounts			−55						
Unobligated balance available, end of year			14,373	7,658	4,242				
Budget authority			1,615		3,325				
Budget authority:									
Appropriation			1,900		3,325				
Portion withdrawn (Public Law 91-204, sec. 410)			−285						
Appropriation (adjusted)			1,615		3,325				
Relation of obligations to outlays:									
Obligations incurred, net			227	6,715	6,741				
Obligated balance, start of year			5,905	2,941	4,694				
Obligated balance, end of year			−2,941	−4,694	−3,650				
Outlays			3,191	4,962	7,785				

[1] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $5,177,000; 1970, $2,366,000; 1971, $3,960,000; 1972, $3,621,000.

INTRODUCTION OF MR. SEGGEL AND STAFF

Mr. PATTEN. We would like to hear about the National Institutes of Health buildings and facilities. Is there anyone here we don't know, Mr. Seggel?

Mr. SEGGEL. Mr. Ross Holliday on my left is the Director of the Office of Engineering Services at NIH. On his left is Dr. William Payne, Deputy Director of the National Institute of Environmental Health Sciences. They both have a vital interest in this appropriation and I thought it would be appropriate for them to come up and help support them.

Mr. PATTEN. I think it would be nice, especially since our witness is from the State of New Jersey, if we put his biography in the record.

(The information follows:)

NATIONAL INSTITUTES OF HEALTH

BIOGRAPHICAL SKETCH OF RICHARD L. SEGGEL

Position:

Associate Director for Administration, NIH.

Birthplace and date:

Union City, N.J., Jan. 11, 1914.

Education:

Princeton University, A.B., 1936, major in public and international affairs; University of Cincinnati, graduate program, in public administration; Princeton University, M.A., 1938, Politics (primary field—Public administration).

Experience:

1969–present—Associate director for administration, NIH; 1958–1968—Executive Officer, NIH; 1956–58—Director, Officer, of Management Policy, Office of Secretary, DHEW; 1954–56—Assistant Executive Officer, Public Health Service, DHEW; 1953–54—Assistant Executive Officer, Bureau of State Services, Public Health Service, DHEW; 1951–53—Chief, Program Planning Branch, Health and Special Weapons Defense Division, Federal Civil Defense Administration; 1945–51—Budget Examiner, Bureau of Budget; 1941–45—Military service—private to captain (AGD); 19 months in European theater; 1940–41—Administrative analyst, Bureau of the Budget; 1939–40—Technical assistant, New Jersey Civil Service Commission; 1938–39—Research assistant, Princeton University.

Association memberships:

American Society for Public Administration.

Special awards, citations, or publications:

A. B. with honors, 1936; Superior Service Award by DHEW, 1963; Distinguished Service Award by DHEW, 1970.

BIOGRAPHICAL SKETCH OF ROSS HOLLIDAY

Position:

Director, Office of Engineering Services, ODA.

Birthplace and date:

Strawn, Md., February 12, 1924.

Education:

B.S.M.E., George Washington University, 1949; Graduate study, George Washington University, 1962.

Experience:

Director, Office of Engineering Services, June 1969 to present; Associate Director, Division of Research Services, 1967–69; Chief, Plant Engineering Branch, 1957–67; Chief, Mechanical Engineering Section, 1952–56; Mechanical Engineer, 1949–51.

Association memberships:

National and Maryland Society, Professional Engineers; Registered P.E.—Washington, D.C.

Special awards, citations, or publications:

Quality increase, 1967.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

BIOGRAPHICAL SKETCH OF WILLIAM WALKER PAYNE

Position:

Deputy Director, National Institute of Environmental Health Sciences.

Birthplace and date:

Calverton, Va., June 1, 1913.

Education:

B.S.E. (Civil), University of Virginia, 1935; M.S.E. (Sanitary), University of Michigan, 1947; M.P.H University of Pittsburgh, 1956; Sc.D. University of Pittsburgh, 1959.

Experience:

Deputy Director, National Institute of Environmental Health Sciences, 1967 to present; Deputy Scientific Director, Etiology, National Cancer Institute, 1966–67; Deputy Associate Director, Field Studies, National Cancer Institute, 1963–65; Carcinogenesis Studies Branch, National Cancer Institute, 1963; Environmental Cancer Section, National Cancer Institute, 1954–62; Research Facilities Engineer, National Cancer Institute, 1948–54; Sanitary Engineer, Public Health Service, 1943–48; Engineer, Montgomery County, Md., 1935–43.

Association memberships:

American Association for Cancer Research; Conference of Federal Environmental Engineers; American Industrial Hygiene Association; American Public Health Association.

Special awards, citations, or publications:

American Academy of Environmental Engineers, Diplomate Commendation Medal—January 1968.

GENERAL STATEMENT

Mr. PATTEN. How would you like to proceed?

Mr. SEGGEL. Mr. Chairman, I have a very short opening statement. The purpose of this appropriation is to provide funds for the design, construction, and repair and improvement of facilities for the National Institutes of Health.

In summary, we are requesting a total of $3,565,000 in fiscal year 1972 for the following projects:

Additional design funds for planning the facilities of the National Institute for Environmental Health Sciences at the Research Triangle Park, N.C.	$2,000,000
Design and construction of an incinerator at the Rocky Mountain Laboratory, Hamilton, Mont.	325,000
Modifications in the NIH heating plant at Bethesda	240,000
Repairs and improvements to the existing NIH plant at Bethesda	1,000,000

I will discuss each of these briefly.

Mr. PATTEN. Will any of this be to start new facilities at Bethesda?

Mr. SEGGEL. No, sir; the projects at Bethesda are all modifications of the existing plant. There are no new facilities at the NIH reservation in this budget. However, the Fogarty Center building will go up at NIH on the main reservation.

Mr. PATTEN. You can always cross the road and take a little land from the Navy.

Mr. SEGGEL. I don't think we could take it.

Mr. PATTEN. Did you ever try to get any land from the military?

Mr. SEGGEL. Not that I recall.

Mr. PATTEN. Don't try. Camp Dix is about 40 miles wide and 30 miles of it must be just woodlands. I couldn't buy a couple hundred square feet for a cemetery for veterans. They said they couldn't spare the land.

FACILITY FOR NIEHS

Mr. SEGGEL. The National Institute of Environmental Health Sciences is now located in leased space on the grounds of the Research Triangle Park in North Carolina, adjacent to a 500-acre site which was donated by the park to the Federal Government for the construction of permanent facilities. Planning funds totaling $1,785,000 were appropriated in 1961 and 1965 for the permanent facilities of the Institute. In 1968, a portion of these funds ($107,500) was used to prepare a master plan for the development of the site.

Our studies now indicate, however, that another $2 million in addition to the balance of $1,677,500 remaining available, will be needed to plan a viable first stage in the construction of the permanent facilities. This will include (1) planning site development, roads, a powerplant and other utilities, and (2) designing a research building containing approximately 120,000 net square feet of usable space. The site development and spporting facilities will be designed to support, or be expanded to support, the full development of the site in conformance with the master plan. As you know, Mr. Chairman and members of the committee, research in environmental health problems is a very high priority area. Therefore, we consider this request of $2 million to be a matter of great urgency.

INCINERATOR FOR THE ROCKY MOUNTAIN LABORATORY

To comply with air pollution standards, we are requesting $325,000 in 1972 for the design and construction of a new incinerator at the Rocky Mountain Laboratory, Hamilton, Mont. The existing incinerator, which was built more than 17 years ago, does not meet abatement standards and it cannot be modified to do so within practical limitations. In addition, its capacity is inadequate to handle the refuse load currently being generated. The potentially hazardous nature of the waste precludes the use of municipal resources.

MODIFICATION OF NIH HEATING PLANT

The heating plant on the main reservation is now capable of using only oil. To insure compliance with the recently enacted Maryland Air

Pollution Control Code, we are requesting $240,000 to provide for dual firing—that is, for either natural gas or oil. If the Washington Gas Light Co. should be unable to supply the estimated NIH requirement for natural gas, these funds will be used to equip the boilers with air pollution control equipment required to comply with applicable air pollution abatement criteria.

REPAIRS AND IMPROVEMENTS

The repair and upgrading of our real property are continuing needs. Examples of projects for which we are requesting $1 million in 1972 include: installation of additional fire protection equipment in several laboratory buildings; improvements to the clinical center air-conditioning system to correct air supply deficiencies; installation of emergency electrical generators for permanent buildings at the NIH Animal Center; repair of cooling towers in the central NIH heating and air-conditioning plant; and renovation of older laboratory buildings to correct safety hazards.

I and my associates will, of course, be happy to respond to any questions you may have.

First Phase Design of the NIEHS Facility

Mr. Patten. Thank you. Over half of this request, $2 million, is requested for design of the first phase of permanent facilities for the National Institute of Environmental Health Sciences at the Research Triangle Park, N.C. What is involved in the first phase?

Mr. Seggel. I would like to ask Dr. Payne to speak to this.

Dr. Payne. The first phase of the project to be constructed on the parmanent facility would supplement the interim facilities that we are leasing at present. Originally we had thought when the Institute was established, that we would be able to move in one time to the permanent site, but now it is more feasible to build additional laboratory facilities, on the permanent site, about 240,000 square feet of gross space, or 120,000 square feet of net laboratory space, to supplement the interim facility that we are using now.

TOTAL COST OF THE FIRST PHASE

Mr. Patten. If you need $2 million just for the design, what is going to be the ultimate cost of the finished project?

Mr. Holliday. In the neighborhood of $43 million.

Mr. Shriver. Forty-three million dollars is the first stage?

Mr. Seggel. This is the stage we are talking about. Firm plans haven't been made for any other stage, but this is a large area, 500 acres, and it has potential for further expansion. The $43 million figure, I want to make clear——

Mr. Shriver. That is just the first stage.

Mr. Seggel. Yes, but it includes building the basic core, the roadways, powerplant, supporting utilities, which can be expanded. It is the core.

Mr. Shriver. When do you plan to have it in use?

Mr. SEGGEL. I think the schedule calls for June 1975.

Mrs. REID. Are these the three buildings we were discussing yesterday?

Mr. PAYNE. The three buildings you were discussing yesterday is the most recent, just completed addition to our facilities. It is those facilities that we plan to continue to use, and as Mr. Holliday told you, these are very specialized animal and laboratory facilities. They will continue to use those after the first stage is constructed on the permanent site. The two together, the interim facilities and the first stage would bring us up to about the size that was originally projected for the first stage of the Institute.

Mr. SEGGEL. A lot of costs are involved, Mr. Shriver, in initiating a facility on a new reservation. The building we are talking about, the laboratory building, is no bigger than the new research building that we built for cancer recently at NIH, but we have to put in the utilities, roadways and the rest. Therefore it gets to be kind of expensive, but it is capable of further expansion as the need develops.

Mr. SHRIVER. What did the cancer building cost?

Mr. SEGGEL. The cancer building itself cost around $10 million, but this doesn't involve the cost of running in master utility lines or anything. They were all there.

Mr. SHRIVER. So you think the first stage will run about $43 million.

Mr. SEGGEL. That is the current estimate. Costs have been going up. I am reminded the costs have gone up almost 100 percent since 1965 in construction.

COST OF THE SECOND STAGE

Mr. SHRIVER. What would be the cost of second stage?

Mr. SEGGEL. There have been estimates, but we haven't really planned a second stage in any detail. That is why we are doing it this way. We want to get a viable first stage, a beginning, and then we will see what the further need is for further expansion.

Mrs. REID. Would you yield further?

Mr. PATTEN. Certainly.

Mrs. REID. This is not clear in my mind. Is this an expansion of what we were discussing yesterday?

Dr. PAYNE. It is expansion of the facilities for the Institute, but it would be the first construction on the permanent site. The permanent site is immediately across the road from the leased facilities you were discussing yesterday.

Mrs. REID. That is not a permanent site?

Dr. PAYNE. The buildings are permanent construction, very well built, very functional facilities that we are leasing. They are not temporary type of construction, but ones when no longer needed will be vacated of course. We would retain the three buildings that have just been completed to use those along with the first construction on the permanent site, which is just across the road.

Mrs. REID. When you say they will no longer be needed, does this mean that you will duplicate these at the permanent site?

Dr. PAYNE. They will be needed for a long period, and we would not duplicate them. They will be needed until at least the second stage of the permanent construction.

Mrs. REID. Which would be approximately how long, do you have any idea?

Mr. PATTEN. It will be after 1975, from the way you are talking.

Dr. PAYNE. Yes.

Mr. MILLER. Of course these costs are comparable with everything. The FBI building which started out less than $60 million is up to $100 million now. You just don't get a Federal structure any more for costs less than this.

RATIONALE FOR LEASING

Mrs. REID. Why was it necessary to build what are apparently temporary buildings, these three?

Dr. PAYNE. The Department, when it was given the 500 acre permanent tract, decided that temporary structures should not be put on the permanent site because of possible interference with the full utilization and orderly development of it, so they found they could lease buildings adjacent while the permanent plans were being developed. The permanent plans have taken longer to develop than was ancitipated originally, but the only way the Institute might develop and have facilities, to use was to move into leased buildings.

Dr. SHERMAN. Mrs. Reid, perhaps two things added might help here. One was the urgency to get something started, for which we had no laboratory facilities at the time. Then after the decision was made, to locate the facility in North Carolina. The rental space in temporary facilities became much more expeditious than attempting to wait for the permanent facilities.

The second consideration, I think, is the fact that learning from our own experience, as far as the most effective utilization of the reservation at Bethesda, we have taken—and this is a general decision, concurred in by the Department and the BOB—to try to develop as reasonably as possible the overall site plan, including particularly the plans for sufficient utilities and road network.

Mrs. REID. I did not understand that these were temporary buildings.

Mr. SHRIVER. The leased premises, are they temporary?

Dr. PAYNE. They are permanent type of construction, but we are only leasing them. We do not own them.

Mrs. REID. And they are inadequate?

Dr. PAYNE. With the recent completion of the three buildings, they are adequate for the moment, but the program cannot expand to its original projected level without additional laboratory space to be constructed on the permanent site.

Mrs. REID. From whom are you renting?

Dr. PAYNE. We are renting the first phase from Research Triangle Foundation. The second phase which has just been completed, we are renting from a private investor who has leased the ground from the Research Triangle Foundation.

Mrs. REID. What is the Research Triangle Foundation?

Dr. PAYNE. This is a quasi-State nonprofit foundation that has created Research Triangle Park. It has a board composed of representatives from the Triangle Universities, University of North Carolina, North Carolina State, and Duke University, which operates the Research Triangle Park, and attracts research organizations into the park.

Mrs. REID. How much rental are we paying a year?
Dr. PAYNE. I don't have those figures with me.
Mr. PATTEN. Supply it for the record.
(The information follows:)

Annual rental

Phase I	$179,000
Phase II	469,000
Total	648,000

Mr. PATTEN. What are Mr. Holliday's capabilities? He is on this team. Are you the architect, engineer, construction man?

Mr. HOLLIDAY. I am director of the Office of Engineering Services at the National Institutes of Health. My primary functions involve preliminary program planning associated with new building construction, as well as operation and maintenance of the existing facilities. I am a professional engineer, registered to practice in the District of Columbia.

MODIFICATION OF NIH HEATING PLANT

Mr. PATTEN. You are requesting $240,000 to modify the NIH heating plant to comply with the recently enacted Maryland air pollution control code. Is this the sole reason for this money?

Mr. SEGGEL. We certainly want to reduce the problem ourselves. Yes, we must either convert our plant for gas or install flue gas cleaning equipment.

SCARCITY OF GAS FUEL

Mr. PATTEN. At home our gas company is not supplying the Phillip Carey plant which is a big customer, and the gas industry has come to us pleading for help, so that in our area in New Jersey we are very short on gas.

Mr. HOLLIDAY. This is why Mr. Seggel indicated that there is a very likely possibility that the gas company will not be able to furnish the gas, and consequently we will look toward installing flue gas collecting devices, probably electrostatic precipitators, in order to comply with abatement criteria.

CONTROLLING INCINERATOR POLLUTION

Mr. PATTEN. They condemned the Perth Amboy incinerator. They won't let us use it. I hope somebody here knows something about incinerators.

Mr. SEGGEL. Mr. Holliday does.

Mr. PATTEN. I installed the incinerator in my town. That is a long time ago. This is the one they condemned. Believe me, they should condemn it. I have been trying to find out something about incinerators and the new standards, and how they are going to work. On military construction all over the country the military is spending money on their own incinerators. Everybody says bring the code up to date, but nobody has yet told me what the new construction will be, how we are going to get less smoke going out of that stack. Nobody has been able to pinpoint it, even when I talk to these army people. They are the logistics crowd. They are the engineers.

Mr. HOLLIDAY. The state of the art so far as incinerators are concerned, I believe I would have to say, is not as advanced as it need be. The trend, however, toward controlling or resolving the pollution problem, the emissions problem, is toward application of electrostatic precipitators, or through the use of a water wash centrifugal device, but the latter device has a number of difficulties with it. One, it leaves a plume of air at the point of emission to the atmosphere. It develops a plume, which is looked upon by many people as being smoke and therefore it is undesirable.

Mr. PATTEN. Does the District have an up-to-date incinerator that would meet these standards?

Mr. HOLLIDAY. I doubt that they do. I am not certain.

NONCOMPLIANCE OF FACILITIES WITH POLLUTION ABATEMENT CODES

Mr. PATTEN. Has it been developed that the incinerator is not in compliance, or is it just that you are doubtful and trying to be on the supersafe side?

Mr. HOLLIDAY. We are talking about our heating plant here. There is one abatement project for an incinerator at Hamilton, Mont. The other project is our heating plant on the reservation at Bethesda. It has been determined that both will not be in compliance with abatement criteria when the new abatement criteria go into effect, which I think in Montgomery County is July 1972 for heating plants, and around July 1973 for incinerator plants.

NIEHS FACILITY

Mr. PATTEN. I think your presentation with regard to the National Institute of Environmental Health Sciences facilities in North Carolina is still not clear. If you want these millions, perhaps you would like to embellish a little bit for the record. Mr. Shriver and Mrs. Reid have indicated their concern about this. Why can't we have more on the design and your projected plans, cost per square foot, type of construction, will they be made of wood, bamboo, steel, and so forth.

Mr. SEGGEL. We have all of the details here.

Mr. PATTEN. For the record you ought to detail all this.

Mr. HOLLIDAY. We are estimating that the cost of the first phase of construction will be somewhere in the neighborhood of $70 to $80 per gross square foot. This is equivalent to about $35 to $40 per gross square foot if we date back to 1965. One of the things that has caused people to be shocked by the price is the fact that we have had this inflationary situation in the past 8 or 9 years.

HISTORY OF NIEHS FACILITIES

Mr. PATTEN. I know this has had a long and somewhat confused history. Would you trace that history for us for the record?

Mr. SEGGEL. We can supply all the details.

(The information follows:)

HISTORY OF NIEHS FACILITIES

The following historical narrative places National Institute of Environmental Health Sciences facilities planning and development in perspective.

EARLY PLANNING EFFORTS
(Program Request by House Appropriations Committee)

"The Advancement of Medical Research and Education," a report prepared in 1958 under the chairmanship of Dr. Stanhope Bayne-Jones, called for greatly expanded efforts in environmental health research. The House Committee on Appropriations took note of this in its April 1959 report when it requested the Public Health Service to make a thorough study of needs to cope with environmental health problems. Results of this study were submitted to the Committee in February of 1960, which proposed the establishment of a strong research program in environmental health.

The requirements for additional space to house environmental health programs had also been under consideration by the Public Health Service and the 1961 President's Budget included a request for $785,000 in planning funds to expand the Sanitary Engineering Center in Cincinnati, Ohio.

First Appropriation for Facilities Planning

During the hearings on the 1961 Budget, Congress was informed that the new environmental health facilities would probably not be

located at Cincinnati, but that the Surgeon General would make a more thorough study of facility requirements taking into consideration the February 1960 report. The $785,000 requested for planning was included in the Fiscal 1961 Appropriation.

Preparation and review of plans for an environmental health program prevented the submission of any request to Congress in the original 1962 President's Budget in January of 1961. The 1962 House report commenting on the use of temporary and leased space being used for environmental health research activities stated, "The Committee regards this expedient as being necessary to enable long overdue work to go forward in the environmental health field but points out that such temporary measures are inefficient and costly and urges that planning and implementation for the permanent facilities go forward without delay."

During the Senate hearings on the 1962 appropriations, the President requested an amendment to the budget of $3,515,000. This, together with the $785,000 appropriated in 1961, would have provided $4,300,000 of which $2,070,000 was for site acquisition and $2,230,000 was for planning the first phase of an environmental health center. This proposal called for the construction of a facility to house about 1,600 personnel, containing 450,000 net square feet, costing $33,400,000 to construct, and which was to be located on a 690 acre site several miles north of Rockville, Maryland.

The Senate disapproved the request for $3,515,000 and stated in its 1962 report (July 25, 1961), "It is the view of the Committee that the contemplated site is an extremely poor selection and that inadequate justification was presented in support of the request."

"Gross Committee" Report

The "Committee on Environmental Health Problems," chaired by Dr. Paul M. Gross, and established by the Surgeon General to develop long-range objectives for the environmental health programs of the Public Health Service, submitted their report in November of 1961. It recommended the establishment of an environmental health center in the Washington, D. C., area. The President's February 27, 1962, Health Message recommended the establishment of this environmental health center.

A supplemental request was made in 1962 for $2,761,000 which together with the $785,000 appropriated in 1961 would have provided $3,546,000, including $1,320,000 for the acquisition of a site, and $2,226,000 for detailed plans and specifications. It proposed the purchase of 440 acres in the Washington area for a facility to house ultimately 4,500 to 5,000 personnel.

Proposed Washington Location First Questioned

In its October 1, 1962 report, the House Committee on Appropriations denied the requested supplemental, stating, "The Committee is favorably inclined to the creation of a National Environmental Health Center. However, it is of the opinion that the Washington, D. C., site is an improper location. The Committee therefore suggests that

the Center be passed over for study by the regular subcommittee when the budget estimates for the Public Health Service are considered in the regular bill next year."

In the report on the 1963 Supplemental Appropriation Bill, the Senate Committee concurred in the House action.

Presidential Request

In his February 7, 1963, Health Message, the President stated, "I ask that the Congress approve the funds requested in my 1964 budget for initial steps to establish a central facility in the Washington area which can serve as a focal point for related research, training, and technical assistance in environmental health."

The 1964 request was essentially the same as presented in the 1963 Supplemental. It was indicated that the Center would be located in the Washington area, but no specific site was mentioned.

1964 Request Denied Due to D. C. Location

During the House hearings, members of the Appropriation Subcommittee raised questions about the suitability of the Washington area for the location of the Center. In its April 25, 1963, report on the 1964 appropriation, the Committee eliminated the $2,761,000 item from the bill, stating that it was deferring action on the request because, "The Committee still has serious doubts that it is wise to locate the proposed Environmental Health Center in the Washington, D. C., area."

The Department appealed to the Senate for restoration of the planning funds. At the Senate hearing, the Subcommittee on appropriations was informed that the Secretary of Agriculture had agreed to make available a suitable site for the Center in Beltsville, Maryland, adjacent to the Agricultural Research Center. In its August 1, 1963, report on the 1964 appropriation, the Senate Appropriations Committee recommended a separate appropriation of $1,441,000 for the planning of an environmental health center to be located in Beltsville. The Conference Report (September 25, 1963) on the 1964 appropriation deleted the Senate item of $1,441,000 without specific comment, and thus no funds were appropriated for the proposed Center in that year.

Dual Locations Proposed in 1964

In the 1965 budget submission to Congress, a request of $1,500,000 was included for planning environmental health facilities. This, together with $785,000 appropriated in 1961, would have provided a total of $2,285,000 to prepare specifications for facilities containing 400,000 net square feet to accommodate about 1,600 personnel. The budget estimate did not include any mention of the location of these facilities or any funds for site acquisition.

On March 10, 1964, Secretary Celebreeze presented a supplemental statement to the Labor-HEW Subcommittee of the House Appropriations Committee. He stated that because of the objections of Congress to the Washington location, the Department had reviewed its proposal and

was now requesting that approximately 1,200 personnel be housed in a facility of 300,000 net square feet to be located at Beltsville, Maryland, and that about 400 personnel would be located in a field facility to be built outside the Washington Metropolitan area. He stated that the Committees would be informed later as to that proposed field location.

The House disallowed the request for planning funds and in its April 10, 1964, report on the 1965 appropriation, expressed dissatisfaction with the plans for locating the center stating, "At the time the Public Health Service testified on this item (March 2, 1964), they were not able to tell the Committee where the facility or facilities would be located if Congress appropriated the funds."

Prohibition Against Washington Area Site

The Secretary's statement of March 10, detailing the revised plan was presented to the Senate subcommittee on Appropriations and the Senate included the full $1,500,000 in its recommended bill.

The bill went to Conference and the Conference Report (dated September 2, 1964) stated, "The appropriation provides $1,000,000 for planning a central environmental health facility. The conferees are agreed that this facility shall not be located within a radius of 50 miles of the District of Columbia." The $1,000,000 was contained in the appropriation for FY 1965.

After the 1965 appropriation was enacted, the Public Health Service proceeded with the development of its plans for providing permanent environmental health facilities.

North Carolina Site Selected

On January 7, 1965, Secretary Celebreeze announced the revised plans for construction of these facilities and the functions to be carried on in them. As stated in his press release, the National Environmental Health Sciences Center was to be located in the Research Triangle Park in North Carolina "to serve as a center for research relating to the environmental health program of the Public Health Service and to study the effects on man of environmental contamination." The selection of the North Carolina Research Triangle followed a review of some 40 locations. The State of North Carolina gave a 509 acre site to the Government at no cost. The $1,000,000 in planning funds were to be used to design a center housing approximately 1,000 persons. Interim facilities were leased in the Research Triangle pending completion of the permanent buildings. (See maps)

Creation of Environmental Health Sciences Program

On November 1, 1966, the new Division of Environmental Health Sciences was established in the National Institutes of Health and Dr. Paul Kotin was appointed Director of the Division. (In January of 1969 the Division of Environmental Health Sciences was renamed the National Institute of Environmental Health Sciences.)

Air Pollution Program to Share Site

Prior to the Public Health Service reorganization, in June 1966, the Federal Water Pollution Control Administration, including the Robert A. Taft Sanitary Engineering Center in Cincinnati, Ohio, had been transferred to the Department of the Interior. At the same time, the Public Health Service Division of Air Pollution was upgraded to the status of a National Center for Air Pollution Control. With the loss of the Robert A. Taft Center, it became necessary for the Public Health Service to search for other space in which to conduct air pollution control activities. In the course of this search, 31 locations were examined before the Research Triangle Park was also selected as the site for the National Center for Air Pollution Control. (In December of 1970 the NCAPC was transferred to the newly created Environmental Protection Agency (EPA) and recently has been renamed Office of Air Programs.)

The 1968 budget included an additional $1,815,000 for the costs of designing permanent facilities for the National Center for Air Pollution Control on the selected site.

Leased Facilities

In anticipation that 5 to 6 years would be required to design and construct the National Environmental Health Sciences Center and the Air Pollution Program research center, it was decided to enter into short-term leases of facilities in the Research Triangle Park to house the staffs of the two organizations. These permanent, privately

owned facilities contain administrative and laboratory and special purpose research space leased by the Government, 67,000 square feet has been leased for the National Environmental Health Sciences Center. In addition, the Center utilizes 9,600 square feet of temporary Government-owned office space and 11,000 square feet of Government-owned temporary warehouse space adjacent to the leased buildings.

EPA Leased Facilities Nearby

49,000 square feet in two locations in Durham has been leased for the Air Programs Office of EPA and about 193,000 additional square feet of temporary administrative and laboratory space provided by a private developer for lease to APO. Much of this area is replacement space for programs formerly housed in the Taft Center.

Permanent Site Utilization Plans

Early in FY 1969 APO and NIEHS, through the Department of Health, Education, and Welfare, entered into a contract for preparation of a Master Plan for overall development of the 509 acre Permanent Site. This contract represented the first obligation against the $3,600,000 available to the two agencies for planning ($785,000 to NIEHS in FY 1961; $1,000,000 to NIEHS in FY 1965; $1,815,000 to APO in FY 1968). The contract for site planning has been completed at a cost of approximately $225,000.

The report of the Senate Appropriations Committee on fiscal 1969 appropriations included an admonition to expedite the already protracted process of constructing permanent research facilities.

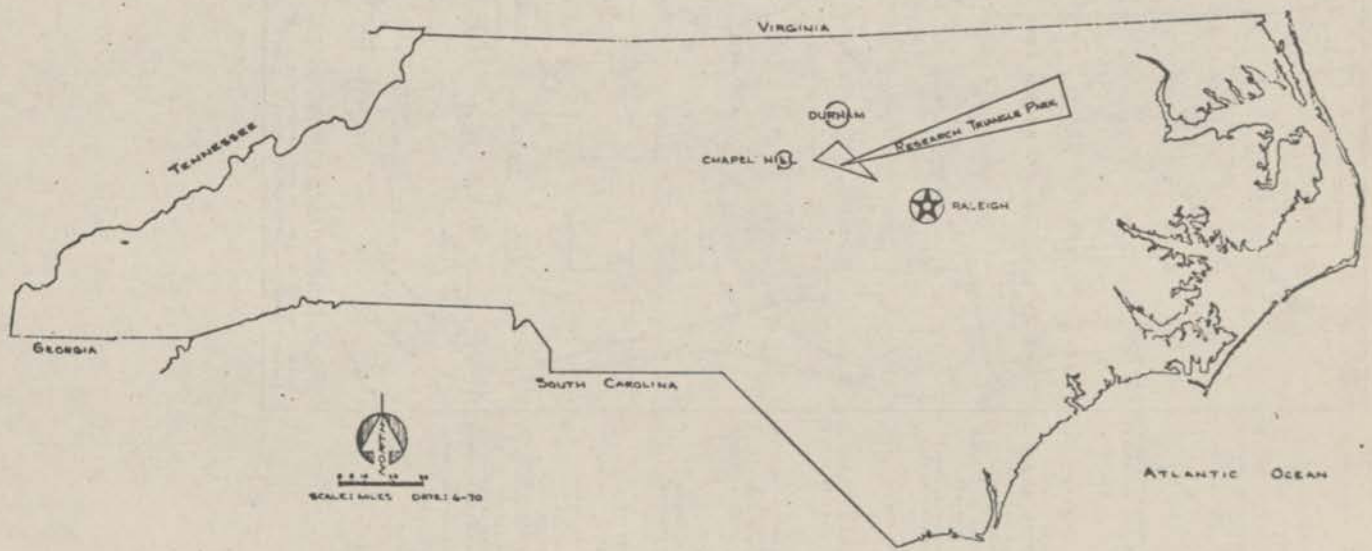
Specific Facilities Now to be Developed

With completion of the Master Site Planning contract, which prescribes overall use of the 509 acre plot, NIEHS is ready to contract for design of specific facilities. A Program of Requirements will be provided to an architectural-engineering firm with a request for detailed plans for: 1) roads systems, utilities systems, landscaping and other site-preparation requirements, -- allowing for ease of future expansion; and 2) some 120,000 square feet of laboratory and special purpose space. (The number and character of buildings to be provided will be determined by the architect.) The current request for $2,000,000, added to the remaining balance of previous appropriations ($1,785,000) is to pay for these detailed plans.

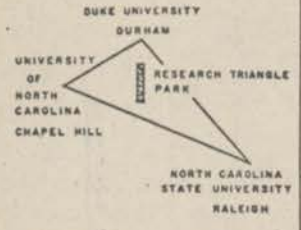
This cost estimate equates to approximately 76 dollars per gross square foot, and compares to 35 dollars per gross square foot in terms of 1966 dollars (determined by applying the Engineering News Record Building Cost Index). The Mental Health-Neuro-Cancer facility, constructed at the NIH in 1966, cost approximately 35 dollars per gross square foot.

Beneficial occupancy of these facilities is anticipated in four years. Meanwhile program growth will be restricted by facilities availability.

National Institute of Environmental Health Sciences



Interim Facilities North Carolina



1 RESEARCH TRIANGLE INSTITUTE

2 CHEMSTRAND RESEARCH CENTER, MONSANTO COMPANY

3 FORESTRY SCIENCES LABORATORY of the U.S. FOREST SERVICE

4 AMERICAN ASSOCIATION OF TEXTILE CHEMISTS AND COLORISTS

5 NORTH CAROLINA SCIENCE AND TECHNOLOGY RESEARCH CENTER

5 TRIANGLE UNIVERSITIES COMPUTATION CENTER

6 Interim Facilities:
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES of the U.S. PUBLIC HEALTH SERVICE

7 Permanent Site:
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
NATIONAL AIR POLLUTION CONTROL ADMINISTRATION
of the U.S. PUBLIC HEALTH SERVICE

8 TECHNITROL, INC.

9 INTERNATIONAL BUSINESS MACHINES CORPORATION

10 BEAUNIT CORPORATION

11 HERCULES, INCORPORATED

12 REGIONAL EDUCATION LABORATORY

13 EDUCATIONAL TESTING SERVICE

14 NATIONAL CENTER FOR HEALTH STATISTICS of the U.S. PUBLIC HEALTH SERVICE

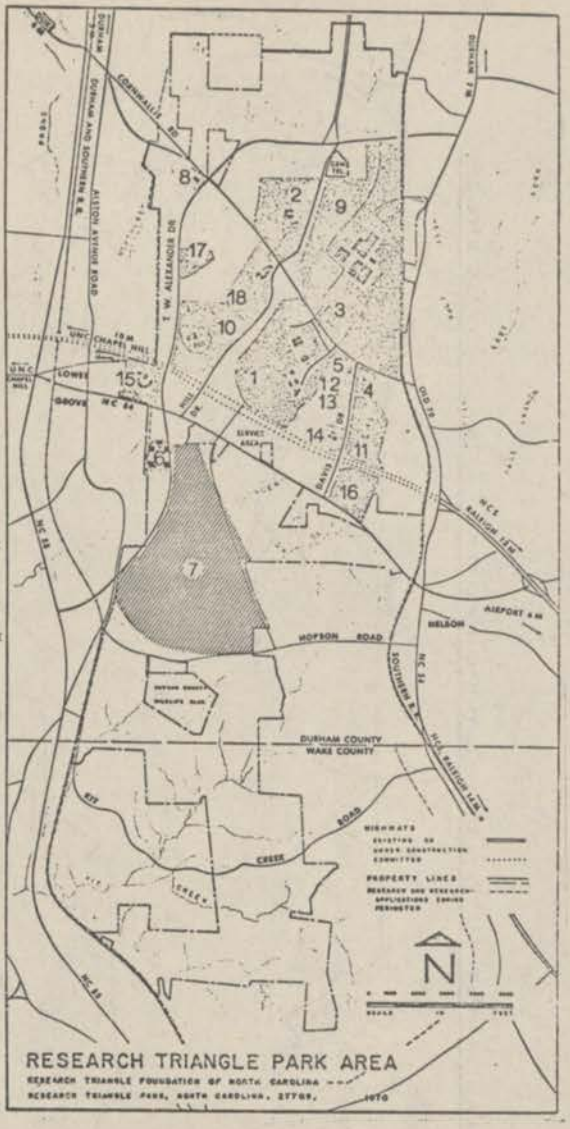
* 15 Interim Facilities:
NATIONAL AIR POLLUTION CONTROL ADMINISTRATION of the U.S. PUBLIC HEALTH SERVICE

16 BECTON, DICKINSON AND COMPANY

17 RICHARDSON-MERRELL, INC.

18 BURROUGHS-WELLCOME & CO. (USA) INC.

* AT 14 IN 1970



BREAKDOWN OF CONSTRUCTION COSTS

Mr. HOLLIDAY. I might add that on the figures we gave you, they break down this way. Construction costs for the site development are approximately $22 million, and the construction costs for the program area are in the neighborhood of $21 million. We will be doing site development in such a way that growth can take place without having to go back and tear out facilities and replace them. We can extend and expand in an orderly way. However, we will not be installing the utility capacity except where necessary in the distribution system. We will not be installing the utility capacity for the future, but designing it in such a way that it can be added to.

Mr. PATTEN. When it comes to hospitals I am very suspect. I hope these estimates won't turn out the same way.

Mr. SEGGEL. These figures have been gone over because we were all concerned.

Mr. PATTEN. Mr. Shriver.

FUTURE DEVELOPMENT OF THE NIH FACILITY

Mr. SHRIVER. What do you plan to have at this center where we are going to be spending $43 million for the first stage, and we don't know what for the second and third stages? What do you have in mind there? What institutes, all of them? Are you moving the entire program down there?

Mr. SEGGEL. No, just the National Institute of Environmental Health Sciences.

Mr. SHRIVER. Only one?

Mr. SEGGEL. Yes, sir. It is very much of a developing area as you know. It is one of our smaller institutes at this point.

Mr. SHRIVER. You are anticipating a second and third stage down the line?

Mr. SEGGEL. I don't think we are talking about anything but a second stage, sir. The precise size of that is not known at this point. We have some estimates, but I would prefer not to present them, since they are nebulous in a sense. We would rather see how things develop within the first stage before we start talking about the second stage.

FACILITIES ENGINEERING AND CONSTRUCTION AGENCY

Mr. SHRIVER. Where does the General Services Administration fit into your building program? Are they involved?

Mr. SEGGEL. They usually let the contracts, and we have to work with them. We have to develop the program plans. Of course we have a central construction agency now in HEW, with whom we have to work, the Facilities Engineering and Construction Agency. We work through them now on most projects as with GSA, but the actual planning we have to do with our own scientific personnel.

Mr. SHRIVER. I notice the Post Office Department is having the Corps of Engineers supervise the building of their new structures over the country.

Mr. SEGGEL. Yes, I have heard that.

Mr. HOLLIDAY. In the past at NIH we have supervised some of the smaller projects with our own staff. Where the projects are larger we

engaged the Public Buildings Service of GSA to handle it for us. In the future the Facilities Engineering Construction Agency DHEW will provide the support service for the larger projects.

FIRST-PHASE COSTS

Mr. SEGGEL. May I reiterate that these costs have been gone over very carefully, as carefully as we could, and the building we are talking about is as I say big enough to be viable but not bigger than that. It is a building approximately the size of the new cancer research building, 120,000 square feet usable space, but as Mr. Holliday has pointed out, a lot of this expense is in the development of the site, the roads, utilities, et cetera. This is a 500-acre plot we are talking about.

Mr. HOLLIDAY. The stage concept creeps into the discussion, because in looking at the 500 and some acres of land, we must look at it in a long-range sense, so we have tried to develop it so that construction could develop in the area. Consequently there are a number of different possibilities for growth. In addition to the site that would be occupied by our National Institute of Environmental Health Sciences, there is a possibility for three additional sites. Some consideration is being given by the Environmental Protection Agency for the use of one of the sites.

Mr. SEGGEL. That is, sites within these same 500 acres we are talking about.

NIEHS GROWTH PLAN UNCERTAINTIES

Mrs. REID. When you say that you cannot estimate the second phase until you know a little bit more about how the first phase is going to develop, it sounds to me as though we are putting money into something that is very nebulous.

Mr. SEGGEL. We need this money just for the first stage, and that is not in our judgment nebulous. That is a very fixed and firm plan. We need this amount of money just for the first stage. What we are doing though is designing it in such a way that it could be expanded if, indeed, the program decision were made that we needed further development at that site.

Mrs. REID. But you are not sure that you will?

Mr. SEGGEL. We are not sure that we will, although as you know, program people have their desires in this regard. However, we have to keep this within reasonable cost proportions, frankly.

Mrs. REID. Which we appreciate.

Mr. SEGGEL. Yes. This has been an area where everybody has tried to keep the costs down, keep the amounts down.

Dr. PAYNE. Another uncertainty is when we give up the originally leased facilities and how long we retain the additional interim facilities after completion of the first stage on the permanent site.

CARRYOVERS OF FISCAL YEAR 1971 FUNDS

Mr. SHRIVER. The justifications show that NIH will have $7,658,000 in unobligated balance available for fiscal 1972, from prior appropriations.

Mr. SEGGEL. Yes, sir.

Mr. SHRIVER. The estimated obligations for fiscal 1972 are $6,981,000.

Mr. SEGGEL. Yes, sir.

Mr. SHRIVER. Why is it necessary then to request an additional $3,565,000?

Mr. SEGGEL. I am glad to clarify that, Mr. Shriver. The money that is carried over at the end of fiscal year 1971, the $7,658,000, is money that is earmarked for certain projects to be carried on in 1972. These are projects that have already been authorized. For example, on the environmental health science project, the project we were just talking about, there is a balance of $1,677,000 in that account, as I mentioned in my opening statement.

That is being carried over to add to the $2 million we are requesting in the 1972 budget, to form a viable planning package for the development of the first stage. That is one item that is carried over. Another item is a project we are reprograming from Puerto Rico. We had some plans to build there, but we decided it is not feasible to continue those plans and we are reprograming those for an addition to the clinical center at the main NIH reservation. However, it is a project that was funded by this committee for the same purpose. We also have some other items in here. We have a dental health center facility for which plans have already been made and developed. They are already completed, and we have some money appropriated in the past for construction of that facility, but it isn't enough. We have to carry that over, in other words, for the actual construction. That is all earmarked money for authorized projects.

Mr. MILLER. Mr. Shriver, this has been gone over very carefully, because NIH, and I think Indian health, are the only two areas in the Department, also the National Technical Institute for the Deaf, the only three areas in the Department where we are asking for new obligational authority under construction. Wherever we are doing work it is mostly with unobligated balances.

Mr. SHRIVER. I wanted the explanation in the record because of what appeared in your justifications.

Mr. SEGGEL. I would be glad to furnish details for the record.

Mr. SHRIVER. It might be a good idea.

(The information follows:)

NIH BUILDINGS AND FACILITIES APPROPRIATION
Project Status by Construction Category
1971 and 1972

	Unobligated Balance 7/1/70	1971 Estimated Obligations	Unobligated Balance 7/1/71	1972 Budget Request	1972 Estimated Obligations	Unobligated Balance 7/1/72
1. Completed Projects - Settlement of Contract Claims						
Cancer-Mental-Neurology Cafeteria	$ 12,321	$ 12,321	$ --	$ --	$ --	$ --
Cancer Research Building	845,386	845,386	--	--	--	--
General Office Building Extension	55,489	55,489	--	--	--	--
Gerontology Research Facility	25,054	25,054	--	--	--	--
Master Utilities Extension - Phase I	86,396	63,396	23,000	--	23,000	--
Stone House Renovations	11,230	11,230	--	--	--	--
Subtotal	$ 1,035,876	$1,012,876	$ 23,000	$ --	$ 23,000	$ --
2. Completion of Projects Under Construction Contract						
Multilevel Parking - Cancer-Mental-Neurology	$ 109,781	$ 109,781	$ --	$ --	$ --	$ --
NIH Animal Center - Phase IA	75,408	65,408	10,000	--	10,000	--
Subtotal	$ 185,189	$ 175,189	$ 10,000	$ --	$ 10,000	$ --
3. Completion of Projects Under Design Contract						
Child Health and Human Development Research Facility	$ 67,064	$ 67,064	$ --	$ --	$ --	$ --
Dental Health Center Addition	3,233,428	24,428	3,209,000	--	--	3,209,000
Multilevel Parking - General Office Building	21,618	21,618	--	--	--	--
Neurology-Child Health Facility, Puerto Rico	31,600	31,600	--	--	--	--
NIH Animal Center - Phase II	126,035	80,000	46,035	--	16,035	30,000
Subtotal	$ 3,479,745	$ 224,710	$3,255,035	$ --	$ 16,035	$3,239,000
4. Repairs and Improvements	$ 627,016	$ 536,197	$ 90,819	$1,000,000	$1,000,000	$ 90,819
5. Construction Contracts to be Awarded						
Modifications to NIH Heating Plant	$ --	$ --	$ --	$ 240,000	$ 240,000	$ --
NIH Incinerator Facility	4,000,863	3,600,863	400,000	--	326,965	73,035
Reproductive and Perinatal Biology Facility	1,970,000	--	1,970,000	--	1,810,000	160,000
Sewage Treatment Plant - NIH Animal Center	447,034	280,000	167,034	--	150,000	17,034
Subtotal	$ 6,417,897	$3,880,863	$2,537,034	$ 240,000	$2,526,965	$ 250,069
6. Design Contracts to be Awarded						
Environmental Health Sciences Center	$ 1,677,500	$ --	$1,677,500	$2,000,000	$3,300,000	$ 377,500
Lister Hill National Center for Biomedical Communications	765,000	700,000	65,000	--	65,000	--
Reproductive and Perinatal Biology Facility	185,081	185,081	--	--	--	--
Rocky Mountain Laboratory - Incinerator	--	--	--	325,000	40,000	285,000
Subtotal	$ 2,627,581	$ 885,081	$1,742,500	$2,325,000	$3,405,000	$ 662,500
TOTAL	$14,373,304	$6,714,916	$7,658,388	$3,565,000	$6,981,000	$4,242,388

SHORTAGE OF NATURAL GAS IN WASHINGTON AREA

Mr. SHRIVER. You mentioned the possibility that the Washington Gas Light Company might not be able to supply your requirements of natural gas. Will you explain that further? We have lots of gas out our way that can be brought in here.

Mr. HOLLIDAY. With the advent of more rigid air pollution abatement criteria, many people are converting their facilities from oil to gas. This seems to be a more economical approach than to purchase and maintain flue gas cleaning devices. We have carried on some negotiations with the Gas Company several times within the last 3 or 4 years. They had indicated that they were trying to make a determination if they could furnish the National Naval Medical Center across the street as well as the National Institutes of Health. The latest thing we have learned from them is they feel now they cannot provide the gas.

Mr. SHRIVER. Because of increased demand in the whole area for use of natural gas. Thank you, Mr. Chairman. That is all.

Mr. PATTEN. Mrs. Reid?

Mrs. REID. Thank you, Mr. Chairman.

REASONS FOR LOCATING NIH IN NORTH CAROLINA

What were the advantages in locating in North Carolina as opposed to any other site?

Mr. SEGGEL. That decision was made some years ago, and before, as a matter of fact, NIH got the responsibility for this particular program. There were originally plans in another part of the Public Health Service before the Environmental Health Science program came to NIH, for doing it in the Washington area.

The Congress, and I am calling on my memory now, was very much opposed to further construction in this area and there were a number of competing forces at the time who wanted this facility located in their particular area.

Mrs. REID. I am sure there were.

Mr. SEGGEL. One of these was West Virginia, as I recall, and one of them was Ohio, and another was North Carolina, and North Carolina made, through the Research Triangle Park organization, a very generous offer of land, 500 acres. That was a major factor, as I understand the history of this, but this was some years ago.

Dr. PAYNE. May I add a little to some of the advantages that we are actually enjoying by being there? We are in the triangle, as I mentioned before, between the three major universities, two of which have medical schools, with a variety of research organizations, both industrial and governmental, within the Research Triangle Park. This gives us an excellent opportunity to cooperate and work with the medical schools and the other research organizations there. This is a big advantage in recruiting professional personnel. It gives our people an opportunity to affiliate themselves through adjunct appointments with one of the major universities and maintain an academic affiliation. It also puts us adjacent to a sister agency with which we have a great deal of contact, the Environmental Protection Agency.

They have a major temporary facility there and will share the permanent site with us.

COORDINATION WITH ENVIRONMENTAL PROTECTION AGENCY

Mrs. Reid. You mentioned the possibility that the new Environmental Protection Agency might in time be a part of this complex. I should think that would make a lot of sense. We were talking about this yesterday, about coordination and trying not to overlap programs.

Mr. Seggel. The Air Pollution Control Agency has had for some time plans to develop a program on this site. That was at the time when it was within the Department of Health, Education, and Welfare. Of course, as you know, it has since been transferred to the Environmental Protection Agency. I am not sure of their current plans, but we are providing for that and we are in close contact with them.

Dr. Payne. Very recent discussions indicated they still plan to develop facilities on the site in accordance with the master plan that was developed.

ROCKY MOUNTAIN LABORATORY RESEARCH

Mrs. Reid. What type of research is carried out at the Rocky Mountain Laboratory?

Mr. Seggel. I am not sure I am capable of answering that in detail, but this used to be known as a tick laboratory and that is where it started, and it is mainly infectious diseases. Rickettsial diseases is where they had their main competence, but I would be glad to elaborate on that for the record. I would like to check with the program people, if I may.

(The information follows:)

ROCKY MOUNTAIN LABORATORY

This laboratory provides unique laboratory and animal facilities for work with a variety of pathogens hazardous to man and which cannot be worked on at the Bethesda campus. These include rickettsial diseases such as Q fever and typhus fever, tularemia, rabies, and tuberculosis. The special animal facilities for "slow" virus diseases permit the 2 to 3 year holding of animals in isolation required between inoculation and onset of diseases. The laboratory also houses the National Museum collection of ticks and mites and is the International Center for identification of ticks and mites associated with human diseases. It is the WHO Center for Rickettsial Diseases for the Western Hemisphere.

Mrs. Reid. Thank you. Thank you, Mr. Chairman.

DESIGN OF NIEH BUILDINGS

Mr. Patten. Just one parting shot. Is this going to be a one-story facility in North Carolina?

Mr. Holliday. We haven't proceeded that far with the design to determine exactly the number of floors. I am sure that it will be a multiple-story building, perhaps in the neighborhood of four to six floors. The planning that we have done to date has primarily been associated with land use and site selection for locating buildings, development of circulation patterns, landscaping, and utility support. We have not yet moved into the actual stage of developing the mass

space relationships of the buildings themselves, although we do have some conceptual ideas.

Mr. PATTEN. You know, all over New Jersey we have hundreds of buildings in industrial parks which have 100,000 square feet or more, and I know what they cost, but they are just four walls and a roof. When you speak of spending over $3,700,000 for design I assume this is a special-purpose building.

Mr. SEGGEL. Oh, yes.

Mr. PATTEN. And wouldn't be comparable to any building of 120,000 square feet for some manufacturer in one of my industrial parks?

Mr. SEGGEL. No, sir; that is right. The utility system is entirely different. This includes animal facilities, and so on, a whole bunch of specialized laboratories.

Mr. HOLLIDAY. Much of the major element of cost is vested in the mechanical/electrical complex in these kinds of highly specialized buildings.

HAZARDOUS NATURE OF ROCKY MOUNTAIN LAB WASTES

Mr. PATTEN. When you were speaking of the exhaust from the Rocky Mountain incinerator you said there might be some special dangers in this facility. Like what?

Mr. SEGGEL. That is because the laboratory there is working on infectious diseases.

Mr. HOLLIDAY. We regard materials removed from some of the laboratories where they are doing hazardous work to be potentially hazardous. Consequently, special care is given in some of the handling to protect the people who are handling it. For this reason we do not consider that a municipal incinerator or municipal land fill would be appropriate for disposal of this type of material.

Mr. PATTEN. Are there municipal facilities that could be used?

Mr. HOLLIDAY. Hamilton is a very small town. I believe there was some open burning when I was there last, but I haven't kept up with that.

Mr. PATTEN. Is there anything further?

PRESIDENT'S ANNOUNCEMENT REGARDING CANCER RESEARCH PROGRAM

Dr. MARSTON. Mr. Chairman, I am back and I thought you might be interested in this. I am sorry that it was necessary to miss these hearings this morning but the President has just made a public announcement on television with Secretary Richardson and Dr. David and with me on a bill that he is introducing this afternoon for a cancer cure program which will maintain the cancer research activities in the National Institutes of Health but will have the Director of the program report directly to him as a way of, as he said, assuring the Presidential presence behind this program which he is personally interested in.

Mr. PATTEN. That is swell. Will that solve some of our issues being raised here in the Congress, do you think?

Dr. MARSTON. I think we will have to wait until we see the outcome of the conference of the Senate subcommittee before one will be able to answer that.

Mr. PATTEN. That is fine, Doctor. Thank you very much, gentlemen.

We are adjourned until 10 o'clock in the morning.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Amounts Available for Obligation

	1971	1972
Appropriation	$ ---	$3,565,000
Unobligated balance, start of year	14,373,000	7,658,000
Unobligated balance, end of year	-7,658,000	-4,242,000
Total, obligations	6,715,000	6,981,000

Obligations by Activity

Page Ref.		1971 Estimate	1972 Estimate	Increase or Decrease
131	Research facilities	$1,879,000	$5,175,000	+$3,296,000
132	Service and administrative facilities	4,836,000	1,806,000	-3,030,000
	Total obligations	6,715,000	6,981,000	+266,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
NATIONAL INSTITUTES OF HEALTH			
Travel and transportation of persons	$ ---	$ 5,000	$ +5,000
Printing and reproduction	45,000	50,000	+5,000
Other services	1,823,000	4,935,000	+3,112,000
Supplies and materials	---	10,000	+10,000
Lands and structures	3,200,000	1,890,000	-1,310,000
Total, National Institutes of Health	5,068,000	6,890,000	+1,822,000
ALLOCATION TO GENERAL SERVICES ADMINISTRATION			
Travel and transportation of persons	$ 2,000	$ ---	$ -2,000
Printing and reproduction	5,000	---	-5,000
Other services	464,000	16,000	-448,000
Lands and structures	1,176,000	75,000	-1,101,000
Total, General Services Administration	1,647,000	91,000	-1,556,000
Total obligations by object	6,715,000	6,981,000	+266,000

Summary of Changes

1971 Budget Authority	$ ---
1972 Budget Authority	3,565,000
Net change	+3,565,000

Program Increases:	Base	Change from Base
1. Research facilities	$ ---	+$2,000,000
2. Service and administrative facilities	---	+1,565,000
Total	---	+3,565,000

Explanation of Changes

1. Research facilities -- The $2,000,000 increase is for the National Environmental Health Sciences Center.

2. Service and administrative facilities -- The $1,565,000 increase represents increases of $1,000,000 for repairs and improvements, $325,000 for an incinerator at the Rocky Mountain Laboratory, and $240,000 for modifications in the NIH heating plant at Bethesda.

Buildings and Facilities

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1961	$ 3,135,000	$ 3,135,000	$ 3,470,000	$ 3,470,000
1962	21,745,000	18,230,000	18,230,000	18,230,000
1963	29,761,000	31,000,000	33,200,000	33,200,000
1964	19,072,000	13,811,000	16,311,000	16,311,000
1965	21,512,000	21,512,000	23,012,000	22,512,000
1966	7,781,000	9,431,000	8,977,000	8,977,000
1967	18,279,000	18,279,000	18,279,000	18,279,000
1968	10,715,000	10,715,000	15,075,000	10,715,000
1969	12,495,000	---	5,310,000	---
1970	1,000,000	1,000,000	1,900,000	1,900,000
1971	---	---	---	---
1972	3,565,000			

Note - Prior to 1970, funds include all DHEW health activities. Separate NIH appropriation enacted in 1970.

General Statement

This appropriation includes all proposed direct construction items of the National Institutes of Health and all continuing projects except the Mental Health-Neurology Research Facility, which was appropriated under "Mental Health Activities" and "Neurology and Blindness Activities" in 1961, and the John E. Fogarty International Center for Advanced Study in the Health Sciences, for which planning funds were appropriated in 1968 under "John E. Fogarty International Center for Advanced Study in the Health Sciences".

Research Facilities

National Environmental Health Sciences Center

1972 appropriation estimate..... $2,000,000

Funds requested in 1972 of $2,000,000, together with planning funds appropriated in 1961 and 1965, will provide for the design of the first phase of permanent facilities for the National Institute of Environmental Health Sciences at Research Triangle Park, North Carolina.

This phase will provide an estimated 240,000 gross square feet of program space plus site development and supporting utilities. The site development and supporting utilities will be central facilities in support of all users of the site at Research Triangle Park, North Carolina.

The research mission of the National Institute of Environmental Health Sciences is to identify the chemical, physical, and biological factors in the environment that can adversely affect man; to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents; and to provide the scientific basis for the development of control measures by other agencies.

Estimated Progress Schedule

Design
- Award..... April 1972
- Completion..... Incrementally April 1973 to April 1974

Construction
- Award..... Incrementally July 1973 to July 1974
- Completion..... Incrementally August 1975 to August 1976

Repairs and Improvements

1972 appropriation estimate..... $1,000,000

In 1972, $1,000,000 is requested for repairs and improvements to the existing NIH plant. The NIH plant is quite extensive and many of the buildings and facilities are now approaching 20 or 30 years of service. The need for repairs and improvements is a continuing one. Examples of projects which require financing in 1972 include: installation of additional fire protection equipment in several laboratory buildings; improvements to the electrical system at the Rocky Mountain Laboratory; improvements to the Clinical Center air conditioning system to correct air supply deficiencies; installation of emergency electrical generators for permanent buildings at the NIH Animal Center; repairing cooling towers in the central NIH heating and air conditioning plant; renovation of older laboratory buildings to correct safety hazards; remodel freight elevator in the initial NIH building constructed in 1938; and improvements to cage washing equipment.

Incinerator - Rocky Mountain Laboratory, Hamilton, Montana

1972 appropriation estimate..... $325,000

In 1972, $325,000 is requested for the replacement of the incinerator at the Rocky Mountain Laboratory, Hamilton, Montana. The existing incinerator cannot comply with the criteria for air pollution control, nor can it be modified to do so within practical limitations. In addition, its capacity is inadequate to handle the refuse load currently being generated. Municipal resources cannot be employed due to potentially hazardous waste.

The structural condition of the existing incinerator, its lack of control equipment, and its general antiquated design dictate a complete replacement rather than a modernization of the existing facility. The limited capacity of the existing equipment has made it necessary to resort occasionally to open burning, a practice that must be eliminated.

Estimated Progress Schedule

Design
- Award..... April 1972
- Completion..... February 1973

Construction
- Award..... June 1973
- Completion..... June 1975

Modification to NIH Heating Plant, Bethesda, Maryland

1972 appropriation estimate..... $240,000

In 1972, $240,000 is requested for the conversion of the NIH heating plant to dual firing (capable of using either natural gas or oil), to ensure compliance with the recently enacted Maryland Air Pollution Control Code. If the Washington Gas Light Company is unable to supply the estimated NIH requirement of natural gas, these funds will be used to equip the boilers with air pollution control equipment required to comply with applicable air pollution abatement criteria.

WEDNESDAY, MAY 12, 1971.

NATIONAL LIBRARY OF MEDICINE

WITNESSES

DR. MARTIN M. CUMMINGS, DIRECTOR
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. G. BURROUGHS MIDER, DEPUTY DIRECTOR, NATIONAL LIBRARY OF MEDICINE
DR. LEROY L. LANGLEY, ASSOCIATE DIRECTOR, EXTRAMURAL PROGRAMS, NATIONAL LIBRARY OF MEDICINE
KENT A. SMITH, EXECUTIVE OFFICER, NATIONAL LIBRARY OF MEDICINE
B. FRANK GARDNER, JR., ACTING ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 estimate	1972 estimate
Personnel compensation:			
Permanent positions	5,671	5,995	6,287
Positions other than permanent	134	203	203
Other personnel compensation	83	89	89
Total personnel compensation	5,888	6,287	6,579
Personnel benefits: Civilian employees	501	547	567
Travel and transportation of persons	165	167	167
Transportation of things	16	33	33
Rent, communications, and utilities	1,176	1,704	1,704
Printing and reproduction	247	481	498
Other services	6,110	4,756	4,925
Supplies and materials	291	379	265
Equipment	475	467	373
Grants, subsidies, and contributions	5,697	5,818	5,906
Total costs, funded	20,566	20,639	21,017
Change in selected resources	−778	608	499
Subtotal	19,788	21,247	21,516
Quarters and subsistance charges	−30	−40	−30
Total obligations	19,758	21,207	21,486

PERSONNEL SUMMARY

Total number of permanent positions	467	467	474
Full-time equivalent of other positions	16	18	18
Average number of all employees	483	485	489
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 estimate	1972 estimate
Program by activities:			
1. Medical library assistance	5,697	5,818	5,906
2. Direct operations:			
(a) Lister Hill National Center for Biomedical Communications	997	1,388	1,103
(b) National Medical Audiovisual Center	2,219	2,081	1,989
(c) Library operations	7,836	7,626	7,869
(d) Toxicology information	1,351	1,241	1,215
(e) Review and approval of grants	703	627	685
(f) Program direction	1,733	1,818	2,220
Total, direct operations	14,839	14,781	15,081
Total program costs, funded [1]	20,536	20,599	20,987
Change in selected resources [2]	−778	608	499
Total obligations	19,758	21,207	21,486
Financing:			
Unobligated balance available, start of year	−700		
Unobligated balance lapsing	84		
Budget authority	19,142	21,207	21,486
Budget authority:			
Appropriation	19,682	20,769	21,486
Portion withdrawn (Public Law 91-204, sec. 410)	−310		
Transferred to other accounts	−230	−4	
Appropriation (adjusted)	19,142	20,765	21,486
Proposed transfer for wage-board pay increases		14	
Proposed transfer for civilian pay act increases		410	
Proposed transfer for military pay act increases		18	
Relation of obligations to outlays:			
Obligations incurred, net	19,758	21,207	21,486
Obligated balance, start of year	26,430	21,900	17,672
Obligated balance, end of year	−21,900	−17,672	−17,003
Adjustments in expired accounts	−15		
Outlays, excluding pay increase supplemental	24,273	25,015	22,133
Outlays from wage-board supplemental		13	
Outlays from civilian pay act supplemental		390	22
Outlays from military pay act supplemental		17	

[1] Includes capital outlay as follows: 1970, $475,000; 1971, $467,000; 1972, $373,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1970, $6,847,000; 1971, $7,455,000; 1972, $7,954,000.

NOTES

Includes $112,000 in 1972 for activities previously financed from:

	1970	1971
National Institute of Arthritis and Metabolic Diseases	256,000	
National Institute of Dental Research		112,000

Excludes $38,000 in 1972 for activities transferred to: Office of the Director, 1970, $35,000; 1971, $38,000.

Introduction of Dr. Cummings and Staff

Mr. Flood. We now have the National Institutes of Health, and, more specifically, the National Library of Medicine. The presentation will be made by Dr. Martin M. Cummings, the Director. Do you have anybody with you, Doctor, that you would like us to know?

Dr. Cummings. Yes, Mr. Chairman. I would like to introduce Mr. Kent Smith, who is the new executive officer of the National Library of Medicine. He has come to us from another part of NIH, the Division of Research Resources. I believe you remember Dr. Mider, who has been here previously. I also have with me Dr. Langley, my associate director for extramural programs.

Mr. Flood. Yes; we have a biographical sketch of you, Doctor, which we will include, of course, and if you call upon these other people or they volunteer, will you include sketches of them as well?

Dr. Cummings. Yes, sir.

(Dr. Cummings' and Dr. Langley's biographical sketches follow:)

NATIONAL INSTITUTES OF HEALTH

BIOGRAPHICAL SKETCH OF MARTIN MARC CUMMINGS

Position: Director, National Library of Medicine. Birthplace and date: Camden, N. J., September 7, 1920.

Education: B.S. Bucknell University, 1941; M.D., Duke University School of Medicine, 1914; mixed internship, Boston Marine Hospital, 1944–45; assistant resident, medicine, Boston Marine Hospital Hospital, 1945–46.

Experience: Director, National Library of Medicine, 1964 to present; Associate Director for Research Grants, NIH, 1963; Chief, Office of International Research, NIH, 1961–63; chairman and professor, Department of Microbiology, University of Oklahoma School of Medicine, Oklahoma City, Okla., 1959–61; Director, Research Services, Veterans Administration Central Office, Washington, D.C., 1953–59; special lecturer in microbiology, George Washington University School of Medicine, Washington, D.C., 1953–59; Chief, Tuberculosis Research Laboratory, Veterans' Administration Hospital, Atlanta, Ga., 1949–53; associate professor of bacteriology, 1953, and instructor through associate professor of medicine at Emory University School of Medicine, Atlanta, Ga., 1948–53; director, Tuberculosis Evaluation Laboratory, Communicable Disease Center, U.S. Public Health Service, Atlanta, Ga., 1947–49; U.S. Army, 1942–44, Pfc.

Association memberships: American Academy of Microbiology, Inc.; American Board of Microbiology; American Federation for Clinical Research—Emeritus; American Society for Clinical Investigation—Emeritus Member; American Thoracic Society; Association of American Medical Colleges; Medical Library Association; the Society of the Sigma XI; Council of Biology Editors, Inc.; American Clinical and Climatological Association; American Association for the History of Medicine; board of directors, Gorgas Memorial Foundation; board of directors, Association of Research Libraries; board of visitors of the Medical Center of Duke University.

Special awards, citations, or publications: VA Exceptional Service Medal; DHEW Superior Service Award; DHEW Distinguished Service Award; Honorary Degree, Doctor of Science, Bucknell University; Distinguished Alumnus Award, Duke University.

NATIONAL INSTITUTES OF HEALTH

BIOGRAPHICAL SKETCH OF LEROY LESTER LANGLEY

Position: Associate director for extramural programs, National Library of Medicine.

Birthplace and date: Philadelphia, Pa., December 12, 1916.

Education: A.B., U.C.L.A., 1938; M.A., Stanford University, 1939; Ph. D., Yale University, 1942; LL.B., Birmingham School of Law, 1954.

Experience: Associate director for extramural programs, 1970 to present; Chief, Training Grants and Awards Branch, National Heart and Lung Institute, 1964–1970; assistant professor through professor of Physiology, University of Alabama School of Medicine, 1949–1964; honorary research fellow, Institute De Biofisica, Rio De Janerio, 1946–1948; Lieutenant (Senior grade) U.S. Naval Reserve, 1943–1946.

Associate memberships: American Physiological Society; American Association for the Advancement of Science; Sigma XI; Alabama Bar Association; Medical Library Association.

Special awards, citations, or publications: Best basic science teaching award University of Alabama School of Dentistry, 1961, 1964; author of 15 textbooks 47 scientific articles; Victor E. Hall Lectureship, U.C.L.A., 1970.

GENERAL STATEMENT

Mr. FLOOD. You have a prepared statement. How do you wish to proceed?

Dr. CUMMINGS. I would like to present my statement and then be available for questions, with your permission.

Mr. FLOOD. Very well.

Dr. CUMMINGS. Mr. Chairman and members of the committee: Effective communication among all members of the biomedical community is essential to facilitate progress of research, prevent wasteful duplication of effort, and encourage application of new knowledge to

the treatment and prevention of illness. Publication of biomedical date in recent years has overwhelmed the conventional channels by which health science information is transmitted. Over 6,000 useful medical journals in 40 different languages are published in the world today. This abundance of new information has overloaded traditionally oriented communications channels. We at the National Library of Medicine are convinced that many of the technological advances which have enabled the sicentific community to increase new knowledge also provide the means for improved collection, organization, and dissemination of that knowledge.

This year marks two anniversaries in the history of the National Library of Medicine. It is the 135th year since the establishment of the collection out of which the NLM has grown, the library of the Surgeon General's Office, United States Army; and is the 10th anniversary of the dedication of the NLM's modern building in Bethesda, Md. Today, the National Library of Medicine is the principal repository of the world's biomedical literature, with a collection of more than 1.3 million items uniquely organized to meet the needs of health professionals and students. In 1972 the Library will make approximately 115,000 interlibrary loans and respond to over 81,000 requests from readers in its own facility. It will provide 11,000 reference services. In addition, it will index 230,000 articles in the journal literature, catalog 17,500 books and monographs, and with participating organizations at home and abroad will respond to requests for about 28,000 specialized computer searches.

THE ROLE OF MEDLARS

MEDLARS is the National Library of Medicine's computer-based Medical Literature Analysis and Retrieval System, which contains bibliographic citations to articles in 2,300 of the world's medical and health-related journals. It has grown steadily since 1964 in number of bibliographic citations, in the quantity of articles indexed—from 144,000 articles per year to 230,000—and in sources of indexing, which now include analysts in seven foreign countries, trained at the National Library of Medicine. MEDLARS continues to produce publications, such as "Index Medicus," the comprehensive monthly bibliography, and the annual "Cumulated Index Medicus," of the most significant portion of the world's biomedical periodical literature, the latter now filling over 10,000 pages in eight volumes.

Next year will mark the 100th anniversary of the printing of a 454-page catalog of the Surgeon General's library. A modern successor to that publication, our computer-produced "Current Catalog," provides cataloging information on books and monographs which is sold to libraries throughout the world. This reduces redundant cataloging and saves times and money for smaller libraries. In addition, since January 1970, MEDLARS has been used to produce an "Abridged Index Medicus" designed to afford rapid access to 100 leading English language journals selected from the 2,300 foreign and domestic journals covered by "Index Medicus." Its select content and low cost make "Abridged Index Medicus" particularly useful to the individual practitioner and to the libraries of small hospitals and clinics. Subscription response from physicians, medical libraries and medical editors has been enthusiastic.

MEDLARS also produces 23 recurring bibliographies in specialized

subject areas, such as "Parkinson's Disease and Related Disorders," prepared for and supported by various Federal agencies or professional organizations. The newest product, "Selected References on Environmental Quality as it Relates to Health," facilitates access to that part of the biomedical literature needed by environmentalists.

MEDLARS II

The National Library of Medicine is working to develop a second-generation system, MEDLARS II, to expand capabilities of the prototype. Deficiencies in specificity of recall will be corrected by greatly augmenting the controlled vocabulary.

Mr. FLOOD. What is MEDLARS II?

Dr. CUMMINGS. MEDLARS II, in essence, is a more sophisticated, more refined version of our present computer-based information system. Its main effect in the future will be to give the user a more relevant output by having a more comprehensive vocabulary built into the system.

I want to report, Mr. Chairman, that the contractor developing this new system has slipped seriously in meeting some of the deadlines and cost estimates, although the latter still fall within the amount budgeted for this effort. Examination of the developing system by our staff and by consultants from December 1970 through April of this year revealed deficiencies in the contractor's systems design of which the most important was the probable need for excessive computer time for MEDLARS operations. Therefore, we have decided to allow this contract to terminate, and in its place we are planning to extend our highly successful on-line system which we call AIM–TWX, Abridged Index Medicus, to perform the expanded MEDLARS II functions.

FEE-FOR-SERVICE TO FOREIGN USERS

Limited resources compelled the Library in 1970 to discontinue interlibrary loans, MEDLARS searches, other reference services, and film loans to foreign countries not covered by the National Library of Medicine agreement with the Agency for International Development. In response to urgent requests from members of the biomedical community abroad, who had depended upon our unique collections throughout the Library's history, some services were restored on a fee-for-service basis in 1971. We charge $2 for each interlibrary loans and $10 for each film loan, which recaptures the costs of processing and postage. Fees are also being charged for MEDLARS computer searches, by our foreign MEDLARS centers.

MEDICAL LIBRARY ASSISTANCE ACT PROGRAMS

The National Library of Medicine has provided 600 awards in the past year to medical, hospital, and allied health libraries in 49 of the 50 States for the strengthening of their collections, professional staff, and reader services, under the conditions of the Medical Library Assistance Act of 1965 (Public Law 89–291).

The Library also has designated 10 institutions, chosen on the basis of geographic location, the size and scope of their collections, and service performance, as regional medical libraries. They serve as backup facilities for local libraries and encourage maximal utilization of existing resources.

Mr. FLOOD. Suppose you list those.

Dr. CUMMINGS. Yes, sir; I would be very pleased to list those for you.

Mr. FLOOD. For the record.

Dr. CUMMINGS. I will provide them for the record.

(The information follows:)

REGIONAL MEDICAL LIBRARIES

1. Francis A. Countway, Library of Medicine, Boston, Mass.
2. The New York Academy of Medicine, New York, N.Y.
3. Library of the College of Physicians of Philadelphia, Philadelphia, Pa.
4. Wayne State University, Detroit, Mich.
5. A. W. Calhoun Medical Library, Emory University, Atlanta, Ga.
6. The John Crerar Library, Chicago, Ill.
7. University of Nebraska Medical Center, Omaha, Nebr.
8. University of Texas Southwestern Medical School at Dallas, Dallas, Tex.
9. University of Washington, Seattle, Wash.
10. University of California, Los Angeles Biomedical Library, Los Angeles, Calif.

Dr. CUMMINGS. They also make the full range of MEDLARS services more accessible to users throughout the Nation. The Medical Library Assistance Extension Act of 1970, authorizes the National Library of Medicine to use contracts as well as grants for the funding of the regional medical library programs. Therefore the Library intends to support service functions at the regional medical libraries by contracts, to improve management, and control the costs of services.

LISTER HILL NATIONAL CENTER FOR BIOMEDICAL COMMUNICATIONS

The Lister Hill National Center for Biomedical Communications has been designated the DHEW focal point for the coordination of biomedical communications systems and network projects and has been assigned the responsibility for applying computer and communications technology to improve the delivery of health care, medical education, and biomedical research. It is pursuing this goal through inexpensive, precedent-setting experimental services. The Center has initiated and successfully operated an experimental on-line computer bibliographic search service of the leading 100 English language journals in clinical medicine (AIM–TWX). More than 35 hospitals, medical libraries, and research institutions have used the service, and 93 percent of the searches have been of value to the users. This is the first such national medical information service available from any teletypewriter or TWX terminal in the country for the price of a phone call. Planning is underway to extend and expand the service.

The Center is continuing to cooperate with the National Aeronautics and Space Administration, the University of Washington, and Stanford University, using satellite communications technologies to conduct and expand technical experiments which permit verbal consultation and data transmission between physicians in remote areas of Alaska and the medical facilities of Stanford, Washington, and the National Institutes of Health.

The Center has also committed itself to develop a communications network for Vermont and New Hampshire physicians to assist in continuing education and support of patient care activities. A prototype link between Dartmouth and a small hospital at Claremont, 30 miles away, is in operation, and technical planning has been completed to extend the network to 15 hospitals and two other medical centers.

NATIONAL MEDICAL AUDIOVISUAL CENTER

The National Medical Audiovisual Center in Atlanta, Ga., is the Department's central resource for the distribution and utilization of medical films, videotapes, and other audiovisual materials. A shift in allocation of the Center's resources from the production of such materials has permitted greater concentration on upgrading the quality of acquisitions, improving the systems of distribution, and increasing the Center's consultative services to teach institutions. A completely automated booking system for the distribution of materials in the Center's collection was recently put into operation. The National Medical Audiovisual Center has loaned about 100,000 items annually for the last several years. Most of the requests have been received from schools of nursing and the allied health professions. During the last year the interest of medical schools has increased enormously. This probably reflects the trend towards telescoping the undergraduate medical curricula that will require changes in pedagogical technology. Consequently the Center will soon implement a cooperative media program through which it will work with teaching institutions and professional groups to develop innovative teaching aids for health professional education. The objective is to produce comparatively small modular packages of information which can be grouped in different ways to meet the diverse needs of medical education.

TOXICOLOGY INFORMATION PROGRAM

The National Library of Medicine's toxicology information program is establishing a system for providing data on the harmful effects of chemical compounds on humans. Among its efforts directed towards bringing toxicological data from many sources into a coordinated, computerized storage and retrieval system, the toxicology information program has developed a directory of toxicological information sources; compiled a toxicity bibliography and a registry of 30,000 chemical compounds important to health interests; consolidated toxicity information on approximately 1,000 compounds; and initiated development of the necessary computer software to process these files. A file on pesticide toxicity is being developed that will include toxicological information obtained from pesticide petitions granted by the Food and Drug Admnistration. The Library is grateful for the cooperation of the FDA in this venture. The concentrated nature of the data reduces the cost of file building substantially, and the result should be much more comprehensive than it would have been if obtained from literature sources alone.

Plans for 1972 include the creation of a MEDLARS-based abstract journal, Health Effects of Environmental Pollutants. The journal will cover an estimated 13,000 articles annually and make bioenvironmental toxicology information more readily available both to the scientific community and to the growing number of public officials concerned with environmental protection. Our plan is to use existing abstracts to reduce costs and repackage them rather than to create wholly new summaries.

The toxicology information program also plans to establish a query-response center in conjunction with the Oak Ridge National Laboratory of the U.S. Atomic Energy Commission, which will be able to draw as necessary on the large number of scientific disciplines represented at the National Laboratory.

In the aggregate all of the above-mentioned activities reflect an active information and communications program which has been developed cooperatively with other agencies in both the Federal and private sectors. These developments have taken place with fewer personnel than were available in previous years. This in large measure results from the successful application of new technologies to the solution of old problems.

In summary, our request for 1972 is $21,981,000, an increase of $471,000 over the amounts available for obligation in 1971. The net increase reflects the annualization of 1971 pay cost increase, within-grade increases and additional payments to the National Institutes of Health management fund.

BUDGET INCREASES AND DECREASES

Mr. FLOOD. Now, the summary of changes. Take a look at page 95. That shows that you have program increases totaling $200,000 and further down the page I see you have program decreases totaling $200,000. Is that by design? Were you told by somebody to come up here with a net increase of zero and then spread plusses and minuses as you wished? What were the guidelines?

Dr. CUMMINGS. Mr. Chairman, the decision regarding the priorities of the distribution of the funds allowed the Library was mine, that is to say, it was my judgment that certain increases were essential in one part of our program, to be offset by decreases in another part of our program.

With regard to the increases, Mr. Chairman, they occur in the extramural program which has had no substantial increases in its budget for a period of 3 years. We have on-going obligations to regional medical libraries, particularly, which have rising costs of doing business, as we do. They had to be met by providing an increase in their budget. We have sacrificed certain central functions within our own Library operations and have also sacrificed the support of certain local libraries to offset this. We were operating within a fixed dollar amount and these were judgments made on a priority basis.

Mr. FLOOD. By you?

Dr. CUMMINGS. I will assume the responsibility for them; yes, sir.

REDUCTION IN PROJECT CONTRACTS FOR LIBRARY OPERATIONS

Mr. FLOOD. That is important. Now, you have a decrease of $100,000 for Library operations. Take a look at page 96. You say this, and I quote: "The decreases represent planned reductions in project contracts."

Planned when? When did you plan this? Project contracts for what purpose? Wouldn't that interest you if you were sitting here? Planned when?

Dr. CUMMINGS. I would have to admit, Mr. Chairman, that these decreases were not part of any long-range design or plan. They are consequences, again, of having to do business within the framework of a fixed budget.

Mr. FLOOD. When did you do that?

Dr. CUMMINGS. The decision to reduce this effort was made at the time the Library learned of its mark for fiscal year 1972.

Mr. FLOOD. Its what?

Dr. CUMMINGS. Fiscal mark for its budget. I also want to clarify the language of that particular item.

Mr. FLOOD. Project contracts for what?

Dr. CUMMINGS. These are funds that are used for acquisition of the literature and for acquisition of materials that we get in the Library that cost more than $2,500. In part, this will represent a reduction in acquisition of historical materials.

Mr. FLOOD. What is an example of a historical material?

Dr. CUMMINGS. A notable work of an author in the field of medicine published more than a hundred years ago.

Mr. FLOOD. Not necessarily America?

Dr. CUMMINGS. No; it would not necessarily be by an American author.

MEDLARS II IMPLEMENTATION SCHEDULE

Mr. FLOOD. Now take a look at page 108. I am trying to prove to you fellows that we go through these justifications.

Dr. CUMMINGS. We are aware of that.

Mr. FLOOD. There you say this, and I quote: "The first phases of MEDLARS II will take place in about the second quarter of fiscal 1972."

Well, of course, the obvious question is: What was the original schedule for the first phases when you began to develop the second-generation in 1968?

Dr. CUMMINGS. Yes; that is a very pertinent question, Mr. Chairman, and I tried to deal with it in my opening statement by pointing out——

Mr. FLOOD. I noticed that.

Dr. CUMMINGS (continuing). That the contractor developing this system has slipped.

Mr. FLOOD. Yes. I thought that.

Dr. CUMMINGS. This statement, as it now appears in the record, should be corrected because I would say it is overly optimistic. We will not have this system completed in fiscal year 1972.

Mr. FLOOD. Well, you are honest about it, anyhow. We suspected that. If you had been on the Defense Department Appropriations Subcommittee as long as I have, this is nothing uncommon. We use a different phrase down there, and much bigger money.

Was this delay due to lack of funds, or bad mistakes, or what?

Dr. CUMMINGS. This delay was not due to lack of funds, Mr. Chairman. This slippage was due to several factors: First, an underestimation on the part of the contractor of the complexity of the task. Second, I would say that the delay was in part occasioned by the difficulty in keeping abreast of the changing needs of the National Library. There were a number of proposals to terminate this project made to me as far back as 6 months ago and I bit the bullet about a month ago.

Mr. FLOOD. What do you mean? The contractor wanted to bail out, or what?

Dr. CUMMINGS. No.

Mr. FLOOD. Your people?

Dr. CUMMINGS. My own advisers and consultants had suggested to me about 6 months ago that the design for MEDLARS II might prove to be so cumbersome that its maintenance and its cost for operation would not be attractive. I made the decision a month ago that they were correct and that we would finish the system both in-house and by joining the successful AIM–TWX system to this project.

Mr. FLOOD. You are not fooling around with building blocks. This is no game for boys.

Dr. CUMMINGS. You are absolutely right.

Mr. FLOOD. When do you expect the second generation to be in full operation?

Mr. CUMMINGS. I could give an estimate. I am hopeful that the complete system will be fully operational by the end of calendar year 1972.

Mr. FLOOD. You are on top of this yourself?

Dr. CUMMINGS. I am on top of this myself, with my senior staff and with the board of regent technical consultant who oversees this development.

Mr. FLOOD. You haven't farmed this out to Joe Zilch? You are stuck with it?

Dr. CUMMINGS. I assume the responsibility for its success or failure.

Dr. MARSTON. Mr. Chairman, the Library of Medicine has kept my office informed of what has really been a very difficult and in some ways disappointing event. I think they have, throughout, stayed right on top of it and, indeed, are to be complimented for doing that.

ADVANTAGES OF MEDLARS II

Mr. FLOOD. Well, he is a very honest gentleman. What will you be able to do that you can't do now, if and when?

Dr. CUMMINGS. Well, there would be several major advantages to the implementation of this system. The first thing that we will be able to do is to place into the data bank a depth of information and a precision of information that the present system doesn't allow—more terms, more descriptors, a better vocabulary to give a better printout. The second thing it will provide is a much faster throughput. The processing time on the system that we now use which we designed in 1964 is like comparing the Model T Ford to a modern automobile. We will have much more responsive processing time.

LISTER HILL CENTER SERVICES

Mr. FLOOD. Take a look at page 105. You say there that the Lister Hill National Center for Biomedical Communications "is now providing an experimental service to over 30 hospitals and libraries."

Dr. CUMMINGS. That is correct.

Mr. FLOOD. Tell us about the services.

Dr. CUMMINGS. Sir, what we have done is installed terminals in strategically selected small community hospitals as well as some large academic libraries——

Mr. FLOOD. Do you go out looking for business, or do they come to you?

Dr. CUMMINGS. Oh, no, sir; the community that is interested in improving its information service makes their needs known to us. Our problem is making prudent selection rather than in stimulating business.

Mr. FLOOD. What is your specialty, yourself?

Dr. CUMMINGS. My own specialty?

Mr. FLOOD. Yes.

Dr. CUMMINGS. I am a physician——

Mr. FLOOD. General medicine?

Dr. CUMMINGS (continuing). Trained, and with a special interest in infectious diseases and immunology.

ORGANIZATION AND COST OF LISTER HILL CENTER

Mr. FLOOD. About this Lister Hill National Center, we have the impression that this is going to be a really big deal, to the point where we are beginning to feel that the tail will be wagging the dog. What is going on?

Dr. CUMMINGS. Not in the immediate future, Mr. Chairman, but I think in response previously to a question from Congresswoman Reid or Congressman Shriver—I am not sure—I did indicate that, in my view, in the long look ahead the National Library of Medicine might in fact become a part of the Lister Hill Communications Center, that I could forecast in time an inversion of these two relationships.

Mr. FLOOD. It is beginning to show signs of that. Well, what about that?

Dr. CUMMINGS. Well, I think that would not be a bad thing for the Nation. I think this cannot occur, obviously, until the Lister Hill Center has demonstrated its capability in providing useful and economic information services, and until it has sufficient muscle, both in terms of manpower and resources, to accomplish this.

Mr. FLOOD. What do you think the center is going to cost when it is in full operation?

Dr. CUMMINGS. We made an estimate to the Congress, in 1970, of $15 million, and I think that estimate is still a good one.

GOALS OF THE LISTER HILL CENTER

Mr. FLOOD. Now, tell us what this center's function will be. What is the breadth of its activities?

Dr. CUMMINGS. Its basic objective——

Mr. FLOOD. When it is fully developed.

Dr. CUMMINGS (continuing). Is to adapt existing technologies, not to invent new hardware, to bring to bear on the medical communication problem; that is to say, the center is trying to apply technology to improved information handling. Thus it has been involved in the interactive television communications field. It has been involved, as I reported this morning, with NASA in the satellite communication experiment.

Mr. FLOOD. You could be a big help to the regional medical programs of the Nation, couldn't you?

Dr. CUMMINGS. We believe that we should try to serve all elements of health, local, regional, and national, urban and rural. We have a constituency that includes educational institutions, health care delivery requirements, as well as research.

Mr. FLOOD. But you would be of inestimable help to the regional medical operations.

Dr. CUMMINGS. We would hope to be able to be helpful; yes, sir.

TOXICOLOGY INFORMATION PROGRAM

Mr. FLOOD. Why should the toxicology information program be a separate and distinct program rather than just an activity under the Lister Hill Center?

Dr. CUMMINGS. Well, there is a history that I must share with the committee to answer your question fully. This program came to the

National Library of Medicine as a result of recommendations made by the President's Science Advisory Committee in 1966. The President asked the Department to establish such a program somewhere within DHEW. The library was asked to assume this responsibility because we were already engaged in processing other forms of information with computer technology. In the sense that it was a Presidentially directed program, it has its own identity and we came to Congress requesting support for it as a line item.

I think your question, however, has a very important implication, namely, that in time this, too, should be absorbed by the Lister Hill Center, and I have no reservations in my own mind that this should be considered.

AUTHORIZATIONS FOR EXTRAMURAL PROGRAMS APPROPRIATIONS

Mr. FLOOD. Suppose you tell us the relationship between the authorization for your extramural program and the appropriation. In other words, in terms of dollars and percentages how much of the authorization is being requested for fiscal year 1972?

Dr. CUMMINGS. First, may I say, since I have recently reviewed this activity for a talk I am about to give, that the NLM has received during the first 5 years of the Medical Library Assistance Act about 45 percent of the funds authorized by the original act.

Mr. FLOOD. What about for fiscal year 1972?

Dr. CUMMINGS. For fiscal year 1972 the budget before you would represent about 45 percent of the amount authorized in the act as extended last year for those programs administered by the National Library of Medicine.

OPTIMAL FUNDING LEVEL FOR 1972

Mr. FLOOD. I notice you have a very modest increase in your budget request, less than the cost of what we call the cost of living increase. What would you consider to be an optimal level of funding for 1972?

Dr. CUMMINGS. Well, if I may view the budget in its two elements, first the direct operations of the Library, I would answer that the cost-of-living increases would require——

Mr. FLOOD. What would be tops?

Dr. CUMMINGS (continuing). A minimum of $1 million, and probably an optimum figure of $1.5 million for direct operations. For the extramural program, however, since it has had essentially no increases for a long period of time, I think the requirements would be greater and my estimate would be about $2 million for the six programs involved. I would like Dr. Langley to elaborate on this, if he wishes.

Mr. FLOOD. Yes; we are concerned about that, Doctor.

Dr. LANGLEY. Yes, if I may. As Dr. Cummings said, for the extramural programs the 1972 budget shows approximately $6 million. We consider an increase in these six programs of $800,000 to be necessary to maintain our existing level of activities. To expand them to provide the services needed, we think that these programs should be increased by $2 million. I would be glad, Mr. Chairman, to indicate in each of the six programs, if you wish——

Mr. FLOOD. Not now. Put that in the record; each one.

Dr. LANGLEY. Yes, sir.

(The information follows:)

Optimal and minimal request, fiscal year 1972, budget needs—National Library of Medicine

ACTIVITY

EXTRAMURAL PROGRAMS (MEDICAL LIBRARY ASSISTANCE)

	Increase needed
Optimal request:	
Training	$200,000
Special Scientific Projects	-------
Research	150,000
Library Resources	895,000
Regional Medical Libraries	498,000
Publications Support	210,000
Total	1,953,000
Minimal request:	
Training	200,000
Special Scientific Projects	-------
Research	50,000
Library Resources	400,000
Regional Medical Libraries	100,000
Publications Support	50,000
Total	800,000

EFFECT OF RESEARCH EFFORT ON INFORMATION NEEDS

Mr. FLOOD. Isn't it true that the greater the research effort throughout the country, the greater the demand for medical libraries? That is a leading question if I ever heard one.

Dr. CUMMINGS. When medical research or medical education or medical practice expands, there is a greater need for medical information. It is not just related to support of research, Mr. Chairman.

Mr. FLOOD. In other words, if an additional $100 million were appropriated for the cancer program, which will likely happen, and additional amounts for other disorders, additional funds will be required for the associated library services?

Dr. CUMMINGS. I would think that the expansion of a program such as the cancer conquest program would require expanded information and library resources. I know from brief conversations with Dr. Baker that he has this in mind, that he recognizes that there is such a need.

MEDICAL LIBRARY RESOURCE GRANTS

Mr. FLOOD. How do your resource grants help physicians? How do they help scientists? How do they help students?

Dr. CUMMINGS. The resource grants go primarily to the smaller libraries in community hospitals and small institutions where the physician works.

Mr. FLOOD. Do any funds go to local county medical societies if they have a library?

Dr. CUMMINGS. Some county libraries have support from the National Library of Medicine.

Mr. FLOOD. I have one. I am just wondering how they get into the act.

Dr. CUMMINGS. I don't know whether the county society that you have in mind is supported by our Library.

Students and scientists use a larger information base and they get their information resources from the academic libraries of medical schools, health professional schools, and from the 10 regional libraries supported by NLM.

COST OF THE LISTER HILL BUILDING

Mr. FLOOD. Last year you received funds to plan a new building. Are those plans finished? How much would be required for the new building, if and when?

Dr. CUMMINGS. We have completed the program of requirements for the Lister Hill Building. Those requirements have been transmitted to NIH where I understand they are now under review and then will be transmitted to the Department for a second review. We have completed writing the program of requirements.

Mr. FLOOD. Do you have any idea what it will cost?

Dr. CUMMINGS. Yes, sir, we do have an idea, and I would go back to the first discussions that we have had with this committee. We projected a need for approximately $10 million for construction of the Lister Hill Center in 1970. Judging by the increasing costs of construction I would guess it may be closer to $15 million by the time a contract is let, assuming the same dimensions and other factors.

Mr. FLOOD. Thank you, Doctor.

Mr. Michel?

NLM BUDGET SINCE 1967

Mr. MICHEL. Doctor, I look back in the record here and I see that for the National Library of Medicine in 1967 the budget was $19.2 million; in 1968 it was $21.1 million; 1969, $19.1 million; 1970 $22.8 million; 1971 $20.2 million; and proposed for 1972, $21.4 million. Taking your shop against all the others we hear coming before this committee, there is quite a striking difference in the sense that you have kind of just managed to hold your own over 5 years. I looked over here in the personnel summary and the figures I have available show that back in 1970 you had 467, the same for 1971, and in 1972 it is 474. How do you manage to get by without cutting back in some areas, or do you just have that much better an operation?

Dr. MARSTON. May I just make one comment?

Mr. MICHEL. Go ahead, Doctor.

Dr. MARSTON. I think those figures reflect the overall NLM budget including construction grants which were transferred out of the National Library in December 1969, however, even without these construction funds the NLM budget has been relatively stable over the period.

Mr. MICHEL. How many people do you now have working out there at the National Library of Medicine?

SERVICES DROPPED TO MAINTAIN LEVEL BUDGET

Dr. CUMMINGS. About 470 people, and I believe the figures you read, Mr. Michel, are correct for the budget history for the National Library of Medicine. I would answer your question by saying we have had to reduce certain services and drop certain functions.

Mr. MICHEL. What are those?

Dr. CUMMINGS. We have closed the Library on Sundays for the first time in many, many years. We have for a period of time reduced the number of inter-Library loans that we would provide from a list of 100 journals that we felt were common titles and that we should no longer provide loans of these journals. We have reduced the acquisitions program of the History of Medicine Division so that we no longer compete for acquisition of rare historical materials. We have ceased providing MEDLARS services abroad. Generally, we have limited or reduced services to stay within our manpower limits.

Mr. MICHEL. These inter-Library loans you speak of are to whom?

Dr. CUMMINGS. These are loans that we make to other libraries that do not have the material that exists in the National Library. They are usually to small community hospital libraries or academic libraries or free standing libraries. We are a library's library providing material to the physician, scientist or student through his local library.

NLM BOARD OF REGENTS

Mr. MICHEL. Did I understand that the President appoints a Board of Regents to provide policy and operational guidance to the National Library of Medicine?

Dr. CUMMINGS. Yes, sir. Since 1956 when the National Library of Medicine Act was passed there has been a Presidentially appointed Board of Regents. It consists of 10 members of the health community or community that relates to information and communications technology who meet regularly not only to advise on the review and approval and payment of grants, but also they have the authority by law to oversee all of the direct operations, and I can tell you, Mr. Michel, they do. They are a very hard-working, tough-minded Board, one that I would say would be comparable to a board of directors in industry.

Mr. MICHEL. Did you say there are 12 members?

Dr. CUMMINGS. There are 10 Presidentially appointed members. In addition, there are seven members named by statute by virtue of their position. The four Surgeons General are members of the Board. The Librarian of Congress is a member of the Board as is the chief medical director of the Veterans' Administration.

Mr. MICHEL. Why don't you display for the record, then, the complete composition of this group—those who make up this board?

Dr. CUMMINGS. I'll be very happy to do that.

(The information follows:)

BOARD OF REGENTS, NATIONAL LIBRARY OF MEDICINE

Anlyan, William G., M.D., vice president for health affairs, Duke University, Durhan, N.C.

Augenstein, Bruno W., vice president for research, Rand Corp., Santa Monica, Calif.

Baker, William O., Ph. D., vice president in charge of research, Bell Telephone Laboratories, Murray Hill, N.J.

Ebert, Robert H., M.D., dean, Harvard Medical School, Boston, Mass.

Fletcher, James C., Ph. D., president, University of Utah and College of Eastern Utah, Salt Lake City, Utah.

Layton, Jack M., M.D., professor and head, Department of Pathology, University of Arizona College of Medicine, Tucson, Ariz.

McGovern, John P., M.D., professor and chairman, Department of the History of Medicine, University of Texas, Graduate School of Biomedical Sciences, Houston, Tex.

Michael, Max, Jr., M.D., executive director, Jacksonville hospitals educational program, Duvall Medical Center, Jacksonville, Fla.

Teuscher, George W., D.D.S., dean, Dental School, Northwestern University, Chicago, Ill.

Wagman, Frederick H., Ph. D., director, University of Michigan Library, Ann Arbor, Mich.

Ex officio members:

Carlson, Harve J., D.P.H., division director for biological and medical sciences, National Science Foundation, Washington, D.C.

Davis, George M., vice admiral, M.C., the Surgeon General, Department of the Navy, Washington, D.C.

Musser, Marc J., M.D., Chief Medical Director, the Veterans' Administration, Washington, D.C.

Jennings, Hal B., Jr., lieut. general, M.C., the Surgeon General, Department of the Army, Washington, D.C.

Mumford, L. Quincy, LL.D., the Librarian of Congress, Washington, D.C.

Towner, Alonzo A., lieut. general, M.C. the Surgeon General, Department of the Air Force, Washington, D.C.

Steinfeld, Jesse L., M.D., the Surgeon General, U.S. Public Health Service, Washington, D.C.

ANTECEDENTS OF THE NLM

Mr. MICHEL. As a matter of fact, you made mention of the anniversaries being celebrated this year. Why don't you set out in the record here the forerunners of the National Library of Medicine. It didn't just grow out of nowhere.

Dr. CUMMINGS. I'll be very pleased to do that. I can do that by recitation if you will give me the time.

Mr. MICHEL. All right.

Dr. CUMMINGS. The Library was founded in 1836 as the Library of the Army Surgeon General. It became the Army Medical Library, then the Armed Forces Medical Library in 1952 and subsequently the National Library of Medicine in 1956. It is, Mr. Michel, the only National Library with its own statute, its own congressional mandate. This is a very remarkable thing not only in this country but internationally. We are very proud of the rich history of the Library involving the military because the antecedent libraries, all in their own time, enriched the collection and services and brought new technology to bear to serve the Nation. Even when it was an Army Library it served as a National Library. It not only served the military officers, it shared its collection freely with all of American medicine and, indeed, with all of global medicine.

NLM ACHIEVEMENTS

Mr. FLOOD. How long have you been head of this shop?

Dr. CUMMINGS. I have been Director of this Library almost 8 years now. The Library has some fascinating technical achievements behind it. It was the first library to use microfilm in lieu of lending original documents. Dr. Billings, the first Director of the Library, working with a young engineer, Herman Hollerith, actually designed the first electric tabulator. That tabulator was used for the Census of 1890 and took advantage of Dr. Billings' idea that a punch card

be made to run through this electric counting machine. That is really the predecessor of the modern computer. The original records are all in the National Library.

It was Dr. Billings who improved the ventilation of this building in which we sit. He was asked to be consulting ventilation engineer for the Capitol, and reading the reports of those days is quite fascinating. I don't know how good you consider the ventilation now.

Mr. MICHEL. What was his special expertise?

Dr. CUMMINGS. He came to the Library from the Battlefield of Gettysburg where he was brought in after 6 or 7 days of intensive surgery to be rehabilitated. Surgeon General Lovell suggested that he tidy up the Army Surgeon General's bookcases and that is how he got into the library business. He parlayed that assignment into the great Library that I now enjoy the privilege of heading. It is a fabulous history.

Dr. MARSTON. I think that it is important to mention, in addition to the things that Dr. Cummings has said, that the National Library of Medicine operates in quite a different way from the repository libraries that people normally think of when you say "library." I mentioned this in my opening statement. It has been dynamic—I don't know what word you would use, Dr. Cummings—but it has taken the initiative to move out and see the problems and to try to meet them rather than sitting back to do cataloging or tidying up bookshelves.

NLM'S WORLD REPUTATION

Mr. FLOOD. What is its repute with the profession?

Dr. CUMMINGS. Well, I have to be immodest to answer your question, but I shall be. I think the National Library of Medicine is judged by nearly all leading librarians as being the most advanced institution of its kind in the world. And we have evidence of that, Mr. Flood, from visitations from my counterparts in Russia and many other countries, as well as from my counterparts in this country. We are very proud of our advanced posture in this field. It has really been made possible, of course, by your allowing us to operate in certain new areas and not holding us to being a conventional or traditional library.

THE MEDLARS II CONTRACTOR

Mr. MICHEL. Doctor, who is that Medlars II contractor?

Dr. CUMMINGS. That contractor is a firm called Computer Sciences Corp.

Mr. MICHEL. Have they done other work in this field?

Dr. CUMMINGS. To my knowledge, they have never undertaken a large library-oriented information systems job. Yet they are an extraordinarily large software firm. They are not a small inexperienced firm.

EFFECT OF FEES ON FOREIGN USERS

Mr. MICHEL. Last year in my line of questioning I made a point with respect to these user fees, particularly for the foreigners, and I think in your testimony you touched on it.

Dr. CUMMINGS. Yes; I did.

Mr. MICHEL. Has the institution of those fees tended to inhibit in any way the number of inquiries you get?

Dr. CUMMINGS. Yes; I think there has been a marked reduction in the number of foreign requests for service since we instituted our user fees. The information that I have suggests it is not because the foreign library is unwilling to pay $2 for a loan. It is because they say it takes $10 worth of effort to get their institution and their government to allow this kind of reverse dollar flow. Now, that is my impression. There is no question that it has reduced the number of requests for service.

Mr. MICHEL. By roughly how much, percentagewise?

Dr. CUMMINGS. I am sorry, I don't have that figure. May I provide it for the record?

Mr. MICHEL. Yes; put a ball park figure in the record.

Dr. CUMMINGS. I can get a precise figure and I prefer to do that.

(The information follows:)

There has been a reduction of 68 percent in the number of interlibrary loan requests received from non-AID countries since the institution of the $2 fee for service. There has also been a 66-percent decrease in the number of audiovisual loan requests from non-AID countries since the establishment of a $10 fee for this service.

MEDICAL SCHOOL ACCESS TO MEDLARS

Mr. MICHEL. How many of our medical schools are tied into Medlars?

Dr. CUMMINGS. In a sense, every medical school has access to Medlars, but officially there are seven medical schools which serve as Medlars operational centers and they are geographically spread around the country.

Mr. MICHEL. Geographically situated around the country?

Dr. CUMMINGS. Yes, sir.

Mr. MICHEL. Is it fair to say that all our medical schools are at least indirectly tied in with the system?

Dr. CUMMINGS. Yes, sir; that would be a fair statement because any health professional in a medical school can receive Medlars services from his nearest regional Medlars center and has the same privilege that an individual would have within that particular institution.

PUBLIC LAW 480 FUNDS FOR TRANSLATION

Mr. MICHEL. How much assistance are you getting in translating that is funded out of Public Law 480 funds abroad?

Dr. CUMMINGS. We have a fair apportionment of Public Law 480 funds from the NIH allotment, much of which is used for translation of foreign materials, particularly in countries that have language capabilities that we don't enjoy. At the moment this work is done for us in Israel, Poland, and Yugoslavia. I don't want to mislead the committee and have you believe that we translate everything that they generate. We are very selective. There is a group that reviews a new field or a new area of development that makes these choices for us.

BUDGET NEEDS OF NLM'S PROGRAM

Mr. MICHEL. With respect to those figures that will appear in the record in response to the chairman's line of questioning about so many increases that would be needed for an optimum program, do I understand those figures to be requests that were officially made and you were cut down by the budget or by some higher authority, or are those just figures you put together over a period of time as the amounts that could be used and you would like to have if resources were available?

Dr. LANGLEY. These are figures derived from looking at each of our programs and the need for each of the programs. These are figures that we constantly update for our own operation.

CONSTRUCTION OF LIBRARY AND RESEARCH FACILITIES

Dr. CUMMINGS. If I may, Mr. Michel, I want to point out that in my personal judgment a program closely associated with ours, the Bureau of Health Manpower Education, which now has a responsibility for all educational construction in my view has a great need for library construction funding. We used to have an appropriation under our authority to fund medical library construction. Now that that is part of the Bureau of Health Manpower, I believe they have had no funds for this purpose. Here I know from very careful study that there are great needs within our Nation to upgrade the medical library facilities in many institutions.

Dr. MARSTON. The authorization for the construction grants by the Bureau includes both research and library facilities, if they are part of the educational purpose—they must be part of that. So, while under the specific authorizations for research and library construction there has not been an appropriation in recent years, this does not mean that no construction for these purposes has been possible. It does mean that the construction for research and for libraries has had to be justified on the basis of the HPEA educational purposes.

Mr. MICHEL. What is that total figure?

Dr. LANGLEY. It is the total minimal needs for the extramural programs and adds up to about $800,000.

Mr. MILLER. There is one point I would like to make here. The new health manpower legislative proposals contain new provisions for the construction programs. These provisions are consistent with our general policy on all HEW construction programs in that we are trying to meet the needs through interest subsidies and loan guarantees rather than through direct grants.

Mr. MICHEL. That is all, Mr. Chairman.

Mr. FLOOD. Mr. Natcher?

Mr. NATCHER. No questions, Mr. Chairman.

Mr. FLOOD. Mr. Smith?

FLUCTUATION IN ANNUAL GRANT FIGURES

Mr. SMITH. I notice that it shows in the justification 405 grants for 1972, 534 last year and 397 the year before. Why this range of figures?

Dr. CUMMINGS. With the grants, Mr. Smith, there are some of our programs which have a finite grant period. Our resource grants, for

example, are on a declining formula, so that grants started 5 years ago would be completed today. We have had a certain number of grants that have been completed and another number that have been started. This would account for the fluctuation that you have perceived.

In addition, the average size of grants has increased annually, and therefore, the number of grants that we can award each year has been reduced within a fixed budget.

Mr. SMITH. It went up and then down.

Dr. CUMMINGS. That is correct. It went up when we introduced another series of small resource grants for the community hospital libraries, for example, and then went down when the first set of awards ran out, so we do have this peak-and-valley effect that you have observed.

RESOURCES GRANTS TO LOCAL LIBRARIES

Mr. SMITH. How many local libraries are you financing?

Dr. CUMMINGS. Dr. Langley, can you provide that figure, about 300?

Dr. LANGLEY. By local libraries you mean community hospitals?

Mr. SMITH. Yes.

Dr. LANGLEY. It would be close to 300.

Dr. CUMMINGS. I should point out that there are 6,000 libraries in the country, and we are supporting only a very small segment.

Mr. SMITH. 6,000, you say?

Dr. CUMMINGS. There are 6,000 medical libraries in the United States.

Mr. SMITH. And how many do you make a contribution to in one way or another?

Dr. CUMMINGS. In the aggregate of all programs, 600. About 10 percent of all medical libraries have some support in one form or another from the National Library, mainly in the form of the resource grant.

Mr. SMITH. What would be the amount on an average of those resource grants?

Dr. CUMMINGS. Most of the small hospital library grants are in the order of $3,000 per year. Most of the academic library grants would be in the order of $30,000 per year, and then the few regional libraries throughout the country would have support at a level of $100,000 to $200,000 per year.

Mr. SMITH. What would the $3,000 be used for?

Dr. CUMMINGS. It is used to improve gaps in the collection that are related to the interests of doctors that work in that institution, and to provide some assistance in personnel staffing such as supporting part-time librarians. It is obviously not an extensive investment, but we have learned from studies that a $2,000 collection of books and journals can respond to 75 percent of a doctor's literature needs, when he has to make a decision in a hospital. One hundred journal titles, and 50 contemporary books are often all that are needed to answer three out of four questions. We are taking advantage of that in seeding these small libraries throughout the country.

Mr. SMITH. Do these works need to be supplemented each year, or are they of a nature that very seldom need supplementing?

Dr. CUMMINGS. Usually, Mr. Smith, the subscription for a medical

journal is carried on year after year, and as the information gets stale, it is either put aside or discarded. One keeps the library pruned or weeded by retaining only the latest information. You are buying new and discarding old, in the small library setting. In our library, we must keep everything, so there is one copy one place in the Nation.

USE OF MICROFILM AND MICROFICHE

Mr. SMITH. We had some testimony, I don't know if it was here or not, 3 or 4 years ago. People were excited about the possibility of taking a little 2-inch by 2-inch piece of plastic with impressions, flash it on a screen, and it could be seen in any library anywhere in the country. Do you know what I am talking about?

Dr. CUMMINGS. I believe I know what you are referring to. I think I can tell you that if we are talking about microfilms or microfiche, this is in fact now a reality. Images of pages of information have been compressed in microfilm, and they can be enlarged and transmitted from point to point. We have in fact, filmed the part of our collection that is deteriorating. Because of the decay of paper with aging, we try to make a microfilm, so that we have a permanent record before that information is lost.

Mr. SMITH. I have one which has the entire Holy Bible on a little piece 2 inches square. This can be done, and as I understood it the machines are rather inexpensive which could receive the information. It seems to me that this would be a lot less expensive way to provide library service, and maybe better. You would have a better library at a central location, and you would be able to have a receiver at each one of these local libraries.

Dr. CUMMINGS. This is a very important and a very fascinating statement. The Encyclopaedia Britannica already has reproduced small libraries in microform, and you can buy a collection of books in these forms for something like $20,000. I am told that such a microfilm collection could serve the needs say of a junior college or a community college. Some people feel such collections are that good.

With regard to our application in medicine, it is true that you could put the Bible on a small piece of film, but we have 350 million pages of information in our library, and the cost of converting all of that into such a format would be prohibitive. I think the right judgment here would be to select from this vast area of information that portion that we would think would be helpful, good, and widely used.

In fact, we are doing this in the graphic image system that has been developed for us by Sanders Associates, Inc., where microfilms of the 300 leading journals in American medicine are placed in plastic containers, and through a computer-generated program they can be retrieved and printed out after inspection. The prediction that was made by a member of this committee some 4 or 5 years ago, I believe, is coming to reality.

Mr. SMITH. It was me, and I still think it is really a practical thing. I don't think we are talking about some farfetched idea. I think it is just practical and it ought to be here by now, it seems to me, because it has been available for several years. I understand airline mechanics use this kind of system. They don't need to put their greasy fingers on every page in the instruction book because they can just throw this page up on the wall, there is their diagram and they go to work.

Dr. CUMMINGS. The military has made a great contribution to this field in their work.

Mr. SMITH. This is all I have.

Mr. FLOOD. Mr. Patten?

1972 BUDGET COMPARED WITH 1967

Mr. PATTEN. Doctor, I notice in 1967 your Department received $20,192,000, and this year you have about the same amount. Your program is being carried out at pretty much the same level as the previous year, is that right?

Dr. CUMMINGS. Yes; that is obviously correct. As we discussed earlier, we are really seriously feeling the results of 5 years of inflation. Let me say, for example, that just the cost of acquiring materials has gone up at a rate of 12 percent per year. I would have to say it is getting extremely difficult to be able to absorb those costs within a stable budget.

USE OF NLM BY PUBLIC MEDIA

Mr. PATTEN. You keep talking of professionals in the medical schools. Do the public media use your service? Some newspapers have beautiful health features on a Sunday, eight and 10 pages. It is really wonderful and good reading. I don't know whether the newspapers will continue that—that is their business, but for me and for my family some of these health features are very interesting. I don't think they did it 10 years ago or 5 years ago. They will take different subjects and treat them almost professionally. Does TV and newspapers use your services much for material?

Dr. CUMMINGS. I think a frank answer would be no, that they do not use the NLM much, in comparison to other users, but they do use it. For example, we are always quickly informed as to who the new Nobel laureates are, because some of the newspapers, when they get the ticker tape word, call us for a photograph of Dr. X, Y, or Z. They know that we may have such things. They come and use the collection when they are doing research for an article such as the one you have just characterized. We are used infrequently by the public media.

We are used by attorneys who are interested in forensic medicine or legal problems associated with health programs. We make our collection available to anyone who has a bone fide need to have the information, or who is a professional. It is not a public library in the sense that children can come off the street and browse.

NLM'S INFORMATION TECHNOLOGY IN THE FUTURE

Mr. PATTEN. Doctor, if you have to dream a little bit, what do you think the work will be like 10 years from now? You spoke of satellites and microfilm, cables, audio playback systems, that TV project up at Dartmouth that will help probably 30 hospitals. How many have you?

There was a series on TV, science fiction.

Dr. CUMMINGS. We have been accused already, Mr. Patten, of being involved in science fiction. We talked about using satellites for medical communications 6 or 7 years ago. We are now able to do it, by virtue of the fact that NASA had a satellite in space that was pro-

jected to go down 2 years ago but didn't. Since it stayed up they were kind enough to let us use some of its band width capacity.

With regard to your question about looking ahead, I think we try to look ahead at a reasonable level of projection, maybe 5 to 6 years, not 10 to 20 years. Because I am impressed that the technology is changing so fast that if we tried to daydream way out, we may be disappointed.

Computer technology has changed enormously. You get twice the speed of processing now for half the cost. Audio visual projection equipment, such as electronic video recording, is coming from seven or eight major industries now. I think rather than say that we are looking 10 or 20 years ahead, we are constantly looking for what is available today that we can efficiently apply tomorrow. That is essentially the philosophy under which I have worked.

Mr. PATTEN. Do you think the time will come when a doctor can relax at 5 o'clock, lay back in his chair, and either through a hearing device or something listen to 15 minutes of the latest in research, just as we pick up a newspaper, to read the latest in politics—do you think a doctor can stay in his office and rest, and listen to the latest in the world medical research?

Dr. CUMMINGS. I don't know whether he is going to be able to relax as you put it and do this, but he can today drive his automobile and plug in an audio tape and get a series of lectures on the treatment of heart disease, which are produced by the American College of Cardiology. He can go home and he can look at a video tape, if he has a projector, he can go to a modern library and have this whole area of material at his hand.

The answer to supportive information services for the practitioner is for us to get materials to him and not force him to come to us. I think that is coming, and very soon.

PRIORITY OF NLM AS A PUBLIC NEED

Mr. PATTEN. If we took a public poll, what kind of a rating do you think your library would get? Suppose we put up 10 questions about how I should spend money as a Congressman, Where do you think you would rate? The reason I ask that is this: The first budget I made in 1934, we weren't even paying our employees. We were paying them wooden money. We were bankrupt. We came down to the city hall and said, "We can't come in with this budget. We have to cut it." Of course you know what went out first, the library money and recreation. In all my time in the State and county making up budgets, I always experienced that when you felt you wanted to cut further, you cut library money and recreation money before you cut anything else that was considered to be the meat of the budget. I just wonder how much you think you are appreciated across the board by the 200 million people?

Dr. CUMMINGS. I know how much we cost the taxpayer. Our institution costs each citizen 10 cents a year for what we do for the health program.

Mr. PATTEN. We may cut that, you know. There is great talk here of adopting a 6 percent across-the-board cut as we did last year. You won't mind that if we help the taxpayer. It won't affect your department if we cut you 6 percent more?

Dr. CUMMINGS. It will affect us.

Mr. PATTEN. Mr. Miller is going to tell you that they don't cut it across the board but rather that there is an interplay of funds and you won't get hurt. Nothing further, Mr. Chairman.

INFORMING POTENTIAL USERS OF NLM SERVICES

Mr. FLOOD. Mr. Shriver?

Mr. SHRIVER. Dr. Cummings, in your discussion of the National Medical Audiovisual Center in Atlanta, you say that most of the requests come from schools of nursing and the allied health professions. I have several of these in my congressional district, and I would especially mention a new College of Allied Health Professions at Wichita State University. How are these schools informed about the services offered by the Audiovisual Center? How are they informed about available services from other programs under your jurisdiction?

Dr. CUMMINGS. Information on the National Medical Audiovisual Center programs, services, and activities, is disseminated through NLM publications; the NMAC Film Catalog Film Reference Guide, NMAC Listing of Videotapes Available for Duplication, and a series of workshop/seminar program announcements. In addition, specialized information about NMAC is promulgated at professional meetings and conferences and through various Government publications issued by program sponsors of films in the NMAC distribution collection; that is, GSA, National Audiovisual Center Sales Catalog, Air Pollution Release Announcements, and other environmental program announcements, and so forth. Further information is supplied on request from individuals and professional organizations through normal correspondence channels.

Information regarding other available program is disseminated through a monthly newsletter, National Library of Medicine News, distributed on request. The Medical Librarians at Wichita State University, Veterans' Administration Center and St. Joseph Hospital in Wichita all receive it. In addition, information is disseminated through fact sheets and brochures describing NLM's grant program and library services; and regular publications such as Index Medicus and Guide to MEDLARS Services. The Regional Medical Library Network also sponsors workshops, demonstrations, and consultation visits to familiarize librarians with services available.

NLM INFORMATION ON ENVIRONMENTAL POISONS

Mr. SHRIVER. On page 7 you talk about the toxicology informtaion program and the abstract journal, Health Effects of Environmental Pollutants. I have been trying to ascertain if there is an adequate central clearinghouse-type system from which anyone could obtain an up-to-date summary of information regarding environmental dangers to health. Would these publications serve that purpose?

Dr. CUMMINGS. The toxicology information program's (TIP) proposed new abstract journal, Health Effects of Environmental Pollutants will contain abstracts of review articles on environmental dangers to human health, provided these articles were originally published in the scientific lierature which will be covered by this new abstract journal. Furthermore, one important function of the new Toxicology

Information Query Response Center, formed by TIP at the Oak Ridge National Laboratory, will be to prepare up-to-date state-of-knowledge reviews on such topics as the effect of certain environmental pollutants on human health. Thus, TIP, as a whole, will serve as a clearinghouse for information on the health effects of environmental pollutants and will provide both evaluated and unevaluated information to users.

Mr. SHRIVER. Are any of your activities participating in the study of the proposed atomic waste disposal project in Lyons, Kans.?

Dr. CUMMINGS. No sir.

COORDINATION WITH AID

Mr. SHRIVER. Would you explain further the Library's agreement with the Agency for International Development, which you mention on page 4?

Dr. CUMMINGS. Under an agreement with the Agency for International Development, the Library responds to the needs of AID missions, and medical institutions and individuals in 47 developing countries. Annually, our Library provides approximately 15,000 interlibrary loans, 250 Medlars demand searches, 50 reference services, and 50 subscriptions to NLM publications to support AID health activities. This year audiovisual films were included as a new service, and approximately 50 such loans have been made.

The subject coverage of these information services relates to all aspects of health, with some emphasis in such fields as communicable diseases, nutrition, and population. These services, thus, constitute a unique resource available only through this NLM/AID mechanism; and an impact is made on medical research, education, and health services in these countries.

COMMUNICATIONS NETWORK FOR VERMONT AND NEW HAMPSHIRE

Mr. SHRIVER. On page 5 you say the Lister Hill National Center for Biomedical Communications has committed itself to develop a communications network for Vermont and New Hampshire physicians. Our friends in those States will be happy to hear of this, but why was that particular area chosen?

Will similar networks be supported in other areas? Something like this would be of great assistance to our Central Plains area physicians.

Dr. CUMMINGS. NLM has been charged with the planning, development and technical management of a nationwide biomedical communications network to support health services delivery, education, and research. In the pursuit of this objective, NLM is in the process of developing a number of experimental communications systems to evaluate their potential usefulness and cost effectiveness on either a nationwide basis or in some large problem area. The New England network is one such pilot system. The area was chosen because of the interest and enthusiasm of the medical schools, medical societies, and hospitals in the area, the geographic problems which the area presented, both in terms of topology and population, and the existing institutions all of which combined to make this a highly suitable experimental model. The lessons learned from it may be incorporated into the overall planning of a nationwide biomedical communications network.

The Lister Hill Center which is sponsoring this project has funds for only a limited set of such pilot systems. Therefore, similar projects are not planned until this project demonstrates its value. Mr. Flood? Mrs. Reid?

PRINCIPLE USERS OF TOXICOLOGY INFORMATION

Mrs. Reid. Who are the principle users of your services under the toxicology information program?

Dr. Cummings. Currently principle users of the toxicology information program's services are varied and include scientific and technical personnel from other Federal agencies—for example FDS, EPA, Council on Environmental Quality, and so forth—industries, academic institutions, and so forth. With the establishment in the last quarter of fiscal year 1971, of TIP's query response center at the Oak Ridge National Laboratory as an information analysis center, it is expected that the number and variety of users and the types of questions asked will increase considerably.

ADEQUACY OF NLM FUNDING

Mrs. Reid. There have been some who feel that the National Library of Medicine has not been adequately funded for the 5-year period 1968 through 1972. Of course most agencies could always use more money, but how do you feel about this—do you feel that sufficient process has been made?

Dr. Cummings. The National Library of Medicine is responsible for acquiring and organizing the steadily increasing volume of biomedical information produced in the United States and abroad as well as providing support to other medical libraries in the country. Additionally, through programs such as the Lister Hill National Center for Biomedical Communications the NLM is exploring new applications of technology to promote the most efficient communication of biomedical information. The NLM has attempted to perform these varied functions during the past 5 years on what basically has been a relatively constant budget. These fiscal constraints occurred during a period of an unprecedented information explosion and spiraling inflation costs. We, at the Library, recognize the need for a setting of priorities in the funding of health programs. However, the need is great in the field of biomedical communications and the potential payoff high in the form of improved health services, medical education, and research. The NLM, through a reordering of its priorities and the implementation of austere operating budgets, has managed, over the past few years, to perform its mission although on a restricted basis. Importantly, programs such as the Lister Hill National Center for Biomedical Communications have not had the resources to advance significantly beyond a few experimental and demonstration projects.

The Congress, through its authorizations under the Medical Library Assistance Act, has clearly envisioned significant support to medical libraries throughout the country. For example, in fiscal year 1972, $13.5 million was authorized for programs administered by the National Library of Medicine, a figure considerably above the 1972 budget request of $6,092,000.

We believe that many worthwhile efforts have been launched through NLM funding during the past 5 years but if the Library is to adequately explore and develop new information services it must have more adequate financial and human resources.

Mr. FLOOD. Thank you, Doctor.

Dr. CUMMINGS. Thank you, Mr. Chairman and members of the committee.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Amounts Available for Obligation

	1971	1972
Appropriation	$20,769,000	$21,981,000
Real transfers to:		
"Departmental Management"	-4,000	---
Real transfers from:		
"National Institute of Environmental Health Sciences" (Proposed transfer for increased pay costs)	442,000	---
"National Institute of General Medical Sciences" (Proposed transfer for increased pay costs)	229,000	---
Comparative transfers to:		
"Office of the Director"	-38,000	---
Comparative transfer from:		
"National Institute of Dental Research"	112,000	---
Total obligations	$21,510,000	$21,981,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Medical Library Assistance:						
101	Training	---	1,000,000	---	1,000,000	---	---
102	Special Scientific Projects	---	5,000	---	95,000	---	+90,000
102	Research	---	590,000	---	600,000	---	+10,000
103	Library Resources	---	2,205,000	---	2,105,000	---	-100,000
104	Regional Medical Libraries	---	1,912,000	---	2,002,000	---	+90,000
104	Publications Support	---	280,000	---	290,000	---	+10,000
	Subtotal	---	5,992,000	---	6,092,000	---	+100,000
	Direct Operations:						
105	Lister Hill National Center for Biomedical Communications	10	1,370,000	17	1,398,000	+7	+28,000
106	National Medical Audiovisual Center	105	2,023,000	105	2,127,000	---	+104,000
107	Library Operations	274	8,016,000	247	8,125,000	---	+109,000
109	Toxicology Information	18	1,237,000	18	1,237,000	---	---
110	Review and Approval of Grants	32	665,000	32	704,000	---	+39,000
110	Program Direction	55	2,207,000	55	2,298,000	---	+91,000
	Subtotal	467	15,518,000	474	15,889,000	+7	+371,000
	Total obligations	467	21,510,000	474	21,981,000	+7	+471,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	467	474	+7
Full-time equivalent of all other positions	18	18	---
Average number of all employees	485	489	+4
Personnel Compensation:			
Permanent positions	$6,135,000	$6,679,000	+544,000
Positions other than permanent	203,000	203,000	---
Other personnel compensation	89,000	89,000	---
Subtotal, personnel compensation	6,427,000	6,971,000	+544,000
Personnel benefits	515,000	577,000	+62,000
Travel and transportation of persons	167,000	167,000	---
Transportation of things	33,000	33,000	---
Rent, communications, and utilities	1,704,000	1,704,000	---
Printing and reproduction	468,000	468,000	---
Other services:			
Project contracts	3,572,000	3,447,000	-125,000
Payment to NIH Management Fund	981,000	1,046,000	+65,000
Other	818,000	868,000	+50,000
Supplies and materials	370,000	245,000	-125,000
Equipment	463,000	363,000	-100,000
Grants, subsidies and contributions	5,992,000	6,092,000	+100,000
Total obligations by object	21,510,000	21,981,000	+471,000

Summary of Changes

1971 estimated obligations	$21,510,000
1972 estimated obligations	21,981,000
Net change	+471,000

	Base		Change from Base	
Increases:	Pos.	Amount	Pos.	Amount
A. Built-in				
1. Annualization of 1971 pay increase cost	---	---	---	+232,000
2. Within grade pay increase	---	---	---	+145,000
3. Extra days pay FY 1972	---	---	---	+24,000
4. FTS rate increase	---	---	---	+5,000
Subtotal	---	---	---	+406,000
B. Program				
1. Special scientific projects	---	5,000	---	+90,000
2. Research	---	590,000	---	+10,000
3. Regional medical libraries	---	1,912,000	---	+90,000
4. Publications support	---	280,000	---	+10,000
Subtotal	---	---	---	+200,000
C. Payment to "National Institutes of Health Management Fund" for centrally furnished services	---	981,000	---	+65,000
Total increases	---	---	---	+671,000
Decreases:				
A. Program				
1. Library resources	---	---	---	-100,000
2. Library operations	---	---	---	-100,000
Total decreases	---	---	---	-200,000
Total, net change	---	---	---	+471,000

Explanation of Changes

Built-in Increases -- These increases will provide: $232,000 for the annualization of the 1971 pay increase cost authorized under Executive Order 11576; $145,000 for within grade pay increases in 1972; $24,000 for extra days pay in 1972 and $5,000 for increased cost in 1972 of using the Federal Telecommunications System.

Special scientific projects grants -- An increase of $90,000 will bring the total for this program to $95,000. This increase will permit the funding of three new projects.

Research grants -- An increase of $10,000 will bring the total for this program to $600,000. This will permit the continuance of this program at the 1971 level.

Regional medical libraries grants -- An increase of $90,000 will bring the total for this program to $2,002,000. The 1972 amount will fund continuation of the ten existing regional medical libraries and provide some increases in services to meet rising user demand.

Publication support grants -- An increase of $10,000 will bring the total for this program to $290,000. This increase will permit the funding of this program at the 1971 level.

Library resource grants -- A decrease of $100,000 will bring the totals for this program to $2,105,000. This will reduce by 135 the number of grants to be supported in 1972.

Library operations -- A total of $8,125,000 and 247 positions is requested in 1972, a program decrease of $100,000. The decrease represents planned reductions in project contracts.

Authorizing Legislation

	1972	
	Authorization Requested	Appropriation Requested
Legislation		
Public Health Service Act		
Section 371 - Purpose and Establishment of Library	Indefinite	15,889,000
Section 394 - Grants for Training in Medical Library Sciences	1,750,000	1,000,000
Section 395a - Assistance for Special Scientific Projects	500,000	95,000
Section 395b - Research and Development in Medical Library Sciences and Related Fields	3,000,000	600,000
Section 396 - Grants for Improving and Expanding the Basic Resources of Medical Libraries and Related Instrumentalities	4,000,000	2,105,000
Section 397 - Grants for Establishment of Regional Medical Libraries	3,250,000	2,002,000
Section 398 - Financial Support for Biomedical Publications	1,000,000	290,000

Explanation of Transfers

	1971 Estimate	Purpose
Real transfers to:		
"Departmental Management"	- 4,000	To establish Facilities Engineering and Construction Agency.
Real transfers from:		
"National Institute of Environmental Health Sciences"	+442,000	Proposed transfer for increased pay costs.
"National Institute of General Medical Sciences"	+229,000	Proposed transfer for increased pay costs.
Comparative transfer to:		
"Office of the Director"	- 38,000	Transfer of research contracts function from NIH Management Fund to Office of the Director.
Comparative transfer from:		
"National Institute of Dental Research"	+112,000	To provide an equitable distribution of the Management Fund in 1972.

National Library of Medicine

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$ 2,066,000	$ 2,066,000	$ 2,066,000	$ 2,066,000
1963	3,335,000	3,335,000	3,335,000	3,335,000
1964	4,074,000	4,074,000	4,074,000	4,074,000
1965	3,678,000	3,858,000	4,058,000	3,958,000
1966	9,185,000	9,185,000	9,685,000	9,685,000
1967	19,231,000	20,092,000	20,192,000	20,192,000
1968	21,162,000	18,662,000	21,162,000	20,192,000
1969	19,172,000	17,149,000	19,172,000	18,160,500
1970	22,882,000	19,682,000	19,682,000	19,682,000
1971	19,769,000	19,769,000	22,233,000	20,769,000
1972	21,981,000			

Justification

National Library of Medicine

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	467	6,942,000	474	7,548,000	+7	+606,000
Other expenses	--	14,568,000	--	14,433,000	--	-135,000
Total	467	21,510,000	474	21,981,000	+7	+471,000

General Statement

The National Library of Medicine is engaged in programs to advance the medical and health-related sciences through facilitating the exchange of information. The Library collects, organizes, and disseminates biomedical information to practitioners, educators, and research investigators, and carries out programs designed to strengthen existing and develop new medical library services throughout the United States.

Through the support programs authorized by the Medical Library Assistance Act of 1965 and its extension act of 1970, the National Library of Medicine has helped biomedical libraries and related institutions to support health care, develop more effective relationships with central resource libraries, improve techniques of information handling, and enhance the role of libraries as learning resources.

Other achievements include the production of new bibliographic publications from the computer-based Medical Literature Analysis and Retrieval System (MEDLARS) and the further development of an improved second-generation system, MEDLARS II. Through MEDLARS, the Library has extended its resources to libraries and individuals throughout the United States and abroad. It has also provided direct reference and interlibrary loan services to thousands of users.

The NLM has responsibility for establishing through its Toxicology Information Program a nationwide system for providing data on the harmful effects of chemical compounds. The program has developed a directory of toxicological information sources; compiled a toxicity bibliography and a register of chemical compounds; and initiated development of software necessary for a computerized information storage and retrieval system.

The Library's Lister Hill National Center for Biomedical Communications has been designated the focal point of the Department for coordinating biomedical communications systems and network projects and is responsible for applying computer and communications technology to the improvement of health care, medical education, and biomedical research. The Center has been pursuing its goals through inexpensive, precedent-setting experiments such as an on-line computer bibliographic search service of 100 clinical journals which can be accessed for the price of a telephone call. In 1972 the Center will continue to explore satellite communications as a means of linking physicians in remote areas to the resources of large medical centers, and its successful demonstration of the use of on-line bibliographic services (AIM-TWX) will be expanded on a national basis.

The 1972 budget request provides the minimum level of funds necessary to maintain the Library's programs at their current level of activity.

GRANTS

The programs authorized by the Medical Library Assistance Act of 1965 (Public Law 89-291) and the Medical Library Assistance Extension Act of 1970 (Public Law 91-212) are designed to meet national needs for better health information services through improved health library resources and facilities, trained manpower, and improved health communications technology. Specifically, the Act authorizes support of projects to develop resources and techniques necessary to collect, preserve, store, process, retrieve, and facilitate the dissemination and use of health science information.

Training and Fellowships

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount
Non-competing continuation grants.....	7	$700,000	7	$810,000	--	+$110,000
New grants.....	5	300,000	4	190,000	-1	- 110,000
Total.....	12	1,000,000	11	1,000,000	-1	--

The 1972 request for training is the same as the 1971. This will support seven non-competing continuation grants and four new grants for training programs in medical librarianship and related biomedical communications specialties. Current estimates indicate that each of 100 medical schools requires an average of 10 professionally trained specialists in this field, and approximately 1,000 other health related professional schools each requires at least one librarian. In addition, many of the 7,200 accredited hospitals need hospital librarians or other medical information specialists. New and growing professional schools, new and developing mechanisms for health care and growing awareness of the importance of maintaining professional skills through continuing education and training will require an increasing number of specialists to provide information services. The growing demand for such services requires development and support for a variety of new training opportunities. In 1970, the National Library of Medicine supported 90 trainees; in 1971, 100 trainees.

Quite clearly the training of 100 librarians and biomedical communications specialists per year will not satisfy the needs in this field for many years. Accordingly, steps are being taken to increase the number of graduates in these programs, particularly medical librarians, without sacrificing quality. In view of the fact that schools of librarian science graduate thousands of individuals with a masters degree, we are experimenting with methods of converting these graduates to medical librarians in a shorter and less expensive procedure than is involved when a college graduate must be supported by these grants from the baccalaureate degree to the masters degree in medical librarianship. In addition, we belisve that the recipients of this new, innovative type of training will be qualified to assume positions of major responsibility and will, in turn, be able to train additional medical librarians.

Special Scientific Projects

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount
Non-competing continuation grants	1	$5,000	--	--	-1	-$5,000
New grants	--	--	3	$95,000	+3	95,000
Total	1	5,000	3	95,000	+2	90,000

The 1972 request of $95,000 for Special Scientific Projects represents an increase of $90,000 over the 1971 level of support.

The purpose and intent of the Special Scientific Project Awards program is to support outstanding scholars who can devote their full time to analysis, evaluation and documentation of major progress in the health sciences. These studies result in the publication of important monographs on advances in science. In this way the massive scientific literature is reduced to a readily accessible and usable form.

The additional $90,000 will permit the National Library of Medicine to support three projects by distinguished senior scientists and physicians to write works on major subjects of broad health interest.

Research

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount
Budget Authority:						
Non-competing continuation grants	11	$380,000	14	$525,000	+3	+$145,000
New grants	9	210,000	3	75,000	-6	- 135,000
Total	20	590,000	17	600,000	-3	10,000

The 1972 request is for $600,000 in new obligational authority. It represents an increase of $10,000 from the 1971 level of $590,000. This amount will support 14 non-competing continuation grants and 3 new projects.

These funds will be utilized for research and demonstration grants to encourage and support the rapidly growing field of biomedical communications research. More scientists are being trained and entering this field, but they can advance the state of the art only if funds to support their research are available. For the health field these funds come almost exclusively from the National Library of Medicine. Many of the national problems of biomedical information services can only be resolved by sophisticated research in this field. This research grant program has supported one project to develop and test an on-line computer-base serials control system for a medical school library; another project compares manual and automated systems for indexing the medical literature for computer-based storage and retrieval of bibliographic citations; a third project will gather and analyze data to characterize the information exchange preferences and needs of several groups of health teachers and researchers.

The continuing high level of the national effort in health service, education, and research produces and requires a constantly growing amount of biomedical information. Knowledge leading to more effective transmission, storage, and retrieval

62-645 O - 71 - pt. 3 - 81

of this information at realistic cost-benefit ratios is an important goal of biomedical information research. Projects will be supported in: (1) information seeking practices of health professionals; (2) improvement of the biomedical vocabulary for written and mechanized information handling; (3) improved information systems; and (4) development and testing of various information media. Demonstration projects are needed to show how the findings of this research can improve information services to health professionals.

Library Resources

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount
Non-competing continuation grants.....	394	$1,500,000	165	$ 830,000	-229	-$670,000
New grants.....	147	705,000	241	1,275,000	+ 94	+ 570,000
Total.....	541	2,205,000	406	2,105,000	-135	- 100,000

The 1972 request of $2,105,000 for library resources grants represents a decrease of $100,000 in the level of support from 1971. This sum will permit the Library to support the 165 non-competing continuation grants in hospitals and health professional educational institutions, and to make 241 new awards.

Medical Library Resource Grants are designed to assist in the establishment, improvement, and expansion of the Nation's health science libraries, and to encourage increased community support for the local library. Grants for a one-year period are made to health institutions which demonstrate a need to establish basic collections and services. Grants are also made to institutions with existing health science libraries for the support of projects designed to make the evergrowing and already overwhelming scientific literature more rapidly accessible to health professionals throughout the United States. Funded applications include cooperative programs in which a strong resource library undertakes to provide training, consultation and loan services for the small community hospitals, clinics and other health facilities; projects which seek to speed the delivery of services through the use of modern communication devices and automation techniques; and projects which simply increase the information resources of an institution after an assessment of needs of the health professionals.

This program is also important in complementing the expanding service activities of the Regional Medical Library Program. The full benefits of the Regional Medical Library networks can be realized more effectively if local library resources are selectively improved.

Regional Medical Libraries

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount
Budget Authority:						
Non-competing continuation grants.....	10	$1,912,000	10	$2,002,000	--	+$90,000
New grants.....	--	--	--	--	--	--
Total.....	10	1,912,000	10	2,002,000	--	+ 90,000

The 1972 request for $2,002,000 represents an increase of $90,000 over the 1971 level. This amount will allow the Library to maintain the support of the 10 active regional libraries and will cover the increased costs of operation for improved service to meet rising service demands. The objective of this program is to develop a system of Regional Medical Libraries with the necessary depth and scope to supplement the services of other medical libraries in their designated region. Back-up library services in the form of inter-library loans, MEDLARS literature searches and other reference services are now available across the Nation.

In 1970, complete geographic coverage was achieved with the establishment of the Mid-Continental Regional Library located in Omaha, Nebraska and the South Central Regional Library located at Dallas, Texas. In 1972 approximately 70 percent of the appropriation will be used to expand and improve the Regional Medical Libraries. The remainder of the funds will be granted to regional libraries to support programs designed to improve the methods of providing information to all qualified users. Ready access to the literature by physicians is vital to the health of the citizens of the United States, and its availability to educators assists in the development of health manpower.

Publications Support

	1971 Estimate		1972 Estimate		Increase or Decrease	
	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount
Non-competing continuation grants.....	5	$ 41,000	7	$ 161,000	+2	+$120,000
New grants.....	12	239,000	7	129,000	-5	-110,000
Total.....	17	280,000	14	290,000	-3	+ 10,000

The 1972 request of $290,000 for publication support grants will allow the Library to support seven continuing projects and seven new projects.

The purpose of this program is to assist in the publication of works vital to improving the health of all the people of this country. Support is provided for preparation and publication of abstracts, bibliographies, handbooks, critical reviews, monographs and translations for health scientists, educators, and practitioners. Publications supported by the program are those of need and merit which cannot be financed by commercial publishers. Among the funded projects are reviews of recent research on environmental health and substances toxic to man; assistance for a new periodical to provide needed information on nutrition education to workers in this field; the development of a manual of community medicine for use by physicians in remote or relatively underdeveloped regions; and experimental or innovative publications to improve and promote self-instruction by medical students.

Current trends indicate increased need for the publications supported under this program to meet the challenge of the increasing output of new knowledge of health and disease.

DIRECT OPERATIONS

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	467	$ 6,942,000	474	$ 7,548,000	+7	+$606,000
Other expenses	--	8,576,000	--	8,341,000	--	- 235,000
Total	467	15,518,000	474	15,889,000	+7	+ 371,000

Lister Hill National Center for Biomedical Communications

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	10	$ 210,000	17	$ 338,000	+7	+$128,000
Other expenses	--	1,160,000	--	1,060,000	--	- 100,000
Total	10	1,370,000	17	1,398,000	+7	+ 28,000

The Lister Hill National Center for Biomedical Communications is the focal point for coordinating the biomedical communications systems for the entire Department and is responsible for developing a Biomedical Communications Network. It is now providing an experimental service to over 30 hospitals and libraries using teletypewriter terminals to access bibliographic citations to current medical information stored in an on-line time-sharing computer. The capability thus being explored enables users to access the literature from the 100 leading English language medical care journals for the price of a telephone call. This experimental service has been very successful, cutting retrieval times from weeks to minutes at reduced costs for bibliographic service when compared with older computer systems. The development is now aimed at improving this system and making it one which can be operated on other computers in the United States and abroad. The Center has also explored such projects as support for self paced learning and education for medical students and practicing physicians with the use of new multi-media devices; satellite communications for exchange of medical information between the community hospital or academic medical center and remote health stations. In addition, the Center is making efforts to select and evaluate curriculum content for medical education and to develop systems for the sharing of such material among medical colleges.

The augmentation provided by the Congress in the 1971 budget is being used to expedite the experiment in satellite communications for Alaska to provide medical consultation and education to remote parts of the state.

Preliminary experiments have been run using the Application Technology Satellites of the National Aeronautics and Space Administration which demonstrated the feasibility of this approach for voice, pictures in color, computer information, and electrocardiograms. Further experiments are anticipated soon testing the satellite communications between health personnel in Alaska, and Stanford University, the University of Washington, and the University of Wisconsin. These experiments are designed to verify the capability of such satellites to meet dispersed communications needs where telephones are unavailable, and provide reliable communications where radio is unreliable because of the effects of the aurora borealis.

In addition, some of the funds are being used to speed the development of a two-way color television network linking the medical schools and hospitals in Vermont and New Hampshire. An experimental link in this network is now operating from Dartmouth to Claremont Hospital and has been successful in bringing the expertise of the medical center to that hospital, particularly in the intensive care of heart and cancer patients. The overall network will link 15 hospitals and 3 university medical centers in what is hoped will be a mutually reinforcing program of improved health care delivery and education.

The 1972 budget request represents a continuation of the program at its present level, with enough additional funds to cover within-grade pay increases. There is, however a proposed redistribution of resources between contract funds and in-house personnel. One hundred thousand dollars has been reallocated out of contract funds to provide seven additional personnel positions in the Center. The present personnel level of 10 (7 professional and 3 secretarial) has been found inadequate to manage the projects of the Center as they move toward operational capabilities. In particular, the increase in technical assistance provided by the Center to other elements of the government, medical schools, hospitals, and professional societies has created a requirement for additional staff. In essence, the Center is becoming the major technology transfer element between the computer and communications communities and the medical community. Continuation of this development cannot be accomplished solely through contracts, and therefore, requires additional personnel.

National Medical Audiovisual Center

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	105	$1,464,000	105	$1,568,000	--	+$104,000
Other expenses.....	--	559,000	--	559,000	--	--
Total.....	105	2,023,000	105	2,127,000	--	+ 104,000

The NMAC, located in Atlanta, Georgia, administers programs aimed at improving the quality and use of biomedical audiovisuals in schools of the health professions and throughout the biomedical community.

Following recommendations of the Board of Regents of the National Library of Medicine, NMAC was reorganized in 1971 to shift a major portion of its resources to acquisition, distribution, and reference services; educational research and consultation; and systems evaluation and application. Under its revised operating policies, NMAC acquires audiovisual materials which have been reviewed for their direct relevance to contemporary professional education in the health sciences. The Center also supports such education through media production workshops, seminars, conferences, training programs, and on-site surveys. These are designed to assist in the rapid development of health manpower.

In 1972 the Center will expand the acquisition and evaluation of materials to support its professionally-oriented distribution activity. A significant number of educational materials will be produced and field-tested in cooperation with health professionals and institutions, and experimentation will continue in the design and production of modular audiovisual units which can be excerpted, updated, and restructured by health professional educators to meet their individual needs. The Center also will continue to explore the value of new instructional packages for self instruction within NMAC and within cooperating educational institutions throughout the country.

Library Operations

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	247	$3,514,000	247	$3,773,000	--	+$259,000
Other expenses	--	4,502,000	--	4,352,000	--	- 150,000
Total	247	8,016,000	247	8,125,000	--	+ 109,000

Library Operations provides bibliographic, reference, and loan services as a central resource for a nationwide network of regional and local medical libraries. Approximately 250,000 such services were provided in 1971 at the NLM in addition to an estimated 305,000 provided by the regional libraries.

More than 95 percent of document requests originating in all regions of the country are now being filled more promptly than ever before. Eighty-five percent are filled in approximately three days as compared to a week or more in the past. One factor responsible for the reduction in time is that document requests are now transmitted by telecommunications. The NLM indexes annually about 210,000 medical and health articles for inclusion in Index Medicus, a comprehensive monthly listing of citations to current world-wide biomedical literature. Fifty-five hundred subscriptions to the publication were sold by the Superintendent of Documents in 1970. Citations are stored in the computerized Medical Literature Analysis and Retrieval System (MEDLARS) and retrieved for publication of Index Medicus, Cumulated Index Medicus (an annual product of about 10,000 pages with sales of approximately 4,500), and various recurring bibliographies which are prepared for and supported by specialty groups in fields such as medical education, dentistry, neurosurgery, and epidemiology. The data base also is used to provide on request over 20,000 bibliographies to health professionals.

In January 1971, the Library began publishing a new bibliography, "Selected References on Environmental Quality as it Relates to Health," which provides ready access to all of the material in the MEDLARS data base pertaining to environmental health.

Another new NLM publication appeared in 1970. Abridged Index Medicus, which contains information from 100 high quality English language journals selected with particular reference to their orientation to patient care and the training of health manpower, is particularly suitable for small hospitals. During 1970, more than 3,000 subscriptions to the monthly publications were sold, and a cumulated volume of Abridged Index Medicus also was produced.

During 1971, a graphic image storage and retrieval system, containing microfilms of documents from publications in greatest demand, will become operational. With a capacity of about 200,000 documents this system will provide rapid and reliable document delivery for interlibrary loans on an automated basis. Delivery of equipment is scheduled for the Spring of 1971.

The National Library of Medicine also publishes a computer-generated Current Catalog, which provides announcement and cataloging information for medical libraries throughout the world. A recently developed computer-generated announcement service, appearing on a semi-weekly basis, was implemented in 1970. Published in cooperation with the Medical Library Association, the publication is providing announcement and citation data for almost 300 libraries in the U.S. and saves many small libraries the cost of redundant cataloging.

During 1970, Library Operations field-tested and evaluated the AIM/TWX on-line bibliographic retrieval system developed cooperatively with the Lister Hill Center.

As a result of successful field-testing, an expanded data base and network for the system will be extended to all the regional libraries and MEDLARS centers and will be integrated with MEDLARS II as its on-line component. Implementation is scheduled for the end of 1971.

The request for Library Services in 1972 is $4,518,000 and 195 positions. These funds will permit the processing of 116,000 interlibrary loan requests; 19,000 domestic computer-generated demand searches; 80,000 reader requests (direct use of the collection); indexing of 230,000 articles; and publication of 21 recurring bibliographies. The funds will also permit the Library's collection to be augmented by 110,000 serial pieces and 40,000 monographs. Maintenance of the collection will include the binding of 22,000 volumes and the preservation and graphic image storage microfilming of 700,000 pages.

Development and implementation of a second-generation MEDLARS (MEDLARS II)

The National Library of Medicine began the development of a second-generation Medical Literature Analysis and Retrieval System (MEDLARS II) in 1968 through a major contract with the Computer Sciences Corporation. The contract included responsibilities for system analysis, design and software implementation, and the MEDLARS II plan called for a three to four year project of development and incremental upgrading.

Under present project schedules; implementation of the first phases of MEDLARS II will take place in about the second quarter of fiscal 1972. This delay is due principally to an underestimate of the magnitude of the task to be accomplished. When completed, the new system should provide important systems support to several technical functions within the Library.

In full operation, MEDLARS II will incorporate the following technical elements: increased processing capability; internal on-line storage devices permitting direct access to the data base; multi-programming capability which will permit several tasks to be performed by the computer simultaneously; and limited on-line access to data bases from remote terminals. Translated into program capabilities, the new features will provide for: a greatly increased file capacity to allow the maintenance of abstracts, summaries, and bibliographic service requests; the processing of more current data through direct input and on-line updating of the file; an automated acquisition and cataloging system with availability of cataloging data to and from medical libraries; development of specialized information files to support the Library's toxicology information programs through the addition of chemical name and structure search capabilities; and, support of data processing and data transmission activities of the biomedical communications network.

Experience with the MEDLARS II system as developed thus far has led to the conclusion that the present hardware configuration is not capable of handling the tasks involved in the development work and that a more sophisticated computer will be required for implementation. Funds to provide for this upgrading on a lease basis are included in the 1972 budget request.

The 1972 request includas $3,607,000 and 52 positions to operate the MEDLARS I system and to continue development, implementation, and operation of the MEDLARS II system, including lease of a more sophisticated computer configuration.

Toxicology Information Program

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	18	$ 349,000	18	$ 374,000	--	+$25,000
Other services	--	888,000	--	863,000	--	- 25,000
Total	18	1,237,000	18	1,237,000	--	--

The Toxicology Information Program (TIP) was established by Presidential order following recommendations of the President's Science Advisory Committee on the Handling of Toxicological Information (1966). In 1967, responsibility for its implementation was delegated to the National Library of Medicine by the Secretary of Health, Education, and Welfare.

Toxicological data currently are dispersed among numerous non-mechanized and uncoordinated information sources. The mission of the Toxicology Information Program is to provide for the selection, analysis and automated storage and retrieval of such information. The effective implementation of the program requires close collaboration with other government agencies and the creation of a capability to respond to requests for information. This in turn requires access to toxicology information from scientific literature and the files of government and industry.

Collaborative Activities with Other Organizations:

The TIP has developed (1) a computerized data bank for 400 primary pesticide petitions (in cooperation with the FDA and the newly-created Environmental Protection Agency); (2) a centralized automated data system for studies of individuals occupationally exposed to pesticides; (3) an on-line computerized search system based on the journal, Health Aspects of Pesticides Abstract Bulletin; (4) a computerized index to the Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health; (5) a comprehensive bibliography on a selected list of food additives generally recognized as "safe;" and (6) has maintained and enhanced a data base of 35,000 chemicals of major biomedical interest.

In 1972, efforts will be directed toward the maintenance of current working agreements and the initiation of new agreements with governmental agencies which either have files of interest to the Toxicology Information Program or needs for TIP products and services. Attempts will be made to establish similar collaborative arrangements with academic and industrial organizations. Specifically, efforts will be made to organize data bases which are initiated, maintained, and directed by the Toxicology Information Program, but financially supported by other Federal agencies and private institutions which will use the system.

Development of Specialized Files Based on the Published Literature:

In 1970 and 1971, TIP's activities included (1) the preparation of a publication on drug-drug and drug-chemical interactions; (2) creation of a computerized service ("Toxitapes") for industrial and pharmaceutical toxicology based on articles selected from Biological Abstracts; (3) enrichment of the NLM's on-line Abridged Index Medicus retrieval system by the addition of journals having clinical toxicology content; and (4) preparation for a journal on the "health effects of environmental pollutants" containing 13,000-14,000 abstracts per year.

Automated Systems:

The TIP has completed the evaluation of a pilot computer system to handle toxicology data. In 1972, the program will attempt to take advantage of software systems already owned or under development by the Federal Government. Activities in 1972 will include minimum maintenance of the Toxicology Roster System, extension and expansion of the interaction of MEDLARS and Chemical Abstracts systems, and extension of the Toxicology Vocabulary.

Query Response Center:

TIP has established an information analysis center for pesticides and environmental toxicology at the Atomic Energy Commission's Oak Ridge National Laboratories. Funded and supervised by TIP, the center draws on scientists from various disciplines on an ad hoc basis. It can thus respond to queries from the scientific community by providing in-depth literature searches and data analysis and state of the art reports. In addition, the specialized data files assembled by the Toxicology Information Program are accessible to the center.

Review and Approval of Grants

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	32	$541,000	32	$580,000	--	+$39,000
Other services	--	124,000	--	124,000	--	--
Total	32	665,000	32	704,000	--	+ 39,000

This activity provides the administrative staff and program direction for the six grant programs authorized by the Medical Library Assistance Act of 1965 and its extension act of 1970, as well as for the international activities of the NLM which are funded by the Scientific Activities Overseas appropriation.

The increase of $39,000 is for pay increases.

Program Direction

	1971 Estimate		1972 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	55	$ 864,000	55	$ 915,000	--	+$51,000
Other services	--	1,343,000	--	1,383,000	--	+ 40,000
Total	55	2,207,000	55	2,298,000	--	+ 91,000

Program direction provides support for the immediate Office of the Director, the Office of Administrative Management, the Office of Public Information and Publications Management, and payment to the National Institutes of Health Management Fund for centrally furnished services. The activity thus provides the program leadership and centralized administrative support necessary for the coordinated operation of the various NLM activities.

The increase of $91,000 is for costs of services furnished through the NIH Management Fund, and pay cost increases.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Training Grants (Medical Library Assistance Extension Act of 1970, P.L. 91-212, Section 394)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,000,000	$1,750,000	---	$1,000,000

Purpose: The training program authorized by the Medical Library Assistance Act, and extended by the Medical Library Assistance Extension Act of 1970, is intended to help meet the Nation's need for medical librarians and other medical information specialists. The emphasis of the program is on training for creative leadership in positions of major responsibility.

Explanation: Project grants are awarded to institutions to assist individuals in obtaining post-baccalaureate degrees, to librarians or other biomedical information specialists for intensive training or retraining, and to institutions for the support of training programs and medical library internships.

Accomplishments in 1971: It is estimated that 12 grants will be awarded in Fiscal Year 1971. Of these, seven are continuations of previously awarded projects and five will be new awards.

Objectives for 1972: The estimate for Fiscal Year 1972 provides the same level of funds as in 1971. This will allow the Library to support 11 projects. Of these 11, 7 will be continuations and 4 will be new awards, which will support an estimated 100 trainees.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Special Scientific Project Grants (Medical Library Assistance Extension Act of 1970, P.L. 91-212, Section 395a)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$5,000	$500,000	---	$95,000

Purpose: The grants are intended to support outstanding scholars in full-time analysis and documentation of major advances in the health sciences, the results to be published as monographs on advances in biomedicine.

Explanation: Project grants are awarded to physicians and other health sciences practitioners, scientists, and public or non-profit private institutions on behalf of such people.

Accomplishments in 1971: It is estimated that one project grant will be partially supported in 1971.

Objectives in 1972: The $95,000 in Fiscal Year 1972 will provide support for three projects by highly qualified scholars to synthesize the literature in their particular fields.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Research Grants (Medical Library Extension Act of 1970, P.L. 91-212, Section 395b)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$590,000	$3,000,000	---	$600,000

Purpose: The intent of the research grants program is to develop methods of processing and making accessible the rapidly growing body of biomedical information. If such information is to have the maximum amount of impact on further research in the health-related sciences and ultimately on health care, an enhanced capability for processing, storing, and retrieving the data is essential.

Explanation: Project grants are made for research, investigations, and demonstrations in medical library science and for the development of new techniques, systems, and equipment for the processing of biomedical information.

Accomplishments in 1971: It is estimated that 20 grants will be awarded in Fiscal Year 1971. Of these, 11 will be non-competing continuation awards and 9 will be new projects.

Objectives for 1972: The request for 1972 will permit the support of 14 non-competing continuation grants and 3 new awards.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Library Resource Grants (Medical Library Assistance Extension Act of 1970, P.L. 91-212, Section 396)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$2,205,000	$3,500,000	---	$2,105,000

Purpose: The purpose of the grants is to provide financial assistance and incentive for improving the basic materials, equipment, and services of medical libraries. The emphasis is on rapidly upgrading the medical libraries supported by hospitals, educational institutions, and medical societies.

Explanation: Project grants are made for the acquisition of books, journals, and other materials; cataloging, binding, and other processing services; acquisition of duplicating and other equipment to facilitate service; and the introduction of new technologies in medical librarianship. No grant may exceed $200,000 for any fiscal year, and the Secretary may prescribe grant amounts with a view to assuring adequate continuing financial support from other sources during and after the period of Federal assistance.

Accomplishments in 1971: The Library expects to make 541 awards in 1971; 394 will be continuing projects and 147 will be new grants.

Objectives in 1972: The requested level in 1972 will allow the support of 165 continuing grants and 241 new ones for a total of 406 awards.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Regional Medical Libraries Grants (Medical Library Assistance Extension Act of 1970, P.L. 91-212, Section 397).

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,912,000	$3,250,000	---	$2,002,000

Purpose: The program is intended to develop a system of Regional Medical Libraries with the scope and depth necessary to supplement significantly the services of local medical libraries in each region. Backup services to such libraries include interlibrary loans, MEDLARS literature searches, and other reference services to user organizations. The Regional Medical Library is of particular benefit to medical practitioners who lack access to a major medical library.

Explanation: Project grants are awarded to improve regional service in libraries selected because they already have a sound base. In 1970 complete geographic coverage was achieved with the establishment of the Mid-Continental Regional Library located in Omaha, Nebraska and the South Central Regional Library located in Dallas, Texas.

Accomplishments in 1971: In 1971, 10 continuing projects will be supported.

Objectives in 1972: The 1972 request represents a $90,000 increase. This amount will allow the Library to maintain the support of the ten active regional libraries and will cover the increased costs of operation and some increase in service to meet rising service demands.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Publications support grants (Medical Library Assistance Extension Act of 1970, P.L. 91-212, Section 398)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$280,000	$1,000,000	---	$290,000

Purpose: This program assists in the development of useful, selected publications to help American health professionals digest and utilize the tremendous output of new information in the biomedical sciences.

Explanation: Project grants provide support for the preparation, and/or publication of secondary tools such as abstracts, bibliographies, handbooks, and critical reviews, as well as monographs and translations which condense, synthesize, evaluate, or otherwise repackage information for health scientists, educators and practitioners.

Accomplishments in 1971: It is estimated that 17 grants will be awarded in Fiscal Year 1971. Of these, five will be continuing projects and twelve are new projects.

Objectives for 1972: The 1972 request will provide support for 14 projects; 7 continuing projects and 7 new projects.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Lister Hill National Center for Biomedical Communications

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
10	$1,370,000	--	17	$1,398,000

Purpose: The Lister Hill National Center for Biomedical Communications provides a mechanism for the transfer of computer and communications technology to improve biomedical research, medical education, and health care delivery.

Explanation: The Lister Hill Center maintains a program to identify new developments in information technology. In parallel, it reviews the needs of the medical community to identify areas of need which could be met by the application of such technology. On the basis of correspondence between priority needs and technological capabilities, the Center develops experimental services and manages their evaluation.

Accomplishments in 1971: In 1971, the Center has demonstrated the utility of on-line bibliographic access in more than 30 hospitals, libraries, and medical research facilities. The Center has experimented with satellite communications for voice, data, facsimile, and analog signals and has planned a major experiment with Alaska to test this new communication modality. The Center is evaluating an experimental, two-way TV link for patient care and medical education and has planned a communications network for medical schools and hospitals in Vermont and New Hampshire. Three other projects have been directed toward cooperative development of multimedia educational materials to be shared by medical schools.

Objectives in 1972: The requested funding in 1972 will allow the operational test of satellite communications in Alaska and the development of the initial portions of a network in Vermont and New Hampshire. It will provide augmented in-house staff for the Center to meet the growing demand for managerial and technology transfer functions. It will permit the transition of the experimental on-line bibliography to an operational service to the medical community. Finally, it will allow new initiatives in experiments related to communication services into homes via cable and audio playback systems.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: National Medical Audiovisual Center

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
105	$2,023,000	--	105	$2,127,000

Purpose: The Center administers programs to improve the quality and use of biomedical audiovisuals in schools of the health professions and throughout the biomedical community.

Explanation: NMAC acquires, organizes, and distributes audiovisuals; provides educational research and consultation; and performs reference services and evaluation of audiovisual systems.

Accomplishments in 1971: NMAC provided approximately 100,000 units of educational service or assistance in 1971 to well over 31,000 representatives of schools of the health sciences or organizations of the biomedical community. The services included educational consultation, workshops, and seminars, national conferences, systems surveys, video tape duplications, reference services, audiovisual loans, and assistance to professional groups in the development and evaluation of instructional materials.

Objectives for 1972: The Center will expand its acquisition and distribution activities; produce and field-test educational materials in cooperation with health professionals; and experiment with self-instructional technology and with modular audiovisual units valuable for their ease of up-dating and flexibility of use. The reallocation of resources within the Center which was initiated in 1971 will permit approximately a 20 percent increase in the amount of educational services rendered and the number of professionals served.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Library Operations

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
247	$8,016,000	--	247	$8,125,000

Purpose: In order to advance medical and related sciences through the collection, organization, and dissemination of biomedical information, the Library acquires and maintains materials pertinent to biomedicine; compiles and publishes catalogs, indices, and bibliographies of such materials; and provides reference and other assistance to practitioners, students, and researchers.

Explanation: Under this activity the Library acquires and catalogs materials and analyzes and indexes biomedical literature for incorporation into MEDLARS, the NLM's computerized bibliographic information storage and retrieval system. From the MEDLARS data base the Library publishes Index Medicus, 23 other specialized bibliographies of journal articles, and a Current Catalog of recently acquired books, monographs, and technical reports. The Library also manages and coordinates a network of domestic and foreign MEDLARS stations to obtain indexing of the world's most important biomedical literature and to disseminate MEDLARS services widely in the United States and abroad; and, through its History of Medicine Division, acquires, organizes and maintains the historical source materials of biomedicine.

Accomplishments in 1971: The NLM rendered approximately 250,000 services in its dual capacity as a central national backup facility and as one component in a network of regional libraries. Such services included bibliographic references and interlibrary loans from the collection. In addition, the Library indexed roughly 210,000 articles for inclusion in the monthly Index Medicus (to which in 1970 there were 5,500 subscriptions) and published the annual Cumulated Index Medicus, a product of about 10,000 pages with sales of approximately 4,500. In 1971 the Library began publication of a new bibliography, Selected References on Environmental Quality as it Relates to Health, and continued publishing the monthly and annual volumes of Abridged Index Medicus, to which 3,000 subscriptions were sold in 1970 and which has been found particularly suitable for individual practitioners and for small hospital libraries. Also becoming operational in 1971 is a graphic image storage and retrieval system containing microfilms of documents from publications most in demand, with a capacity of about 200,000 documents, which will provide rapid, automated delivery of interlibrary loans.

Objectives for 1972: Plans for 1972 call for continuation of the operations outlined above at approximately the same level of activity. Specifically, the Library anticipates that it will process 116,000 interlibrary loan requests; perform 19,000 domestic computer-generated demand searches of the biomedical literature; process 80,000 reader requests; index 230,000 articles; publish 21 recurring bibliographies; augment the collection by 110,000 serial pieces and 40,000 monographs; bind 22,000 volumes; and microfilm a total of 700,000 pages.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Toxicology Information

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
18	$1,237,000	--	18	$1,237,000

Purpose: The Toxicology Information Program supports the development and operation of a computer-based toxicology information system and accompanying information products and services to satisfy the needs of other agencies, industry, the scientific community and the public at large.

Explanation: Toxicological information and data are currently scattered among numerous non-mechanized and uncoordinated information sources. The Toxicology Information Program is organizing toxicologic data to facilitate retrieval and provide information upon request through automated processing.

Accomplishments in 1971: The program collaborated extensively in 1971 with other Federal agencies to automate pesticide petition toxicology data (EPA/FDA) and human epidemiological data on pesticides (EPA); established a Query Response Center (Oak Ridge National Laboratory, AEC) to provide a toxicological information analysis function for the scientific community; extended the development and use of specialized toxicological information and data files (e.g., a roster of 3,100 toxicology experts, a file of 1,000 biomedical professionals' information usage needs, and a data base of toxicology on 1,000 chemicals); initiated development of new information products and services (e.g., "Toxitapes" covering industrial and pharmaceutical toxicology, a Drug Interaction Bibliography, a computer-based abstract journal on the "Health Aspects of Environmental Pollutants," and a Toxicology Thesaurus).

Objectives for 1972: The TIP will emphasize in 1972 its collaborative efforts with other Federal agencies and establishment of similar activities with academic and industrial organizations; continuation of the activities and capabilities of the Query Response Center; initiation, development and dissemination of new products and services to meet user needs; and continuation of the development, maintenance, expansion and dissemination of specialized toxicological information and data files, with special emphasis on pesticides and other bio-environmental toxicants.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Review and Approval of Grants (Public Health Service Act, Title II, Part I)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
32	$665,000	--	32	$704,000

Purpose: This activity provides support for staff to manage the six grant programs authorized by the Medical Library Assistance Act of 1970, as well as international activities of the NLM funded by the Scientific Activities Overseas appropriation.

Explanation: The functions of this office include the processing of grant applications and their review by program officers, staff assistance to reviewing committees, grants management and direction, and program review and evaluation.

Accomplishments in 1971: This office provided the administrative support and program leadership necessary for a coordinated approach to the development of biomedical communications materials and systems.

Objectives for 1972: This activity will direct a portion of its efforts towards implementing the redirections of the NLM training grant program. Steps are currently being taken to train more medical librarians without significantly increasing cost. At present, schools of librarian science graduate a large number of students each year with a master's degree in librarianship. Conceivably the graduates could be converted to medical librarians faster and less expensively than is now required to produce a medical librarian starting at the baccalaureate degree level.

62-845 O - 71 - pt. 3 - 82

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Program Direction (Public Health Service Act, Title III, Part I)

1971		1972		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
55	$2,207,000	--	55	$2,298,000

Purpose: This activity provides the program leadership and centralized administrative support necessary for the coordinated operation of the various NLM activities.

Explanation: Program direction provides support for the immediate Office of the Director, Office of Administrative Management, the Office of Public Information and Publications Management, and payment to the National Institutes of Health Management Fund for centrally furnished services.

Accomplishments in 1971: Supervision of NLM activities throughout the fiscal year.

Objectives for 1972: Efforts in 1972 will be directed towards the development of new and the improvement of current systems being utilized in the dissemination of biomedical data. Specific emphasis is being placed on the systems design for the distribution of toxicity information utilizing MEDLARS II and the Lister Hill Center's Biomedical Communications Network. Additionally, a concerted effort is being made to provide entry to MEDLARS via chemical nomenclature. There will be an additional emphasis on overall program evaluation and analysis.

NEW POSITIONS REQUESTED
Fiscal Year 1972

	Grade	Number	Annual Salary
Lister Hill National Center for Biomedical Communications			
Medical Officer	GS-15	1	$24,251
Information Specialist	GS-14	1	20,815
Engineer	GS-14	1	20,815
Information Specialist	GS-12	1	15,040
Electronics Technician	GS-11	1	12,615
Statistician	GS-9	1	10,470
Secretary	GS-7	1	8,582
Total, New Positions		7	$112,588

THURSDAY, APRIL 22, 1971.

SCIENTIFIC ACTIVITIES OVERSEAS (SPECIAL FOREIGN CURRENCY PROGRAM)

WITNESSES

DR. S. PAUL EHRLICH, JR., DIRECTOR, OFFICE OF INTERNATIONAL HEALTH
LINDA ALLISON, COORDINATOR, SPECIAL FOREIGN CURRENCY PROGRAM
GERALD F. MEYER, CHIEF, HEALTH BRANCH, DIVISION OF BUDGET

SCIENTIFIC ACTIVITIES OVERSEAS (SPECIAL FOREIGN CURRENCY PROGRAM)

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 est.	1972 est.
PUBLIC HEALTH SERVICE			
Travel and transportation of persons	61	65	65
Other services	2,677	28,645	24,964
Grants, subsidies, and contributions	311	525	516
Total, Public Health Service	3,049	29,235	25,545
ALLOCATION TO NATIONAL SCIENCE FOUNDATION			
Other services, National Science Foundation	953		
Total obligations	4,002	29,235	25,545

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 est.	1972 est
Program by activities: Foreign health research	4,002	29,235	25,545
Total obligations	4,002	29,235	25,545
Financing:			
Unobligated balance available, start of year	−838	−291	
Unobligated balance available, end of year	291		
Budget authority	3,455	28,944	25,545
Budget authority:			
Appropriation	3,455	32,444	25,545
Transferred to other accounts		−3,500	
Appropriation (adjusted)	3,455	28,944	25,545
Relation of obligations to outlays:			
Obligations incurred, net	4,002	29,235	25,545
Obligated balance, start of year	26,873	23,122	40,875
Obligated balance, end of year	−23,122	−40,875	−49,200
Outlays	7,753	11,482	17,220

Note.—Excludes $10,674 in 1972 for activities transferred to Scientific activities overseas (special foreign currency program), Environmental Protection Agency, 1970, $220; 1971, $3,500.

INTRODUCTION OF DR. EHRLICH AND ASSOCIATES

Mr. SMITH. The committee will come to order. This morning we have the Office of International Health.

You are Dr. Ehrlich?

Dr. EHRLICH. Right. Good to see you.

Mr. SMITH. Dr. Ehrlich, if you have biographical sketches we will insert them in the record at this time.

(The sketches follow:)

BIOGRAPHICAL SKETCH OF S. PAUL EHRLICH, JR., M.D., M.P.H.

Position: Director, Office of International Health.
Birthplace and date: Minneapolis, Minn.—May 4, 1932.
Education:
University of Minnesota: 1953—B.A. (Sociology); 1955 B.S.; 1957 M.D.
Internship PHS Hospital, Staten Island, N.Y. 1958.
University of California (Berkeley) 1961 M.P.H.; 1961–63 Resident in Epidemiology.
Experience:
Present: Director, Office of International Health, Office of the Secretary.
1969–1970: Acting Director, Office of International Health, Office of the Secretary.
1968–1969: Deputy Director, Office of International Health, Office of the Secretary.
1967–1968: Associate Director for bilateral programs, Office of International Health, PHS, Washington, D.C.
1967: Deputy Chief, heart disease control program, National Center for Chronic Disease Control, PHS, Arlington, Va.
1966–1967: Assistant Chief for Program Development, heart disease control program, Division of Chronic Diseases, PHS, Arlington, Va.
1961–1965: Chief, Field and Training Station, heart disease control program, Division of Chronic Diseases, San Francisco, Calif.
1959–1960: Grants and Training Branch, National Heart Institute, Bethesda, Md.
1958–1959: Medical Officer, U.S. Coast Guard, Alameda, Calif.
Association memberships:
Diplomat, American Board of Preventive Medicine.
Fellow, American College of Preventive Medicine.
American Medical Association.
Fellow, American Public Health Association.
Fellow, Council on Epidemology, American Heart Association.
American Society for the Advancement of Science.
American Geriatrics Society.
New York Academy of Sciences.
10/1970: Assistant Surgeon General, U.S. Public Health Service.
11/1969: U.S. representative of the executive board of the World Health Organization.
Academic appointments
Present: Clinical Associate Professor, Department of Community Medicine and International Health, Georgetown University School of Medicine, Washington, D.C.
Present: Adjunct Professor of International Health, University of Texas, Houston, Tex.

BIOGRAPHICAL SKETCH OF LINDA A. ALLISON

Position: Coordinator, special foreign currency program, Office of International Health.
Birthplace and date: Hutchinson, Kans., December 17, 1941.
Education: University of Texas, 1963, B.A.

Experience:

Present: Coordinator, special foreign currency program, Office of International Health, Office of the Secretary.

1969–1970: Management intern assignment—Office of the Assistant Director for International Affairs, Health Services and Mental Health Administration.

1969: Management intern assignment—Acting program management officer, panel on effectiveness, Secretary's Task Force on Medicaid and Related Programs.

1969: Management intern assignment—Office for Civil Rights, Office of the Secretary.

1968–1969: Management intern assignment—Division of Personnel Management, Food and Drug Administration.

1967–1968: Management intern assignment—Division of Student Financial Aid, Bureau of Higher Education, Office of Education.

Association Memberships:

Phi Alpha Theta (society recognizing scholarship in history).

Phi Beta Kappa.

Medical Committee for Human Rights.

Awards:

Cash award for performance on a management intern assignment—Food and Drug Administration, 1969.

Cash award for performance with the Medicaid Task Force—awarded by the Community Health Service, 1970.

Mr. SMITH. How do you want to proceed?

Dr. EHRLICH. With your permission, Mr. Chairman, I have an opening statement I would like to read.

Mr. SMITH. All right. Go ahead.

Dr. EHRLICH. May I first introduce Miss Linda Allison, coordinator of our special foreign currency program on my left.

GENERAL STATEMENT

Mr. Chairman and members of the committee, I am Dr. S. Paul Ehrlich, Jr., Director of the Office of International Health which is a staff office reporting to the Assistant Secretary for Health and Scientific Affairs.

The Office of International Health serves as the principal focal point in the Department for policy guidance and program coordination of all international health activities. It participates with the Department of State in formulating U.S. positions and policies relating to the World Health Organization and in other foreign policy health matters; maintains liaison with international health-related institutions and organizations and other departments and agencies; and provides assistance and guidance in the general field of international health to the health agencies administered by the Assistant Secretary. The office has specific responsibility for the administration and coordination of the special foreign currency program under the jurisdiction of the Assistant Secretary for Health and Scientific Affairs. It is the budget for this program that we are presenting today. I have prepared a relatively brief opening statement since I recognize most of the committee members are informed on the history and general details of this 10-year old program as conducted in the Department of Health, Education, and Welfare.

Special Foreign Currency Program

The special foreign currency program in HEW is carried out under the authority of section 104(b) (3) of the Agricultural Trade Development and Assistance Act of 1954, as amended (Public Law 83–480), and the International Health Research Act of 1960, Public Law 86–610, section 308. The program is supported entirely by U.S. owned excess foreign currencies which have been determined by the Treasury Department to be in excess of normal U.S. needs in certain designated countries. These excess currencies must be used in the foreign countries involved and there is no appropriated program dollar outflow from the United States. As the committee is aware, this activity is not in competition in any way whatsoever with the domestic program appropriations.

Our health agencies use these foreign funds to support health research and research related activities in foreign countries that complement and extend their programs to fulfill domestic responsibilities. These foreign currencies have enabled the Department to carry out productive and significant research projects taking advantage of unique resources and conditions within the host country. Primary emphasis is on the development of projects addressed to problems relating to the organization and delivery of health services, disease prevention and control, basic biomedical research, population and family planning, and food and drug consumer protection, all of which are directly relevant to high priority U.S. health needs. Considerable attention has also been given to a program of translating foreign health literature and critical literature reviews for the benefit of the American medical community. This activity makes available important medical and health information and knowledge which are published only in foreign languages.

THE BUDGET REQUEST AND PAST APPROPRIATIONS

For fiscal year 1971 we requested and received an appropriation of $32,444,000 for the use of foreign currencies. The request for this amount was justified and approved on the basis of a large backlog of projects which the health agencies had not been able to fund due to the severely reduced budget for the program in fiscal year 1970. The fiscal year 1970 special foreign currency appropriation was only about $3.5 million and enabled the health agencies to fund just 16 new projects for the entire year. The balance of the appropriation, other than new project funding, was required to provide supplemental funds for ongoing research in order to avoid disruption of work and the loss of scientific data.

When I testified last year at the fiscal year 1971 appropriation hearing, 193 projects totaling the equivalent of $24,576,242 in local currencies were either ready for funding or in the review process. Additional projects were being negotiated or were planned for development during 1971. The fiscal year 1971 appropriation has allowed us to dispose of this large backlog of projects, and at the same time, to develop a significant number of new activities designed to contribute to our high priority domestic health programs.

We are requesting $25,545,000 for fiscal year 1972. This is nearly a $7

million reduction from our fiscal year 1971 appropriation as a result of two major factors. First, with the establishment of the new Environmental Protection Agency and the relocation of selected HEW programs, $3.5 million of our fiscal year 1971 funds were transferred with these activities to the new agency. The fiscal year 1972 request for these and other environmental programs is now included in the Environmental Protection Agency budget. Secondly, the large backlog of unfunded projects is no longer a major problem and the budget accordingly is moving to a lower level consistent with projected requirements. The decrease, therefore, does not represent a reduced program effort but rather reflects a carefully planned increase in funds for new projects.

In developing this program, a number of factors were taken into consideration. These included not only the research needs of the HEW health agencies, but also their staff resources for project planning and monitoring, the prospective research potential in the foreign countries, and the long-range availability of the excess foreign currencies. In addition, we are concentrating on the maintenance of high quality standards through vigorous reviews by highly qualified experts and improved project surveillance. A principal focus in our new program development has been increased attention to national high priority subject matter areas in contrast to the emphasis on more limited basic research interests of the past.

In summary, the favorable congressional action on the fiscal year 1971 appropriation request has enabled us to proceed with planning for a more stable and better organized program at a reduced level for fiscal year 1972. I will be pleased to answer any questions you may have.

COOPERATION WITH OTHER COUNTRIES

Mr. SMITH. Are these projects coordinated with other countries?

Dr. EHRLICH. All of the projects are developed on a collaborative basis with the country in which they are carried out.

Mr. SMITH. I didn't mean that. I mean with countries other than the ones in which they are carried out.

Dr. EHRLICH. We have several projects that have recently been developed that are carried out with the cooperation of the World Health Organization. This is done particularly in areas where the recipient country doesn't have the resource to conduct the project and by bringing WHO into the picture, they can provide the professional backstopping that is necessary.

Mr. SMITH. Do you think you are going to get much help? Is there much progress through coordinating these activities through Geneva?

Dr. EHRLICH. I think very much so. We have one project that I might just mention as an example. It's a project conducted in India to test the feasibility of eradicating certain disease-carrying mosquito vectors by means of genetic manipulation; that is, by introducing a strain of mosquito which is alien to the existing mosquito and thereby producing nonviable progeny.

This is a very exciting project which has the potential for controlling a number of diseases, such as yellow fever or hemorrhagic fever. We have the funds, of course, in India to use, but there was not the expertise in India to carry out the projects.

RELATIONSHIP WITH THE WORLD HEALTH ORGANIZATION

Mr. SMITH. To what extent does the World Health Organization involve you and this particular program in the international drive to eliminate communicable diseases?

Dr. EHRLICH. Specifically I would say there are no direct projects connected with this, other than this mosquito project and two or three international conferences that we have supported with these funds using the sponsorship of the World Health Organization.

Mr. SMITH. Couldn't you, through these funds, do some of the things, if properly coordinated, that we are doing with dollars through WHO?

Dr. EHRLICH. I expect it might be possible to a limited extent. No. 1, WHO will not directly accept any currency other than dollars, Swiss francs or English pounds for the regular assessed budget. So that these funds which we provide to WHO are over and above our normal assessment.

Mr. SMITH. What I am saying is couldn't your contribution be in services in lieu of dollars in some instances and still give WHO what they need?

Dr. EHRLICH. I don't believe it's consistent with the WHO constitutional requirements for membership. We can do it on a voluntary basis over and above our regular assessment, but not to replace part of our assessment.

Mr. SMITH. I think this bears looking into because the dollar assessment wouldn't be as much if we could furnish services in lieu of dollars.

In effect, what we would be doing is what other countries do one way or another. We sell a country something it needs and they take part of the payment in services in that country. That is a service that can make a contribution to a WHO project. The WHO program would end up at the same place.

Dr. EHRLICH. I think the difficulty is that many countries would want to pay in their own currency, if this was allowed. Those currencies are not convertible and are therefore not terribly useful. This is the reason for the limitation.

I might say Mr. Rooney's subcommittee has asked that part of the U.S. assessed budget be paid in U.S. owned excess currencies.

Mr. SMITH. I am on that subcommittee, too. There is a lot more looking needs to be done at some of these international budgets and the way we are treated in comparison with some other countries. It seems as if to say to the United States, "We want only dollars rather than a cooperative project." Some seem to think we have an unlimited till.

UNITED ARAB REPUBLIC PROJECTS

I notice you have a United Arab Republic proposal for $1.375 million. What is that project? Are you in any way involved with refugee problems, and so forth, in the Middle East?

Dr. EHRLICH. No, we are not; not through this program. I am not sure where that figure is. For the United Arab Republic there are a number of proposed projects. It's not a single project but rather a number of proposed projects for which we have a listing. If you would like, we can submit it for the record, or I can introduce it here.

Mr. SMITH. Just submit that for the record.

(The information follows:)

Projects in the United Arab Republic

The health agencies are currently supporting 13 active projects in the United Arab Republic at a total obligated cost of $2,996,642 equivalent. These projects are as follows:

Project Title	*Dollar equivalent*
1. Study of interrelationships of ticks and diseases affecting man and animals, chiefly in Africa, Asia, and Europe	$209,672
2. To study the venoms of the poisonous animals (snakes and scorpions) within Egypt for the development of new and improved antisera	181,975
3. A study of genetic anomalies in Egypt	120,642
4. Study of rickettsial zoonoses in Egypt and adjacent areas	229,919
5. A cephalometric analysis of the Nubians (200 AD to 1964 AD)	126,625
6. Biochemical and physiological studies of certain ticks with special reference to water balance	178,640
7. Incremental dental care and preventive techniques to children in Egypt	374,527
8. Followup studies of mature and premature babies born in the university maternity hospital (Chatby), Alexandria, Egypt	106,857
9. Detection and treatment of inborn errors of metabolism which impair mental health	96,827
10. Computer simulation of population growth	97,549
11. Investigations into methods of prevention of rheeumatic heart disease in Egyptian children	449,964
12. Epidemiology of streptococcal infection, rheumatic fever and rheumatic heart disease, and primary prophylaxis of rheumatic fever in rural school population	683,945
13. Environmental assessment of airborne cotton and flax dusts	139,500

It is anticipated that approximately $1,375,000 equivalent will be obligated for projects in the United Arab Republic during fiscal year 1972. The following is a list of the projects which are currently under consideration. This list includes projects that are being developed, under review, and for which the review has been completed. There can be no assurance, however, about which projects will be approved in the review process and it is possible that some projects presently approved for funding will be replaced by others due to changing priorities when obligations are begun 6 to 8 months from now.

Project Title	*Estimated amount (dollar equivalent)*
Renewals	
1. To study the venoms of the poisonous animals (snakes and scorpions) within Egypt for the development of new and improved antisera	$145,000
2. A study of genetic anomalies in Egypt	50,000
3. Study of interrelationships of ticks and diseases affecting man and animals, chiefly in Africa, Asia, and Europe	120,000
4. Study of rickettsial zoonoses in Egypt and adjacent areas	175,000
New Projects	
1. Morbidity-mortality study of X irradiated patients	40,000
2. Anti-diabetic drug studies	30,000
3. Study of social-economic factors related to fertility	150,000
4. Pilot project on consanguinity studies	10,000
5. PHS fellowship program	75,000
6. Epidemiological study of otitis media	150,000
7. Psychosocial study of individuals utilizing indigenous therapeutic methods vs. Western psychotherapeutic techniques	50,000
8. Exposure to noise in cotton and flax industry	110,000
9. Study of population program in the United Arab Republic	120,000
10. Study of the long-term effects of hashish	120,000
11. History of medicine	35,000

METHOD OF PROJECT FUNDING

Mr. SMITH. Are you still following the policy of obligating funds for the life of a project when it is first funded so that we don't get locked in by moral commitments for appropriations for future years?

Dr. EHRLICH. Yes, we are.

RESEARCH OPPORTUNITIES IN POLAND

Mr. SMITH. I was a little surprised at the statement on page 203, "Poland is specifically noted for its medical progress in occupational health." First, why should this be so? Second, what are you doing under this program to take advantage of that situation?

Dr. EHRLICH. Poland has an intensive occupational health program to protect the health of the worker that has been in operation for many years. Four institutes of occupational health have been established. Each institute is concerned with a specific segment of industry. The institutes are, the Institute for Occupational Medicine in the Chemical and Textile Industries in Lodz; Institute for Occupational Medicine in the Mining and Metallurgical Industries in Zabrze; Institute for Rural Occupational Health and Hygiene in Lublin; and Institute for Marine Occupational Health in Gdansk.

In addition, the regional voivodeship clinics offer clinical support to the regional workers. Each institute has laboratory and hospital facilities and conducts research at the basic, applied and medical levels as well as providing hospital care to workers with occupational diseases. Field and epidemiological studies are also conducted. Each institute is oriented toward a specific group of industries and devotes its energy to the health problems associated with the industries. In general, facilities are good and the scientific staff is excellent. We now know most of the laboratories and key personnel in Poland who are interested in occupational health problems.

The Bureau of Occupational Safety and Health has Public Law 480 projects in force with three of the four institutes. There are 10 more proposals in their fiscal year 1972 budget submission. Included among these are studies of the effects of carbon disulphide on the lipid metabolism in the walls of blood vessels and the influence of industrial poisons and drugs on the activity of microsomal enzymes. All of the proposals have been cleared formally or informally by the Coordinating Commission for Polish-American Scientific Cooperation in Poland.

The Bureau of Occupational Safety and Health utilizes the Public Law 480 projects to supplement and extend work on occupational health problems of concern in the United States. The results of this research are utilized by BOSH, along with data from other sources, to establish criteria for a safe and healthful working environment, the objective expressed in the Occupational Health and Safety Act of 1970.

COLLABORATIVE STUDY OF MEDICAL CARE UTILIZATION

Mr. SMITH. Tell us a little more about this collaborative study of the utilization of medical care mentioned on page 205. What is it? How much will the total study cost? What have we gotten from it, and what more do we expect to get that will be of value to us?

Dr. EHRLICH. Three ongoing Public Law 480 projects are components of a worldwide collaborative study of medical care utilization involving 10 different populations and the systems of medical care represented in seven different countries, (Yugoslavia, Poland, United States, Canada, Great Britain, Finland, Argentina). Even though the delivery system of each country is different, certain commonalities exist. Comparable data for all areas will permit identification of those factors that explain variations in the utilization of hospitals and of physician, nurse, and dentist services in relationship to the prevalence of diseases and disability in general population.

From these studies we hope to obtain valuable information showing what effects different methods of paying for medical care have on costs, efficiency, and the utilization of health services. This should enable us to obtain clues about the consequences of introducing similar features into the U.S. system of medical care. For example, what effects on costs of prescription drugs are various ways of paying for them likely to have? Would we anticipate more or less hospitalization, in terms of number of patients and days in hospital, if certain features now prevalent in some other countries, were introduced here? Would complete coverage of all medical costs through a national health insurance system be likely to significantly increase the demand for ambulatory and hospital medical care by the public and, if so, how much?

Two of the studies that we are supporting are in Yugoslavia and one is in Poland. The total combined cost for these three studies is $870,040 equivalent. This averages out to about $200,000 equivalent per year.

The first results from these studies will become available beginning in July 1971. By 1972, most of the findings will have been published.

OTHER RESEARCH WITH PUBLIC LAW 480 FUNDING

Mr. SMITH. Do you have any other projects that you think illustrate special values to this country as a result of the use of these surplus currencies?

Dr. EHRLICH. Yes, I would like to give you two brief examples. The first is a project in Yugoslavia to investigate the protective value of a live oral, lyophilized vaccine against bacillary dysentery in children. Shigellosis, is a particularly important health problem in the United States. Studies have shown that there are three identifiable high-risk groups: (1) children residing in poverty areas; (2) Indians residing on reservations; and, (3) children living in custodial institutions. Studies have shown that shigellosis is a recurring problem of considerable magnitude which cannot be controlled through presently available methods. Many institutions and Indian health authorities have expressed an interest in a vaccine for the control of dysentery.

The objective of the project in Yugoslavia was to conduct controlled field trials to determine if specific protection against bacillary dysentery could be achieved by administering live oral, lyophilized vaccine. The research project in Yugoslavia has been exceedingly productive, and has demonstrated the efficacy of an oral attenuated streptomycin-dependent vaccine in protecting children against dysentery. The study included a total of 7,500 children who were vaccinated with 4 doses of

vaccine. The vaccine gave up to 91 percent protection against infection with homologous strains and was demonstrated to be safe. This is an important accomplishment because protection was demonstrated against dysentery strains which cause disease in certain high-risk groups in the United States. The scientific information derived from this continued study has been most gratifying.

A second project which is providing outstanding results is being carried out in Israel. The title of this project is "Synthesis of Sphingolipids for Use in Determining the Metabolic Aberrations in Heredity Sphingolipidoses." The objective of this project is to learn the nature of the specific metabolic enzymic defects in a number of hereditary diseases which are characterized by an accumulation of chemically complex fatty substances. Such diseases are called hereditary sphingolipidoses. Prominent among these diseases are Gaucher's disease in which there is an anemia due to accumulation of a fat-related substance in spleen cells; Niemann-Pick disease, an infantile phosphatide disturbance marked by anemia which runs a rapid course ending in death in the first 2 years of life, and is characterized by involvement of the spleen and liver and by fat accumuation in cells of the body. A third condition is Tay-Sachs disease which is characterized by the accumulation of sphingolipids called gangliosides in the neuronal cells of the brain. This disease leads to blindness and mental retardation. Metachromic leukodystrophy is a fourth condition characterized by excess quantities of sulfatides (sphingolipid sulfate esters) with widespread distribution in most body tissues.

Under the project that we are are supporting, two radioactive fatty compounds were synthesized. This led to the discovery and identification of the metabolic defects in Gaucher's disease and Niemann-Pick disease. The lesion in Fabry's disease was also identified. The biochemical abnormality in these conditions has been the subject of previously unsuccessful investigations for more than 50 years.

An easy test for the diagnosis of Gaucher's and Niemann-Pick disease was developed as a beneficial ancillary result from the studies carried out under this project. A patent for these diagnostic procedures was awarded to the U.S. Government in September 1970. The findings to date will, hopefully, lead to rational therapeutic approaches for the treatment of these diseases.

Another accomplishment of this project is the synthesis of two chemical intermediates for investigating the accumulation of gangliosides or fat-related substances in the neuronal cells of the brain in Tay-Sachs disease. This has been a very difficult problem to solve because of the large number of possible chemical configurations in the structure of the molecule of the substances in this disease.

As a result of the fundamental investgiations of the underlying biochemical derangements in these diseases, it is now possible to monitor pregnancies at risk for all of the lipid storage diseases. Thus, accurate genetic counseling is now an established practical benefit.

SUPERVISORY TRAVEL FOR PERSONNEL

Mr. SMITH. I assume there is some overall supervision and control of this program that involves foreign travel on the part of personnel stationed in the United States. How extensive is that type of travel?

Dr. EHRLICH. You are correct in assuming that there is overall supervision and control of the program in the United States. For each project there is a domestic project officer. Part of the project officer's responsibility is to visit the project to consult with the foreign principal investigator and to make an onsite assessment of the problems and progress of the work. On the average, these visits are made every 2 years. At the present time there are 222 active projects. Over 100 additional projects will probably become active during the forthcoming year for a total of more than 300 active projects. In connection with these active projects there will probably be about 150 trips during fiscal year 1972. In addition, about 50 more trips will be made for the purpose of project development and for general program administration. This would make a total of about 200 trips. It should be remembered, however, that not all project officers are government employees and that some of the trips are combined. In other words, when possible, trips abroad are arranged so that a project officer can visit more than one project during a single visit and discuss the development of new research proposals.

Mr. SMITH. How are the expenses of that travel borne?

Dr. EHRLICH. Travel expenses are paid with foreign currencies and are charged against the "Scientific activities overseas" appropriation. This includes the cost of transportation to and from the country, local travel and expenses in the country in accordance with U.S. Government travel regulations, and per diem at the official Embassy rate. The only dollar cost involved is a minor per diem expense while in direct transit to and from the country and perhaps the cost of transportation to and from the airport in the United States. This cost is borne by the agency sponsoring the travel.

Mr. SMITH. Mr. Conte?

HISTORICAL VIEW OF THE PROGRAM

Mr. CONTE. I know you have some countries mentioned in your justifications. Can you give us a history of the countries involved in this program and how much? Just submit that for the record.

Dr. EHRLICH. Yes, sir.

(The information follows:)

SCIENTIFIC ACTIVITIES OVERSEAS—SPECIAL FOREIGN CURRENCY PROGRAM—OBLIGATIONS BY COUNTRY, FISCAL YEAR 1961 TO FISCAL YEAR 1971

	Fiscal years 1961–64	Fiscal year 1965	Fiscal year 1966	Fiscal year 1967	Fiscal year 1968	Fiscal year 1969	Fiscal year 1970	Estimated, fiscal year 1971	Estimated total
Brazil	$65,534	($1,136)							$64,398
Burma	481,897	6,304	($5,000)	($15,003)	($24)				468,174
Ceylon				2,343	6,032				8,375
India	2,687,156	438,804	2,210,232	1,369,876	1,878,205	$4,473,631	($186,855)	$6,045,078	18,916,127
Israel	3,303,893	1,668,110	1,443,348	3,380,803	5,435,382	198,636	2,513,464	2,091,000	20,034,636
Morocco						1,163	902	1,075,000	1,077,065
Pakistan	1,805,396	1,171,480	183,240	1,277,758	2,194,890	3,276,072	38,048	2,728,417	12,675,301
Poland	2,917,276	640,879	1,113,006	1,575,104	1,473,390	1,647,747	(532,203)	4,993,420	13,828,619
Tunisia				250	127,164	564,409	85,745	1,970,805	2,748,373
United Arab Republic (Egypt)	953,856	751,085	1,712,526	861,093	(47,902)	657,050	(100,212)	1,334,591	6,122,087
Yugoslavia	1,216,776	173,429	492,612	773,563	2,323,517	5,972,928	1,230,195	8,996,689	21,179,709
Total	13,431,784	4,848,955	7,149,964	9,225,787	13,390,654	16,791,636	3,049,084	29,235,000	97,122,864

ISRAELI HEALTH SERVICE SYSTEM PROJECT

Mr. CONTE. On page 205, what are some of the features of the Israeli Health Service system that preliminary reports indicate may have useful implications for the United States?

Dr. EHRLICH. The project that is mentioned in the narrative justification in Israel relates to the study of health in a total community within Israel. This study is providing us with the opportunity of following the health status of all of the individuals in a community as individuals or as family members in a manner that could not be carried out in this country. This is possible because of the nature of the health system that exists within Israel.

This study is yielding a very comprehensive and detailed picture of the community's health status and of its unmet medical needs, which is providing us with insight into the development of methods that are important in health planning. Health planning, obviously, is becoming more and more of a subject of deep concern to us.

Mr. CONTE. I thought maybe they were discovering something there.

Dr. EHRLICH. I think we are. We are discovering, for example, that certain parts of comprehensive care can be provided by individuals with training less than that of a physician.

Mr. CONTE. Are we doing that right now? My people up home are working on that—the corpsmen, for instance, the utilization of corpsmen.

Dr. EHRLICH. These studies can be considered to be complementary to ongoing studies in this country, utilizing corpsmen to be trained here.

Mr. CONTE. Give us something more for the record.

Dr. EHRLICH. All right.

(The information follows:)

HEALTH STUDY OF A TOTAL COMMUNITY IN ISRAEL

In 1967, a study was begun in the community of Kiryat Yovel, a community of about 12,000 persons near Jerusalem, to determine the health problems of the community and the use of medical care services by the population in relation to the social and cultural characteristics of various subpopulation groups in the community. The community includes differing ethnic groups of Asian, North African, and European origin, thus providing an excellent population for such a study.

All persons in the community are being called in and examined by physicians using allied health personnel as adjuncts. Using the data gathered by the examination process, patients were classified as being at high, medium, or low risk for cardiovascular disease. This classification was found to have a significant effect on the practice of medical care by clinic physicians. Physicians began to work with the high and medium risk patients to reduce their risk and to gather pertinent data on risk factors as a means of monitoring patient progress. In essence, this had the effect of changing the medical practice in this community for an acute episodic illness orientation to a health maintenance orientation. This has important implications for the United States in that it suggests that the Health Maintenance Organization concept currently under consideration has validity.

The project is also analyzing the reasons for out-patient clinic visits. A prototype community health monitoring system is being developed based upon the data that has been collected. The development of the system is possible because the clinic serves a defined geographic area. This system should enable the project administrator to monitor epidemics and to detect trends in the prevalence of chronic diseases. This concept has applicability in the demonstration health services planning and delivery systems currently being developed in the United States.

Throughout the course of the project, the use of allied health personnel in the delivery of comprehensive care has been studied. The study has shown that many aspects of such care can be effectively provided by persons with less than full medical training. This has had definite and practical implications for the delivery of medical care in certain areas in the United States, such as urban ghettos and isolated rural areas, in which medical care is sporadic, fragmented, and episodic.

RESEARCH INTO THE EFFECTS OF ABORTION

Mr. CONTE. One page 206 of the justifications you state that there is more information that is needed as to the effect that repeated abortions have on the health of women and their ability later on to produce normal offspring. What does your present information indicate about these matters?

Dr. EHRLICH. There are several projects under way in relationship to abortion. I think it's one of the unique features that this particular program offers, that it gives us an opportunity to study abortion as a method of controlling family size that couldn't be done otherwise.

One study, for example, has demonstrated that if one offers to a community contraceptive methods other than abortion, that the abortion rate can be reduced rather markedly. This is a study that was performed in Yugoslavia, where abortion is legal and oftentimes is the only means of limiting family size. In a controlled study they found abortion rates can be cut back significantly.

Mr. CONTE. Do you have anything which we could sink our teeth into to show that repeated abortions leave some effect on future offspring?

Dr. EHRLICH. I would say, one project that comes to mind relates to the problem of RH-negative mothers who have repeated abortions and whether this sensitizes them so that the baby is threatened during a subsequent pregnancy.

There is increasing evidence out of this study, although it's not completed yet, that early abortion does produce sensitivity and that these mothers then have to be watched very closely and perhaps require treatment early in the pregnancy to alleviate difficulty with the offspring.

HEALTH EFFECTS OF URANIUM MINING

Mr. CONTE. As a result of the study of uranium mining in Yugoslavia, in what ways were exposure standards for the U.S. work force in the uranium industry modified?

Dr. EHRLICH. I am not sure I can answer that.

Mr. CONTE. Just put that in the record.

Dr. EHRLICH. I would be pleased to.

(The information follows:)

RADIATION EXPOSURE STANDARDS

Studies on the effects (biochemical, morbidity, and mortality) of radioactive constituents of uranium ore on health of workers are being carried out in Yugoslavia. The scientific data that has been derived from these studies has been utilized, along with data from other sources, to establish the scientific basis for permissible exposure levels for uranium workers in the United States. Recom-

mendations have been made by the Department of Health, Education, and Welfare to the Interagency Uranium Mining Review Group that the exposure level permitted in mines be reduced from 12 to four working levels per year. This supported the Federal Radiation Council Recommendation of 1968.

BUDGET FOR RESEARCH ON NUTRITION

Mr. CONTE. The last question. In view of the increased emphasis upon the problem of hunger and nutrition, not only in the United States but in the rest of the world, why are you requesting fewer funds for the nutrition program in the coming year?

Dr. EHRLICH. I think this represents a general leveling off of the program. Last year more went in nutrition studies because we were funding a large backlog of projects in that area. If one were to smooth the curve, if you will, of growth, what this represents in 1972 is a substantial amount for new projects. Last year's amount really represented an accumulation of projects that could have been funded for the prior 2 or 3 years.

Mr. CONTE. Do you feel we have had an apex in this field?

Dr. EHRLICH. No, I don't think so. In terms of this program it's a question of balancing the resources that are available in the countries that have excess currencies to carry out quality programs and the ability of our own personnel to effectively utilize the funds.

CHILDREN'S HOSPITAL AT KRAKOW, POLAND

Mr. CONTE. I know you have a heart-stroke program for Poland. Do you have anything going with the Children's Hospital at Krakow? I was on the Foreign Aid Committee for several years and we took part in getting money for that hospital. I went there for the dedication. I would think that is a great area for some research.

Dr. EHRLICH. It certainly is. I am not sure offhand, but I would be happy to submit for the record any projects that we do have there.

(The information follows:)

Projects at American Research Hospital, Krakow, Poland

	Amount equivalent
Active projects:	
1. Congenital malformations in the Krakow Region: Epidmiology, treatment and rehabilitation	$187,292
Projects proposed for funding in fiscal year 1972:	
1. Study of the treatment of congenital clubfoot	75,000
2. Study of the organization and operation of an intensive care unit	150,000
3. Studies of gastrointestinal chronic dysfunction in infants with congenital defects	75,000

COORDINATION WITH THE WORLD HEALTH ORGANIZATION

Mr. PATTEN. Dr. Ehrlich, do you coordinate your work with the World Health Organization and the United Nations?

Dr. EHRLICH. I think in several instances. Of course, we are working directly with WHO on programs. I mentioned one earlier in relationship to this bill. That is the program on the genetic control of mosquitoes. I think cooperation with WHO has proved to be even more valuable in the holding of international conferences, dealing with specific areas that we are interested in and that WHO is interested in.

In this instance, WHO has the capability of providing conference support. The country itself is pleased to serve as host and the funds are these excess currencies.

FOREIGN AID ASPECTS OF THE PROGRAM

Mr. PATTEN. You gave me the impression that you bolster research or you try to stabilize health research in other countries? Is that the correct impression?

Dr. EHRLICH. I would say that this program is primarily directed toward our own domestic interests. It's not designed primarily to be of assistance to the country, although, obviously, because it's of a collaborative nature, the country itself will not agree to the project unless it provides them with some degree of support.

I think it should not be confused with the programs, say, conducted by the Agency for International Development, which are specifically designated to help the country. Our projects are designed to complement and extend domestic research, which is going on here.

BREAST CANCER RESEARCH PROJECT IN BOMBAY

Mr. PATTEN. Will you give one illustration of results obtained that gratify you in your work?

Dr. EHRLICH. There is one project that is extremely exciting at the present time. In fact, the Washington Post mentioned it in last Sunday's edition. This relates to the study of breast cancer in Parsi women in Bombay, India. As you may be aware, for some time we have known that in suckling mice it was possible to transmit virus particles from the pregnant mother to offspring. When these particles were transferred in the mother's milk, the offspring developed breast cancer. It was never possible to demonstrate this in humans, because it was very difficult to obtain a large enough sample of mothers, who either themselves had breast cancer or who had relatives who had breast cancer, in order to see if the same thing happened in human beings.

We found in India a group of in-bred women, Parsi women. This is a group that migrated from the Near East to India back in the eighth century. They have remained as a very close group, inbreeding over the past 12 centuries. They have a very high incidence of breast cancer. Fifty percent of all cancers in women in this area are breast cancer and some 25 or 30 percent of the women develop breast cancer. This is opposed to something like 1 or 2 percent in this country and 1 or 2 percent in the other people, Hindus and Moslems, residing in Bombay.

We began a study 2 years ago among these Parsi women and were able to identify these virus particles which, of course, has several very important implications. No. 1, this in fact may be the carcinogenic agent which is transmitted from mother to offspring which leads to the development of breast cancer.

More importantly, these particles may have an immunologic potential. That is, it may be possible—and this is still very debatable—to consider the development of a vaccine which can be prepared from these virus particles to protect offspring. Or of course, if mothers are found to have carcinogenic particles, we may see that the children are not breast fed but are weaned as infants.

Mr. PATTEN. I have nothing further, Mr. Chairman.

Mr. MEYER. I am sure that Dr. Baker can go into some further detail when he testifies on behalf of the Cancer Institute with respect to the program dealing with Parsi women and how it relates to their efforts on breast cancer in this country.

Mr. SMITH. Mrs. Reid?

DOLLAR COST OF SUPPORTING ACTIVITIES

Mrs. REID. We know, of course, that almost 100 percent of this program represents no actual expenditure of U.S. dollars but there is a little U.S. dollar cost in connection with the administration and supporting activities. What is the estimated dollar cost to go along with this request for $25,545,000 in foreign currencies?

Dr. EHRLICH. The estimated cost of the administrative support for the program for a 1-year period is about $149,600.

RESEARCH ON DELIVERY OF HEALTH CARE

Mrs. REID. What might we learn from foreign countries about the delivery of health services?

Dr. EHRLICH. Nearly all of the major health and medical care problems which we in the United States face at the present, exist in similar, and often nearly identical form in many other countries. Among these problems are those relating to the steadily growing costs of hospitalization and ambulatory care, to assessing and assuring the quality of health services, to unequal distribution of medical facilities and manpower, to underutilization and misutilization of medical care by the public, to fragmentation of medical care, to inefficient delivery systems, et cetera.

Millions of dollars are spent yearly in this country on research studies and R. & D. projects aimed at providing us with guidance to solutions of these problems. However, there are restraints on such work in the United States. A major restraint is that all such projects must be carried out within the given system of health services as it exists here. It is usually very difficult if not impossible to learn, for example, whether a proposed innovation would improve on existing deficiencies if it were introduced under a different system of medical care. A second restraint is that in our free enterprise system of medical care we must rely on voluntary cooperation by physicians, hospitals, and other components of the system when we wish to introduce and evaluate innovations in the delivery of health services. Often such cooperation cannot be assured and therefore many potentially important projects cannot be carried out.

These and other restraints do not exist in some other countries. Thus, we can study the introduction of certain innovations. We are, for example, planning a study of the delivery of emergency medical care within the total complex of ambulatory care services. This study is planned for Yugoslavia where there exists—as distinct from the United States—full and continuous access to general practitioners.

In countries where there are more centralized decisionmaking and decision enforcing authorities in the health services system, experiments in different modes of medical care delivery or organization can

be introduced on a large scale with assured cooperation by professional manpower. This allows us to test hunches that cannot be tested in our country. For example, certain clinic hours, staffing patterns, and procedures can be imposed on a sample of clinics to evaluate their effects on the utilization of health services by the public.

Moreover, various countries, facing or having faced the same problems that exist in the United States, have tried to deal with them in a variety of ways. Some of these are similar to ways being considered now as possibilities here, or have certain specific features that are being contemplated as part of the various proposed plans for a better health care system in the United States. By studying these and evaluating their effects in such countries, we can learn what kinds of costs and effects we might anticipate if we tried the same here.

STUDIES ON FAMILY PLANNING

Mrs. REID. What studies are being made regarding family planning?

Dr. EHRLICH. We are currently supporting 16 active population and family planning research projects at a total cost of about $3 million equivalent in eight "excess currency" countries. Five additional projects have been obligated and are pending final approval abroad. These projects vary from basic studies in reproductive biology, with emphasis on fertility regulation, and the development and evaluation of oral contraceptives to studies of the knowledge, attitudes, and practices of individuals concerning family planning. Research in the development of family planning services and methods of program evaluation, population dynamics, the improvement of vital registration, and demographic analysis of populations in transition are being emphasized. All of these studies are viewed as an extension of domestic HEW programs in population research.

"EXCESS CURRENCY" COUNTRIES

Mrs. REID. In how many countries do we have excess currencies at this time?

Dr. EHRLICH. There are currently 10 "excess currency" countries. These countries are Burma, Guinea, India, Israel, Morocco, Pakistan, Poland, Tunisia, the United Arab Republic, and Yugoslavia.

DRUG ABUSE STUDIES

Mrs. REID. Have any studies been made in other countries regarding drug abuse?

Dr. EHRLICH. No. At the present time no studies regarding drug abuse are being supported under the special foreign currency program by the health agencies. There are also no dollar contracts supported by the health agencies for drug abuse studies in any other foreign country.

COORDINATION WITH AID

Mrs. Reid. How do you coordinate your activities with the medical programs of the Agency for International Development?

Dr. Ehrlich. One of the ongoing activities of the Office of International Health is the provision or arrangement for technical and professional support required by the Office of Health or the Regional Bureaus in the Agency for International Development for the implementation of AID's health programs. At the present time there are AID health programs in only four of the excess currency countries—India, Pakistan, Tunisia, and Morocco. In some instances the same PHS operational unit which undertakes Public Law 480 projects in these countries also provides services to the AID mission. For example, in India the Center for Disease Control which has the responsibility for the AID malaria assistance in India also funds and directs the the joint WHO/Public Law 480 project on feasibility studies for the genetic control of mosquitos in India. In Pakistan, the Center conducts a Public Law 480 supported study on the *anopheles stephensi* mosquito, a primary vector of malaria. Also, in Pakistan the South East Asia Treaty Organization's Cholera Laboratory at Dacca, which undertakes applied research in methods for the control of cholera in this area, is operated by the National Institutes of Health with funds made available by AID and an NIH Public Law 480 supported project, and staff from the Center for Disease Control. A large demographic study which is planned in Morocco by the National Center for Health Statistics would be carried out in coordination with the AID family planning program. Thus, I would say that in those countries where there is an opportunity for Public Law 480 research projects to contribute to the AID health program these opportunities are fully utilized.

Mrs. Reid. That is all, Mr. Chairman.

Mr. Smith. Thank you, Doctor.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Scientific Activities Overseas (Special Foreign Currency Program)

Amounts Available for Obligation

	1971	1972
Appropriation	$32,444,000	$25,545,000
Real transfer to:		
"Environmental Protection Agency"	-3,500,000	---
Subtotal, budget authority	28,944,000	25,545,000
Unobligated balance, start of year	291,000	---
Total, obligations	29,235,000	25,545,000

Obligations by Activity

Page Ref.		1971 Estimate	1972 Estimate	Increase or Decrease
200	Foreign health research	$29,235,000	$25,545,000	$-3,690,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Travel and transportation of persons	$ 65,000	$ 65,000	---
Other services:			
Project contracts	28,645,000	24,964,000	-3,681,000
Grants, subsidies and contributions	525,000	516,000	-9,000
Total obligations by object	29,235,000	25,545,000	-3,690,000

Summary of Changes

1971 estimated obligations	$29,235,000
1972 estimated obligations	25,545,000
Net change	-3,690,000

Program Increases:	Base	Change from Base
1. Disease Control	$1,600,000	$+1,023,000
2. Food and Drug Administration	2,026,000	+3,116,000
Total Increases	$3,626,000	$+4,139,000
Program Decreases:		
1. National Institutes of Health	$10,440,000	-1,650,000
2. Health Services and Mental Health Administration	15,161,000	-6,177,000
3. Office of International Health	8,000	-2,000
Total Decreases	$25,609,000	-7,829,000
Total, net change	---	-3,690,000

Explanation of Changes

The net decrease of $3,690,000 represents a leveling off of research support in certain program areas following the funding, in fiscal year 1971, of a backlog of approved research projects which could not be funded in 1970 due to a severely constrained budget.

Program Increases:

1. Disease Control -- The increase of $1,023,000 for a total program level of $2,623,000 will permit increased support for studies of occupational environment and illness, the health effects of radiation on man, and studies aimed at improving community environmental management.

2. Food and Drug Administration -- The requested program increase of $3,116,000 will permit the FDA to increase by $2,014,000 its research on the safety and efficacy of drugs for a total program level of $3,050,000; and increase by $1,102,000 its support of research to solve food-related health problems for a total program level of $2,092,000.

Program Decreases:

1. National Institutes of Health -- The program decrease of $1,650,000 reflects adjustments in the level of support for research in specific program areas. The requested program level will provide an increase of $287,000 for

population research for a total program level of $1,152,000 and an increase of $684,000 for manpower studies for a total program level of $889,000. The level of support for nutrition studies will be decreased by $29,000 to a program level of $571,000 and the programs of biomedical research and communications will be decreased by $2,592,000 to a total program level of $6,178,000.

2. Health Services and Mental Health Administration -- The requested program level of $8,984,000, a decrease of $6,177,000, will provide $1,075,000 for population and family planning studies, a decrease of $475,000; a decrease of $160,000 for manpower development to a total program level of $365,000; and, a decrease of $155,000 for nutrition studies to a program level of $395,000. Support for research aimed at improving the organization and delivery of health services and disease prevention and control will be reduced by $5,387,000 to a total program level of $7,149,000.

3. Office of International Health -- The decrease of $2,000 represents a decrease in the funds required for travel to provide program leadership.

Authorizing Legislation

Section 104(b) of the Agricultural Trade Development and Assistance Act of 1954, as amended. (Public Law 83-480)

"To collect, collate, translate, abstract, and disseminate scientific and technological information and to conduct research and support scientific activities overseas including programs and projects of scientific cooperation between the United States and other countries such as coordinated research against diseases common to all of mankind or unique to individual regions of the globe, and to promote and support programs of medical and scientific research, cultural and educational development, health, nutrition, and sanitation: Provided, That foreign currencies shall be available for the purposes of this subsection (in addition to funds otherwise made available for such purposes) only in such amounts as may be specified from time to time in appropriation Acts;"

International Health Research Act of 1960 Public Law 86-610, Section 308

"To carry out the purposes of clause (1) of section 2 of the International Health Research Act of 1960, the Surgeon General may, in the exercise of his authority under this Act and other provisions of law to conduct and support health research and research training, make such use of health research and research training resources in participating foreign countries as he may deem necessary and desirable."

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer to:		
Environmental Protection Agency	$-3,500,000	Transfer of some activities to the Environmental Protection Agency pursuant to Reorganization Plan No. 3 in December, 1970. This transfer was part of a complete reorganization of the Environmental Health Service.

Scientific Activities Overseas (Special Foreign Currency Program)

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1962	$10,084,000	$8,000,000	$10,084,000	$9,000,000
1963	2,800,000	2,800,000	2,800,000	2,800,000
1964	6,647,000	4,000,000	4,000,000	4,000,000
1965	1,000,000	1,000,000	1,000,000	1,000,000
1966	6,000,000	6,000,000	5,000,000	5,000,000
1967	19,217,000	19,217,000	10,000,000	10,000,000
1968	18,685,000	15,000,000	15,000,000	15,000,000
1969	30,000,000	15,000,000	15,000,000	15,000,000
1970	3,455,000	3,455,000	3,455,000	3,455,000
1971	32,444,000	32,444,000	32,444,000	32,444,000
1972	25,545,000			

Justification

Scientific Activities Overseas (Special Foreign Currency Program)

General Statement

The Scientific Activities Overseas (Special Foreign Currency Program) is carried out under the authority of Section 104(b) of the Agricultural Trade Development and Assistance Act of 1954, as amended (Public Law 480). Activities under the Program are supported entirely by foreign currencies owned by the United States abroad which have been determined by the Department of the Treasury to be in more than sufficient supply to finance normal U.S. needs in certain countries for two years or more.

An appropriation was first received for the Scientific Activities Overseas Program in 1961. At that time the National Institutes of Health was the only health agency participating in the program. Today, each of the health agencies -- National Institutes of Health, Health Services and Mental Health Administration, Food and Drug Administration, and Disease Control (environmental health operating units remaining with the Department) -- is actively involved in the development and implementation of research and research-related activities under the Program. For these organizations the Special Foreign Currency Program has become a very valuable complementary resource for providing research answers to critical questions which must be answered to achieve their domestic health objectives. Reflecting the priority health interests of the health agencies, emphasis has been placed on seeking solutions to problems in the areas of population and family planning, organization and delivery of health services, nutrition, manpower development, environmental health, and consumer protection. Estimated new obligations in fiscal years 1971 and 1972 in support of projects in these priority areas are as follows:

Estimated New Support for Priority Health Areas

	1971 Estimate	1972 Estimate
Population and Family Planning	$2,415,000	$2,227,000
Organization and Delivery of Health Services	9,536,000	5,295,000
Nutrition	1,150,000	966,000
Manpower Development	730,000	1,254,000
Environmental Health	1,600,000	2,623,000
Consumer Protection	2,026,000	5,142,000

The Program is based on collaboration and mutual benefit between the United States and participating countries. A formal review of each project for scientific merit and conformance with national policies and priorities both in the United States and in the host country insures the collaborative nature of the project. To further insure this collaboration as well as the potential success of the research, a U.S. researcher from either the sponsoring health agency or a U.S. academic or research institution is designated as a U.S. Project Officer to work with the foreign researcher, who is designated as the Principal Investigator.

A conscientious effort is made to utilize unique resources in the participating countries. Such resources include the existence of unique population groups, a high incidence of a particular disease of interest to the health agencies, special epidemiological or ecological conditions not found in the United States, and special talents of the foreign scientific investigators and health workers. The Special Foreign Currency Program has enabled the health agencies to take advantage of these resources and thus undertake new research initiatives that might not otherwise have been possible. Frequently, the cost of carrying out the research abroad is substantially lower than it would have been in the United States.

In addition to admirably serving the purpose of utilizing resources in "excess currency" countries to solve American health problems, this Program also renders an important service to other U.S. foreign policy objectives. The Program has strengthened ties with the scientific community in other countries. An unanticipated benefit of the Program, with promise of future intangible benefits, is becoming more and more apparent. Many young people from "excess currency" countries, who have received advanced research training in the United States or have worked on projects supported under the Program, have maintained an active collaboration with their scientific colleagues in the United States and thus become an extension of the U.S. research community.

The Program also serves humanitarian objectives by sharing with participating nations health science findings which will benefit their people as well as people throughout the world. Through the years, the United States has made a substantial investment in assisting lesser-developed countries in their fight against such diseases as cholera, schistosomiasis, malaria, filariasis, and tuberculosis. The Special Foreign Currency Program serves as an important additional resource in this effort by supporting research to prevent and control these diseases.

There follows a discussion of the goals, objectives and specific project plans of the respective health agencies.

A table of estimated obligations by country follows:

	1971 Estimate	1972 Estimate
Guinea	---	50,000
India	6,045,078	6,203,762
Israel	2,091,000	64,000
Morocco	1,075,000	415,000
Pakistan	2,728,417	1,759,738
Poland	4,993,420	7,395,555
Tunisia	1,970,805	942,050
U.A.R. (Egypt)	1,334,591	1,375,100
Yugoslavia	8,996,689	7,339,795
Total	29,235,000	25,545,000

National Institutes of Health

The Special Foreign Currency Program is a unique resource enabling NIH to utilize opportunities within the excess currency countries for advancement of its programs for biomedical research, manpower and translation and dissemination of scientific literature.

The NIH biomedical research program is oriented toward elucidation of fundamental mechanisms involved in disease processes. Epidemiological studies which are a prominent feature of this NIH program are an effective tool in establishing gross cause and effect relationships especially on a cross-cultural basis. Such studies must progress to sophisticated investigations at the cellular and molecular levels which bring the focus of techniques and concepts from many disciplines such as biochemistry, molecular biology, physiology and immunology to bear upon the problem. This program cuts cross the interests, utilizes the resources and contributes to the programs of all NIH Institutes. The neurology, cardiovascular, cancer, dental and metabolic programs of NIH are extensively and productively involved. A study in Poland of neuromuscular diseases supported by NIH has resulted in the writing and publication, both in English and Polish, of a general atlas of these diseases, which occur so frequently in children. Another laboratory studying cultivation of nerve cells outside the body in tissue cultures has been able to demonstrate for the first time production of the same pathological changes in cultured nerve cells as occur in the human patients with Wilson's disease characterized by aberrant copper metabolism. Such a finding holds promise of a laboratory model system for this and similar disorders. Neurophysiological science is prominent among the national priorities recently established for science by the Yugoslavian government. The complementary interest of NIH will facilitate the development of collaborative programs.

A study of the distribution of cancer cases in Bombay, India, has confirmed the high incidence of cancer of the buccal cavity and oral pharynx and a low risk for cancer of the breast and colon but not rectum. Another project concerned with an investigation of the correlation between viruses and breast cancer in Parsi women has produced, in preliminary studies, the very significant finding that viral particles occur more frequently in breast milk of Parsi women who have high incidence of breast cancer than in milk of American women. This finding has great significance for studies of the role of viruses in etiology of cancer.

The NIH nutrition research program covers the full spectrum of nutrition from fundamental studies concerning the metabolic and physiologic actions of the various nutrients and their requirements in man to practical, applied work aimed at alleviation of malnutrition and nutrition deficiency diseases both in the United States and abroad. The program includes projects relating to normal nutrition, nutritional disorders and nutrition in diseases and stress states. New lines of investigation which are proposed include the question of nutritional factors in mental development; prenatal, maternal and postnatal infant supplementation studies on children; relationships between genetic differences, nutritional variations, and environmental factors as they affect physical growth; effects of malnutrition and of various components of the diet on placental function as related to fetal birth weight, infant development and gestational performance of the mother. Nutritional studies of these types have implications for all ages, ethnic groups and socio-economic levels in the U.S.

The NIH is developing a biomedical and social science research program directed toward solution of problems in the field of population and family planning and

fostering international collaboration and interest in research applicable to the world-wide population problem. The biomedical sciences program includes research in reproductive biology and contraceptive development and evaluation of the medical effects of methods of contraception, abortion and sterilization which are currently in use. In the social sciences, goals of the program include the development of data on population trends and fertility rates and on the causes and consequences of alterations in population size and distribution, as well as the psychological and social determinants of family size and contraceptive practice and the effects of various incentive and disincentive policies.

A number of competent reproductive physiologists in India and Pakistan have been contacted and are interested in pursuing collaborative projects in embryology, reproductive endocrinology, and the metabolic effects of steroid contraceptives. One project under development in India will concentrate on male reproductive physiology in subhuman primates which are native to India and difficult to obtain and maintain in the United States; this project could make an important contribution to knowledge of primate reproduction. A study of the effects of oral contraceptives on carbohydrate and lipid metabolism is under consideration in Pakistan.

A project comparing the medical effects of various methods of abortion has been initiated in Yugoslavia. It will provide significant comparative data on the incidence of complications which will be useful in determining the method of choice for inducing abortion and may be especially important in view of the trend toward liberalized abortion laws in the United States.

The National Library of Medicine provides the U.S. scientific community with access to the world's biomedical literature. The Library plans to expand its selective critical review program in Yugoslavia and its program for publication of translations. Support for production of English-language versions of three Yugoslav health science journals (Archives of Biological Sciences, Acta Medica Yugoslavica, and Medical Journal) will be continued.

Plans are being made to develop a resource in India for translation and abstracting Russian biomedical literature. A bibliographic and abstracting activity on the subject of family planning is under active consideration and a program for preparation of selected critical reviews is being developed. An historic study of Arabic medicine is planned for Egypt, utilizing material hitherto not available to the U.S. scientific community. In Pakistan a program for the translation and abstracting of Far Eastern medical literature is being negotiated. Critical reviews in areas of national interest such as occupational and environmental health are scheduled in Poland. A program for the abstracting of oral health publications appearing in Eastern European dental literature will be implemented.

Poland is specifically noted for its medical progress in occupational health. To promote a better understanding by the U.S. scientific community of the advances made by Polish research scientists in studies related to man's work environment, the National Library of Medicine has supported the writing of several critical reviews in this subject area. The publication of a critical review produced in Poland entitled "The Application of Metabolic and Excretion Kinetics to the Problems of Industrial Toxicology" is imminent. A critical review of the "Biological Effect of Microwave Irradiation," which will identify possible hazards to personnel working with industrial microwave generators such as are used in radio navigation, communications and induction heating, used both in industry and increasingly in the home, was recently undertaken. A third publication will review the contemporary state of knowledge of the incidence of pneumoconiosis in coal miners. The Yugoslav scientific community has demonstrated a high degree of competence in the application

of epidemiological techniques to the examination of health problems. To utilize these resources, two Library-sponsored critical reviews are in preparation. One is concerned with "Epidemiology of Functional Psychoses" for the purpose of identifying problems and methodology in unresolved clinical difficulties associated with endogenic psychoses and to point out areas in need of additional research. The other is "Epidemiology of Gastric Cancer". Gastric cancer varies in geographic frequency both internationally as well as within national boundaries. It is currently of interest in migrant population studies and of particular epidemiological interest to this country's biomedical community.

The Bureau of Health Manpower Education objectives for its Special Foreign Currency Program are selected on the basis of their relationships to critical domestic problems of the health manpower pool and specifically to extend and improve programs in dental manpower utilization, particularly in developing new methods of delivering dental services to children and for further studies of nursing needs, resources and career patterns. A study of systems of dental services for children is proposed in both Yugoslavia and Poland to be carried out as a part of a WHO-DHEW international study of dental manpower and utilization and national dental care delivery systems for children. A systematic study such as that proposed would provide an opportunity for the United States to learn first hand, from countries having had long experience in providing dental health services to children, about ways in which new types of manpower have been developed and utilized to make possible the provision of services. A project in Egypt is generating valuable data on an incremental dental care program using mobile units -- a program which provides service to all children ages 6 through 11 without regard to ability to pay. With increasing interest in the United States in the establishment of dental care programs for all segments of the population, including those able to pay for care, a study such as this will be of extreme value in providing data on mechanisms, organization, costs, and manpower including clinical man hours required per child for initial care and maintenance during early adolescence as dental problems change from caries of early childhood to onset of diseases of gingiva and bone. To complement a comprehensive study of the career dynamics of nurses currently underway in the U.S., a study of career patterns among graduates of nursing programs in Yugoslavia is anticipated. Such a study will inquire into the career interests of students and the career patterns of graduate nurses as well as to learn more about the factors leading to change in careers. A study will be made of India's countrywide survey of nursing needs and efforts to relate the data to needs of individual states and national five-year plan. It is anticipated this will contribute to planning for nursing needs as part of total health manpower requirements in the U.S.

Health Services and Mental Health Administration

The Health Services and Mental Health Administration's Special Foreign Currency Program is an important means of strengthening and extending the Administration's domestic research program. Research and training projects carried out under the program are designed to contribute to the accomplishment of HSMHA's primary mission: to become the nation's center of expertise on how health services are organized and delivered to people.

One of the major objectives of the HSMHA Special Foreign Currency Program is to study and evaluate pertinent factors of foreign health systems in order to gain knowledge which can be applied to health services in the United States.

HSMHA health research carried out abroad is differentiated from purely domestic research by utilizing foreign resources which offer unusual research potential; e.g., unique populations, special social conditions or cultural settings. Biological, psychological and cultural factors play varying roles in the etiology, evaluation and outcome of organic and mental disorders. These factors can be better identified and understood when comparative and parallel studies are carried out utilizing as subjects individuals from differing ethnic groups, living in different socio-cultural environments.

Much time is needed for the evaluation of research accomplishments and for their application to currently used techniques in health planning and medical care. Even though the HSMHA Special Foreign Currency Program is quite young some significant accomplishments have already become apparent.

One of the most ambitious HSMHA international projects, still under way, is a broad collaborative study of the utilization of medical care. It encompasses nine studies in seven countries, three of them supported through PL 480 funds. Although the project is not due to terminate until July 1971, the first reports indicate that valuable information with highly practical implications is being obtained in relation to the medical, economic and social factors that affect utilization of medical care and the influence of various features on medical costs in the provision of such care.

A detailed study of the organization of health services in Israel is approaching completion. Progress reports indicate that the project has provided new insights into the advantages and disadvantages of certain features of the Israeli health service system and has allowed us to examine closely those features which have useful implications for the U.S.

A project in India has resulted in greatly improved methods for the isolation and identification of toxic viruses of the gastrointestinal system. These new methods are more sensitive, and less cumbersome, expensive and time consuming.

Another project in Yugoslavia has produced important information with regard to the usefulness of an oral vaccine for the control of dysentery in children.

During FY 1972, HSMHA plans to further develop its Special Foreign Currency Program by renewing a number of highly promising projects and developing new ones in areas of high program priority.

The very successful medical student fellowship programs will be continued and expanded in Yugoslavia. Efforts will be made to develop and operate additional training programs for American medical students and graduate physicians in India, Poland and Tunisia.

To help us find effective ways of dealing with shortages and unequal distribution of physicians, studies will examine various methods of substituting for health manpower, alternate patterns of medical care that conserve manpower, and various means of redistributing available medical manpower.

Studies will also be made to determine more effective and efficient means of organizing medical resources. The major goals of these projects will be to find means of reducing costs, conserving manpower, increasing the effectiveness of medical care by finding ways to minimize hospitalization, and improving and expanding ambulatory care.

Additional studies will be directed at the development of methods to analyze various administrative and technical aspects of medical care (both hospital and ambulatory), and to evaluate the contributions of all types of ancillary health manpower.

FY 1972 plans call for a larger segment of HSMHA funds to be directed toward solving some of the problems of congenital defects and handicapping conditions, a major area of concern in the U.S. New studies will be initiated in six countries and will include such subjects as treatment of congenital bone diseases, incidence and care of congenital amputees, and treatment of various types of severe blood diseases of childhood.

Family planning research continues to have a high priority within HSMHA and studies are planned that will assist in the development of more appropriate and better utilized national family planning services.

HSMHA is also very concerned with the effect of the increased abortion rate on the health of the women and on their subsequent offspring. With the rapid change in state laws removing former restrictions on the performance of abortion, there is a great need to develop more information on what effect, if any, repeated abortions have on the health of women and their ability later to produce normal, healthy children. In Yugoslavia, where women have repeated abortions under what are considered good conditions and where they can be followed up later, we should be able to obtain valuable information that would require many years to obtain in the U.S.

In Yugoslavia and Poland projects will be carried out to determine the effectiveness of early drug therapy in preventing frank hypertensive disease, heart disease, and stroke among population groups with borderline high blood pressure.

In India plans are being made to conduct a pilot study of the delivery of mental health services to the entire population of a circumscribed geographic area. Members of the core mental health professions drawn from primary health centers, the local hospital and the medical school will form an integrated team to develop a community system of coordinated care for the mentally and emotionally ill. The potential of such a system, not only for treatment but for the prevention of mental and emotional illness, is a matter of vital interest among mental health professionals. Renewed support is planned for a research project in Poland which has contributed significantly to the progress of brain-behavior research in that country as well as to the status of similar projects in the U.S.

Finally, in addition to continued support of research projects in such important fields as hepatitis, venereal disease, tuberculosis and hospital-borne infections, HSMHA plans call for new research in areas such as food fortification, food absorption problems in people with gastrointestinal diseases, rheumatic fever, and causative factors in genetic birth defects.

Disease Control

Disease control through environmental health activities is concerned with the preventive public health aspects of the control of environmental hazards to man. The overall effort is aimed at gaining deeper insight into the complex relationship between man and his environment and developing ways of controlling or preventing environmental hazards to human health.

The Special Foreign Currency Program enables the study in excess currency countries of unusual, intensified, or high risk environmental conditions and their health effects. These studies, which provide new knowledge often not readily attainable in the United States, are directed toward meeting U.S. domestic objectives and priorities for occupational health, radiation control, and improving the quality of human settlements.

Occupational environment and illness studies are providing valuable research data on levels of worker exposure to (1) toxic industrial chemicals (lead, mercury, carbon disulfide), (2) industrial heat (heat stroke and heat exhaustion, prevention and treatment), (3) dust related chest diseases (coal mining pneumoconiosis, asbestosis, byssinosis, chemical fertilizers, and pesticide manufacture), and (4) noise and vibration. Generally, such exposures are higher than in the United States and can be closely compared with the toxicologic and other effects on the study population. This is possible because of the stable European work population and the centralized medical services and vital statistics records systems in these countries.

The acquisition of such data on high priority occupational health problems in the United States reduces the need for costly studies of the U.S. work population and provides information which can be used to prevent dangerous working conditions from being practiced or extended into U.S. manufacturing processes. For example, long-term exposure records on the stable uranium mining and processing work population in Yugoslavia have supplemented U.S. scientific data. Thus, modification of exposure standards was expedited so that appropriate control measures could be applied to reduce future occupationally-related deaths in the work force of the U.S. uranium industry. In Yugoslavia, studies involving the use of isoniazid prophylactic treatment for altering the progression of coal workers' pneumoconiosis have allowed a dimension of research on human subjects not possible in the U.S.

Radiation effects on man have been studied in Israel with special concern for latent development of mental and nervous disorders and neoplasms resulting from X-irradiation of the scalp of children for treatment of tinea capitis. Data from a population of 30,000 patients have been developed in this study. The well-developed system of records and vital statistics in Israel have proven to be a valuable resource for this epidemiologic study. Similar valuable records are maintained on tuberculosis patients. By examination of these records it is planned to investigate the effect of X-irradiation of the chest among persons exposed to numerous fluoroscopic examinations of lung and breast cancer which is reportedly excessive among tuberculosis patients. Additional patient groups identified in the Mediterranean area who have received high therapeutic doses of radiation during their youth and who may provide additional morbidity-mortality information on latent effects of radiation exposure will be studied as a coordinated effort in Egypt, Tunisia, and Morocco.

Radiation responsibilities in the Department were greatly expanded with the enactment of the Radiation Control for Health and Safety Act (P.L. 90-602). In

FY 1972 it is planned to institute collaborative research and scientific exchange with experts in Poland, Yugoslavia, and India on such problems as hazard evaluation of neutron generation, particularly as related to particle accelerators; and, evaluation of non-ionizing radiation measurement techniques as related to a wide variety of electronic products which are particularly hazardous due to radiation emissions.

The protection of health and safety of residents of urban, suburban, and rural settlements in specific human ecological areas is of great concern to the Public Health Service. The major focus is on developing means of maintaining or changing both the man-built physical surroundings and the attitudes and behaviors of social environment which are relevant to the healthful and safe use of built environment. Activities are directed toward generating health and safety criteria and standards for the design, maintenance, and use of human surroundings, community environmental management systems as guidelines for planning and implementing health protection programs. Foreign research projects reflect the requirements of domestic programs and are designed to provide insight into means of reducing or preventing physical and mental disease and promoting social well-being.

For FY 1972 research under the Special Foreign Currency Program is planned in three areas. First, human ecology research designed to ascertain the dynamics of health ecosystems, including both the physical and social environmental factors which affect changes in health status and morale. Such studies include investigation of stressors in respect to both the physical surroundings and social environment of human settlements, under different climatic conditions and under land use and population densities ranging from rural to congested urban. Second, basic health and safety criteria research for standards of design, maintenance, occupancy, and use of residential and community recreational environments, followed by evaluative health and safety research of developments built and used under the guidance of such standards. Third, applied and evaluation research and development of community health environmental management systems, including public administration process and procedures, legal relationships and responsibilities, and community organization and health education techniques, which lead to better private and public management as measured by health status change in evaluation of demonstration programs.

Food and Drug Administration

The program needs of the Food and Drug Administration (FDA) are specialized and oriented toward its domestic mission of protecting consumers of foods, drugs, therapeutic devices, cosmetics, and hazardous household products. Research projects supported under the Special Foreign Currency Program are designed to provide research answers to critical issues which bear upon FDA's scientific and regulatory efforts in the United States.

Controlled studies are currently being conducted in Yugoslavia to determine whether there is any relationship between oral contraceptive drug use and abnormalities in cervical cytology and histology, subsequent fertility, and the development of congenital anomalies in the children of women using these drugs. Another related study is attempting to further elucidate changes in carbohydrate and liquid metabolism as induced by selected oral contraceptives.

For FY 1972, a comprehensive foreign research program in a number of critical areas is being developed. Proposed projects include studies to determine the ecological impact of low level usage of antibiotics and their effect on the environment; effect of food additives and industrial chemicals on geriatric and neonatal primates; and problems associated with mycotoxin (aflatoxin) exposure in food and/or diet and its potential association with human liver cancer. A study which is being developed in India will use nonhuman primates to study the effects of exposure to mycotoxins in foods. Through this study, FDA expects to secure important data and information to better regulate fungally contaminated products and thus offer the consumer better protection.

As part of its effort to ensure safe, pure, wholesome and nutritionally adequate foods, the FDA will in FY 1972 concentrate on the development and implementation of research projects aimed at GRAS substances literature search and toxicological examination. The President, in his Consumer Message of October 1969, directed the FDA to review the Generally Recognized as Safe (GRAS) list. The accomplishment of this mission will necessitate a review of the scientific literature relevant to uses and levels of use of approximately 600 compounds for the period 1920-1970 and the screening of these compounds through toxicological testing to determine the effects of the chemicals relevant to a spectrum of adverse results. Since many of these chemicals are of worldwide importance, research collaboration under the Special Foreign Currency Program will be useful in achieving the FDA's goal. Additional planned projects include studies of iodide fortification of foods, composition of fruit and fruit products, and contamination of spices.

High priority is also being given to research concerning drug bioavailability and drug interaction. Controlled drug interaction studies are expensive and difficult to arrange. If satisfactory animal models can be developed for screening, the evaluation of drugs and the development of new drugs can be greatly facilitated. Poland, Yugoslavia, and India offer excellent opportunities for cooperative research in the drug area. India, with its large supply of subhuman primates and widespread experience in the use of this group in testing drugs, provides us with an excellent opportunity to enter into further collaborative projects which will form a base for guidance in drug testing in the United States. In FY 1972 efforts will be made to extend the drug research program to include such important health issues as possible interactions between anti-Parkinson drugs and other CNS-active drugs, drug interactions with insulin, adverse drug reaction reporting programs, and efficacy in selected categories.

Projects are also planned for development in the field of veterinary medicine. Bioavailability of drugs and the development of chemical assay methodology both in animal feed and animal tissue are of special interest to FDA and its mission to protect the public health of the Nation as it may be affected by foods and drugs.

Office of International Health

Travel funds are requested by the Office of International Health to enable the PHS Program coordinator and members of the professional staff to visit countries in which excess currencies are available. Travel will be performed for the purpose of developing policy and program objectives consistent with both United States and host country interests. Working relationships with the Ministries of Health will be developed and potential project areas explored.

SCIENTIFIC ACTIVITIES OVERSEAS (SPECIAL FOREIGN CURRENCY PROGRAM)

Program Purpose and Accomplishments

Activity: Foreign health research (Agricultural Trade Development and Assistance Act of 1954, as amended, Section 104(b); International Health Research Act of 1960, Section 308)

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$28,944,000	Indefinite	--	$25,545,000

Purpose: Funds are used to support collaborative health research and research-related projects abroad. The Program helps achieve the domestic health objectives of the Department and promotes United States foreign policy. Activities are directed toward the prevention and control of diseases and the development of mechanisms for the promotion of health in the United States and other countries.

Explanation: The Program is supported entirely by foreign currencies owned by the United States which have been determined by the Treasury to be in excess of normal United States needs in the countries. Payments are made for necessary expenses for conducting research and other activities, as authorized by law.

Accomplishments in 1971: In 1971 more than 100 new projects were funded, an increase of more than 84 over 1970. Primary emphasis was on studies to improve the organization and delivery of health service and biomedical research.

Objectives for 1972: The estimate for 1972 provides for an estimated 75 new projects and additional support for approximately 30 ongoing projects. Research in the fields of population and family planning; nutrition; and the organization and delivery of health services, particularly in the area of maternal and child health, will be emphasized. The programs of biomedical research and health communications will be strengthened.

WEDNESDAY, MAY 12, 1971.

OFFICE OF THE DIRECTOR

AND

PAYMENT OF SALES INSUFFICIENCIES AND INTEREST LOSSES

WITNESSES

DR. JOHN F. SHERMAN, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ROBERT Q. MARSTON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
RICHARD L. SEGGEL, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
B. FRANK GARDNER, JR., ACTING ASSISTANT DIRECTOR OF FINANCIAL MANAGEMENT (BUDGET), NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

OFFICE OF THE DIRECTOR

OBJECT CLASSIFICATION (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 estimate	1972 estimate
Personnel compensation:			
Permanent positions	5,941	6,130	6,884
Positions other than permanent	189	196	215
Other personnel compensation	137	142	153
Total personnel compensation	6,267	6,468	7,252
Personnel benefits: Civilian employees	484	543	609
Travel and transportation of persons	85	100	117
Transportation of things	3	8	8
Rent, communications, and utilities	158	207	216
Printing and reproduction	182	191	211
Other services	719	1,028	2,819
Supplies and materials	55	79	89
Equipment	38	46	53
Subtotal	7,991	8,670	11,374
Quarters and subsistence	−3	−3	−3
Total obligations	7,988	8,667	11,37

PERSONNEL SUMMARY

Total number of permanent positions	477	487	536
Full-time equivalent of other positions	26	26	30
Average number of all employees	478	479	530
Average GS grade	8.2	8.3	8.4
Average GS salary	$10,694	$11,994	$12,193
Average salary of ungraded positions	$8,450	$8,990	$9,081

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 estimate	1972 estimate
Program by activities:			
Program direction and management services (program costs, funded) [1]	7,771	8,667	11,371
Change in selected resources [2]	217		
Total obligations	7,988	8,667	11,371
Financing:			
Receipts and reimbursements from Federal funds:			
Federal funds			−288
Unobligated balance lapsing	49		
Budget authority	8,037	8,667	11,083
Budget authority:			
Appropriation	7,093	8,206	11,083
Pay increase (Public Law 91–305)	230		
Transferred to other accounts	−14		
Transferred from other accounts	728		
Appropriation adjusted	8,037	8,206	11,083
Proposed supplemental for civilian pay act increases		450	
Proposed supplemental for military pay act increases		11	
Relation of obligations to outlays:			
Obligations incurred, net	7,988	8,667	11,083
Obligated balance, start of year		603	396
Obligated balance, end of year	−603	−396	−354
Outlays, excluding pay increase supplemental	7,385	8,435	11,103
Outlays from civilian Pay Act supplemental		428	22
Outlays from military Pay Act supplemental		11	

[1] Includes capital outlay as follows: 1970, $27,000; 1971, $53,000; 1972, $53,000.
[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1969, $0; 1970, $217,000; 1971, $217,000; 1972, $217,000.

NOTES

Includes $189,000 in 1971 and $197,000 1972 for activities previously financed from: Office of the Secretary, 1970, $69,000

Includes $2,140,000 in 1972 for activities previously financed from (in thousands of dollars):

	1970	1971
Division of Biologics Standards	453	28
National Cancer Institute	576	151
National Heart and Lung Institute	80	71
National Institute of Dental Research	29	31
National Institute of Arthritis and Metabolic Diseases	70	810
National Institute of Neurological Diseases and Stroke	72	67
National Institute of Allergy and Infectious Diseases	355	643
National Institute of General Medical Science	27	21
National Institute of Child Health and Human Development	49	47
National Eye Institute	10	8
National Institute of Environmental Sciences	23	22
John E. Fogarty International Center for Advanced Study in the Health Sciences	1	6
Research resources	8	10
Health manpower	51	36
Dental health	20	15
National Library of Medicine	35	38

Excludes $87,000 in 1971 and $90,000 in 1972 for activities transferred to Office of the Secretary, 1970, $85,000.

Payment of Sales Insufficiencies and Interest Losses

PROGRAM AND FINANCING (IN THOUSANDS OF DOLLARS)

	1970 actual	1971 estimate	1972 estimate
Budget authority:			
Appropriation (definite)	957	3,083	4,000
Transferred to other accounts:			
Health professions education fund	−735	−2,035	−2,432
Nurse training fund	−222	−1,048	−1,568
Appropriation (adjusted)			

INTRODUCTION OF DR. SHERMAN AND ASSOCIATES

Mr. FLOOD. We will now take up the request for the Office of the Director of the National Institutes of Health.

The presentation will be made by Dr. John F. Sherman, Deputy Director. We have your biographical sketch, Doctor.

(The biographical sketch follows:)

NATIONAL INSTITUTES OF HEALTH

Position: Deputy Director, National Institutes of Health, Bethesda, Md.
Personal Information

Birthplace and date: Oneonta, N.Y., September 4, 1919.

Education: February, 1946 to June 1949—Union University College of Pharmacy, Albany, N.Y.; B.S.—June 1949 (cum laude); September 1949 to January 1953—Yale University, New Haven, Conn.—Ph. D. June 1953.

Experience: November 1, 1968 to present—Deputy Director, NIH; January 1, 1964–October 31, 1968—Associate Director for Extramural Programs, NIH; January 15, 1962–December 31, 1963—Associate Director for Extramural Programs, NIAMD, NIH; July 1, 1961—January 14, 1962—Associate Director for Extramural Programs, NINDB, NIH; October 8, 1958–June 30, 1961—Deputy Chief, Extramural Programs, NIAMD, NIH; August 8, 1957–October 8, 1958—Assistant Chief, Extramural Programs, NIAMD, NIH; July 1956–August 1957 Assistant to the Chief, Extramural Programs, NIAMD, NIH; January 1953–July 1956—Research Pharmacologist, LTD, NIAID, NIH.

Mr. FLOOD. Please proceed with your statement, Doctor.

GENERAL STATEMENT

Dr. SHERMAN. Mr. Chairman and members of the committee, this appropriation provides for the central executive direction and management of the various programs of the National Institutes of Health. Specifically, it includes—

(1) The Director and his immediate staff and the offices responsible for program planning and evaluation and public and scientific communications; and

(2) Supporting management functions, involving budget and financial management, personnel management, contract and grant management, and management analysis and review.

IMMEDIATE OFFICE OF THE DIRECTOR

The Director's immediate staff includes the principal associates and others in a supporting role required to assist the Director in directing and coordinating the extensive extramural, intramural, and collaborative programs of the Institutes and research divisions and the programs of the Bureau of Health Manpower Education and the National Library of Medicine. The offices responsible for programs planning and evaluation and for public and scientific communications provide staff support to the Director in carrying out his responsibilities in these areas. As you are aware, there are 17 Institutes and research divisions, plus the Bureau of Health Manpower Education and the National Library of Medicine reporting to the Director, NIH. All together, NIH has more than 140 separately budgeted activities and includes over 45 targeted programs in the research area alone. Many program issues cut across organization lines of the Institutes and the Bureau and may

involve major policy questions which require action by the NIH and the Office of the Secretary. The need for more intensive studies of program progress and program direction is growing as our programs have become more complex and as increasing emphasis is being placed by the executive branch on analytic and planning techniques. All of this places a heavy burden on the resources of the Office of the Director, NIH.

CENTRAL MANAGEMENT SERVICES

The central management services financed by this appropriation support not only the overall direction and management of NIH but also provide a number of services to the individual Institutes and the other operating components of NIH. Since most of NIH is geographically located at one place, it is economical to provide a large number of management services on a consolidated, central basis. These are, therefore, financed through this appropriation. They include central accounting, voucher auditing and payment services for all of our many appropriations and budget accounts; a wide range of personnel management services for over 11,000 employees; contracts and grants management services relating to more than 22,000 projects; and management studies and reviews to promote economies and efficiency of operations and insure effective application of policy and procedural controls throughout all of the operating components of NIH.

APPROPRIATION REQUEST

Mr. Chairman, the request for the Office of the Director is $11,442,000 for 1972, an increase of $556,000 over the comparable 1971 level of $10,886,000. This net increase is, however, entirely attributable to mandatory costs—that is, annualization of the 1971 pay increase costs, within-grade increases, and the like. We are proposing an increase of $24,000 for our program planning and analysis staff to meet the increasing requirements for studies and program evaluations, but this is offset by a $24,000 decrease in our information activities; in other words, there is no net increase for program in this appropriation.

Thank you, I shall be happy to respond to any questions you may have.

Mr. FLOOD. You have no program increase as far as dollars are concerned.

Dr. SHERMAN. No, sir.

Mr. FLOOD. I notice you are budgeting an increase of two in personnel, by cutting back a little bit on nonpersonnel expenditures. How can you budget this precisely? In 1971 you are getting along with 525 employees. In 1972 you want 527. What is so important about that?

Dr. SHERMAN. Well, sir, the way we count people and slots at the present time, it becomes very important, Mr. Chairman. More and more the programs of the research Institutes, but also the other activities as well, involve a much higher degree of cross-Institute activity. This requires, first of all, more extensive and more sophisticated planning, which can be done, we feel, only at the level of the Office of the Director, and with skilled personnel of the type we are requesting the increase for.

Mr. FLOOD. That may sound like nit-picking.

Dr. SHERMAN. Mr. Seggel and I have struggled over those 2's and 3's considerably over the last year. This increased complexity, we feel, is a very appropriate justification for that very small increase.

PAYMENT OF SALES INSUFFICIENCIES AND INTEREST LOSSES

Mr. FLOOD. You have what you call payments of sales insufficiencies and interest losses. Of course there is not very much to talk about in connection with that either. Actually all you are going to do is pay bills that are due and no more nor less; is that it?

Mr. MILLER. This is in a sense an uncontrollable appropriation.

Mr. FLOOD. Of course we will put the justifications in the record to show how this was calculated.

Mr. Michel?

Mr. MICHEL. No questions.

Mr. FLOOD. Mr. Natcher?

Mr. NATCHER. No questions.

Mr. FLOOD. Mr. Shriver?

INFORMATION PROGRAM CUTBACKS

Mr. SHRIVER. What is this $24,000 information reduction?

Dr. SHERMAN. It is primarily as a consequence of the President's attempt to cut back on the type of activities that "primarily sell the agency," Mr. Shriver, such as information monographs about the NIH. It doesn't cut back on such things as providing the ordinary citizen with information about cardiovascular disease or how to seek treatment for dental caries or something of that sort.

Mrs. REID. How much of your appropriation is for informational activities? How many employees are engaged in this activity?

Dr. SHERMAN. In this appropriation it is estimated that $509,000 will be spent on informational activities. A total of 26 employees are engaged in the scientific and public information activities.

GRANT PROCEDURES

Mrs. REID. What is the procedure in the awarding of grants? Do the individual institutes make the awards—and then your office makes the payments?

Dr. SHERMAN. Yes, the individual institutes make the awards for research grants.

All applicants for research grants are received centrally at NIH by the Division of Research Grants. This Division has to make two decisions concerning the subsequent handling of a grant application. First, it decides which of the institutes could most appropriately support the project if the application is approved and then it decides which of the study sections can most appropriately assess its scientific merit. When the study section has completed its review, the application, together with the study section's comments and recommendation, is sent to the institute for submission to its advisory council. As you know, the legislation under which the various institutes were created requires that awards may only be made on the recommendation of the appropriate advisory council. After the advisory council recom-

62-645 O - 71 - pt. 3 - 84

mends approval of a grant application, the institute director must make the final decision whether the award should actually be made. This authority is vested in the Secretary but has been delegated to the Director of NIH who, in turn, has delegated it to the directors of the several institutes—but with two exceptions. All grants of more than $100,000 and all grants to foreign institutions or individuals abroad must be approved by the Director of NIH before an award can be made.

Actual payment of the grant is made by the Treasury either in the form of check or of a letter of credit.

Mr. FLOOD. Mr. Smith?

CANCER PROGRAM'S EFFECT ON DIRECTOR'S BUDGET

Mr. SMITH. Is this budget affected in any way by the cancer program?

Dr. SHERMAN. As of the moment it is not. However, the increase of two people mentioned by the chairman, Mr. Smith, is for the type of program coordination and analysis that will be increasingly required by the expanded cancer effort.

Mr. SMITH. Under the administration's proposal, there will be some change in the way it operates. Whose budget would that come under? Is that all under the cancer budget?

Dr. MARTSON. I think you are speaking to the proposal the President sent to Congress yesterday on this?

Mr. SMITH. Yes.

Dr. MARTSON. As you know, he stressed that the cancer cure program would be separately budgeted. This does not mean that there will not be opportunities to budget for central resources and supplies, as we have done before, but it will be in that budget as a clearly identifiable item.

Mr. SMITH. The personnel involved though would still be under NIH?

PROPOSED LEGISLATION FOR CANCER PROGRAM

Dr. MARSTON. Yes, sir. The President's intention yesterday was to keep the cancer activities within NIH, but, by having the director of the cancer cure program report directly to him, to give this the full drive and push of special and personal Presidential interest in getting it along as fast as possible.

Mr. SMITH. What additional authority do you need to do?

Dr. MARSTON. This has been a question that has been discussed in the executive branch, when S. 34 was first submitted, as to what additional authorities are actually needed. They come down to a relatively small number of additional authorities. Two-year money was something that we have included in the supplemental request.

Mr. SMITH. That didn't require new authorization.

Dr. MARSTON. That did not require new authorization. Actually, as you konw, the Public Health Service Act is so broad that one can accommodate essentially all of the recommendations of the panel of consultants and of the President's program in existing legislation. On the other hand, the President and, I think, the Congress has expressed a

wish to consider the actual organization of the cancer program through the legislative mechanism rather than doing it through the administrative channels.

Mr. SMITH. The administration can do what they want to do without any change in the law. I don't understand why they don't just go ahead and do it, and if Congress doesn't like that organization, the burden is on Congress to come forward with some legislation that provides for change. I don't understand why you propose new legislation to do what you are already authorized to do.

Dr. MARSTON. I think the reason for this is that there already is legislation before the Congress, in S. 34, that proposes one way of legislatively handling the cancer problem.

Mr. SMITH. Frankly I am concerned. It seems to me that there is too much attention on any kind of a public relations gimmick that refers to cancer, instead of getting to the objective. I am not saying that it is just down at the White House. I think it is in Congress, too. It seems to me that a great deal of the talks and the proposed bills are entirely unnecessary to the objective. We ought to just get on with the job.

Dr. MARSTON. I think it was the gist of my testimony before the subcommittee some weeks ago, that we were in complete sympathy with the goals, but that I hoped that we did not get side-tracked into the organizational and administrative details. We have a very, very tough problem.

Mr. SMITH. I thoroughly agree. I don't see any sense in getting all tied up in a big argument over the organization. A non-productive argument is being precipitated by having alternative legislation proposed, especially when the law does not have to be changed in order to permit you to proceed at full speed. I didn't understand the need for the President sending up that message.

RATIONALE FOR REQUESTING NEW LEGISLATION

Dr. MARSTON. The testimony we gave on S. 34 was that we did have the mechanisms to achieve the goals of S. 34. However, as time has gone on, it did seem to be apparent that the Congress wanted to vote on legislation for cancer. The purpose of the President's message yesterday was to achieve the goals of S. 34, but to do it without moving cancer research out of NIH.

Mr. SMITH. Of course we vote on that when we give you the $100 million without any strings attached—nothing requiring an administrative structure which prohibits you from proceeding with the kind of an organization you want. An appropriation without such restriction or direction in and of itself indicates an approval of your proposed organization set-up. Unless somebody attaches some strings to it before it gets through Congress, you can go ahead with the money and administer it the way you told us you were going to do it.

Dr. MARSTON. Yes, sir.

Mr. MILLER. Of course, Mr. Smith, the message did have one practical, immediate impact, and that was to postpone the reporting out of that bill until the committee considered an alternative approach. I think it was important to the administration that the Senate committee take a look at a possible alternative, but I certainly don't disagree with your comments.

Mr. SMITH. The other thing about it is that when one goes to fooling around with legislation specifically authorizing a particular program that was previously authorized in broad terms, one inevitably ends up with less authority and with a more restricted piece of legislation than originally existed.

Dr. MARSTON. I find myself in agreement with everything you have said on this subject. I think there is broad sympathy with the view you have stated that we have gotten into the by-pass of focusing on things other than this very important disease that affects the health of a lot of people. During the time between now and the time that this is taken up again, I plan to spend time focusing all of our energies on how best to move forward with the substance of the program. I will be pleased to talk with you or anyone else about how we progress on that. We have got a major job to do in escalating the level of effort in cancer research above anything that has been done before in this country or in the world. It has got to be done soundly and it has got to be done well and it has got to engage the attention of the best scientific talent in the country.

Mr. SMITH. And not have our attention diverted by some side issue.

Dr. MARSTON. Yes, sir.

Mr. SMITH. That is all.

Mr. FLOOD. Mr. Patten?

Mr. PATTEN. No questions.

CONCLUDING REMARKS OF DIRECTOR AND CHAIRMAN

Dr. MARSTON. Mr. Chairman, could I just follow up on that for a moment, because it seems to me that these have been unusual hearings this year. For one reason, the problem of the allocation of resources has been a keener one because of the cancer question. As I have said for several years now, this overview of our programs is particularly helpful to us, not just in budgetary terms, but because we learn from these exercises of putting together the material to present to you and, more especially, from hearing your comments.

I probably feel more keenly this year than I have in previous years that you have helped us a great deal in looking at the NIH programs broadly, at a time when we are going to be changing some aspects of them, some in cancer and, possibly later on, in some other areas.

Mr. FLOOD. The hearings on the National Institutes of Health are usually good but this year they have been above average. The presentations made by the witnesses, and their response to members questions have indicated that they are really on top of their jobs and have intimate knowledge of what goes on in the areas that they are responsible for. While I think there are many deficiencies in your budget, you and your top people have done a good job of presenting it and have been responsive to some rather difficult questions about these deficiencies.

On behalf of the committee, thank you very much.

Dr. MARSTON. Thank you very much, Mr. Chairman and members of the committee.

Justification of the Budget Estimates

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Amounts Available for Obligation

	1971	1972
Appropriation	$8,206,000	$11,442,000
Real transfer from:		
"National Eye Institute"(Proposed transfer for increased pay costs)	461,000	---
"National Institute of General Medical Sciences" (Proposed transfer for increased pay costs)	236,000	---
Comparative transfer to:		
"Departmental Management"	-21,000	---
Comparative transfers from:		
"Biologics Standards"	28,000	---
"National Cancer Institute"	151,000	---
"National Heart and Lung Institute"	71,000	---
"National Institute of Dental Research"	31,000	---
"National Institute of Arthritis and Metabolic Diseases"	810,000	---
"National Institute of Neurological Diseases and Stroke"	67,000	---
"National Institute of Allergy and Infectious Diseases"	643,000	---
"National Institute of General Medical Science"	21,000	---
"National Institute of Child Health and Human Development"	47,000	---
"National Eye Institute"	8,000	---
"National Institute of Environmental Health Sciences"	22,000	---
"John E. Fogarty International Center for Advanced Study in the Health Sciences"	6,000	---
"Research resources"	10,000	---
"Health manpower"	36,000	---
"Dental health"	15,000	---
"National Library of Medicine"	38,000	---
Total, obligations	10,886,000	11,442,000

Obligations by Activity

Page Ref.		1971 Estimate Pos.	1971 Estimate Amount	1972 Estimate Pos.	1972 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
141	Program direction and management services	525	$10,886,000	527	$11,442,000	+2	+$556,000
	Total obligations	525	10,886,000	527	11,442,000	+2	556,000

Obligations by Object

	1971 Estimate	1972 Estimate	Increase or Decrease
Total number of permanent positions	525	527	+2
Full-time equivalent of all other positions	30	30	--
Average number of all employees	520	521	+1
Personnel compensation:			
Permanent positions	$6,853,000	$7,249,000	+$396,000
Positions other than permanent	222,000	233,000	+11,000
Other personnel compensation	158,000	163,000	+5,000
Subtotal, personnel compensation	7,233,000	7,645,000	+412,000
Personnel benefits	607,000	640,000	+33,000
Travel and transportation of persons	112,000	112,000	---
Transportation of things	8,000	8,000	---
Rent, communications and utilities	212,000	216,000	+4,000
Printing and reproduction	211,000	211,000	---
Other services:			
Payment to NIH Management Fund.	1,311,000	1,442,000	+131,000
Other	1,056,000	1,032,000	-24,000
Supplies and materials	86,000	86,000	---
Equipment	53,000	53,000	---
Quarters and subsistence	-3,000	-3,000	---
Total obligations by object.	10,886,000	11,442,000	+556,000

Summary of Changes

1971 estimated obligations	$10,886,000
1972 estimated obligations	11,442,000
Net change	+556,000

	Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Increases:				
A. Built-in:				
1. Annualization of 1971 pay increase costs	---	---	---	+$275,000
2. Extra day's pay	---	---	---	+29,000
3. Within-grade pay increases	---	---	---	+117,000
4. FTS rate increase	---	---	---	+4,000
B. Program:				
1. Program direction and management services	525	$9,575,000	+2	+24,000
C. Payments to "NIH Management Fund" for centrally furnished services	---	1,311,000	---	+131,000
Total, increases	---	---	+2	+580,000
Decreases:				
A. Program:				
1. Program direction and management services	525	9,575,000	---	-24,000
Total, decreases	---	---	---	-24,000
Total, net change	---	---	+2	+556,000

Explanation of Changes

Built-in Increases -- These increases will provide: $275,000 for annualization of 1971 pay increase costs; $29,000 for the extra day of pay in 1972; $117,000 for within-grade pay increases in 1972; $4,000 for increased cost in 1972 of using the Federal Telecommunications System; and $131,000 for increased payments to the NIH Management Fund for centrally furnished services.

Program direction and management services -- The program increase of 2 positions and $24,000 will be required primarily for the additional responsibilities for analyses and evaluations of program development in the new initiative areas. Reduced information activities account for the reduction of $24,000.

Explanation of Transfers

	1971 Estimate	Purpose
Real transfer from:		
National Eye Institute	$461,000	Proposed transfer for increased pay costs.
National Institute of General Medical Sciences	236,000	Proposed transfer for increased pay costs.
Comparative transfer to:		
Departmental management	-21,000	To provide central guidance and coordination of the total Career Development Program.
Comparative transfers from:		
Division of Biologics Standards	28,000)	Transfer of the research contracting functions from NIH Management Fund to Office of the Director for establishing the Office of Contracts and Grants.
National Cancer Institute	151,000)	
National Heart and Lung Institute	71,000)	
National Institute of Dental Research	31,000)	
National Institute of Arthritis and Metabolic Diseases	66,000)	
National Institute of Neurological Diseases and Stroke	67,000)	
National Institute of Allergy and Infectious Diseases	76,000)	
National Institute of General Medical Science	21,000)	
National Institute of Child Health and Human Development	47,000)	
National Eye Institute	8,000)	
National Institute of Environmental Health Sciences	22,000)	
John E. Fogarty International Center for Advanced Study in the Health Sciences	6,000)	
Research resources	10,000)	
Health manpower	36,000)	
Dental health	15,000)	
National Library of Medicine	38,000)	
National Institute of Arthritis and Metabolic Diseases	744,000)	To provide an equitable distribution of the management fund in 1972.
National Institute of Allergy and Infectious Diseases	567,000)	

Office of the Director

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1970	$7,093,000	$7,093,000	$7,093,000	$7,323,341
1971	8,206,000	8,206,000	8,206,000	8,206,000
1972	11,442,000			

Justification

Office of the Director

Program Direction and Management Services

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	525	$7,837,000	527	$8,282,000	+2	+$445,000
Other expenses.....	...	3,049,000	...	3,160,000	...	+111,000
Total.....	525	10,886,000	527	11,442,000	+2	+556,000

General Statement

The Office of the Director appropriation provides for: (1) the overall direction of the National Institutes of Health, including the immediate office of the Director and the offices responsible for program planning and evaluation, and scientific and public communications; and (2) supporting management services including financial management, personnel management, management policy and review, and grants and contract management.

Program Plans for 1971 and 1972

Executive direction of NIH will reflect a continuing emphasis on making the NIH organization an effective instrument for furthering and coordinating programs in support of the interrelated fields of biomedical research, health professions education and manpower training, and biomedical communications. This involves the collection and evaluation of data, the review and analysis of program issues and proposals, the appraisal of on-going programs, the development of policy position papers and the preparation of long-range program plans, as well as the preparation of information and its dissemination to the scientific and educational communities and to the general public.

The central management services financed by this appropriation support not only the overall direction and management of NIH but also provide a number of services to the individual Institutes and the other operating components of NIH. Financial management includes budget formulation and execution, financial reporting and analysis, grant payment and settlement, and accounting and voucher auditing for over 140 budget activities. Personnel management provides over 11,000 employees with a wide variety of personnel services, including training and employee development, classification and salary administration, employee and labor relations, equal employment opportunities, and recruitment and placement of a great variety of professional and support jobs. Management studies and review are undertaken to promote economy and efficiency of operations and to identify possible weaknesses in policy and procedural controls. The central contracts and grants management services over 22,000 projects.

The net increase of $556,000 requested in 1972 consists of mandatory increases of $117,000 for within-grade pay increases, $29,000 for an extra day of pay, $4,000 for FTS cost increases, $275,000 for annualization of 1971 pay increase costs, and $131,000 for increased payments to the NIH Management Fund. A program increase of 2 positions and $24,000 is requested to expand our efforts for studying and evaluating program plans and progress. A program decrease of $24,000 represents a reduction in preparation, printing and distribution of information monographs.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Program Purpose and Accomplishments

Activity: Program direction and management services

1971			1972 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
525	$10,886,000	N/A	527	$11,442,000

Purpose: The purpose of this activity is to provide overall program direction and central management services to the Bureaus, Institutes and Divisions of the National Institutes of Health.

Explanation: The functions and responsibilities of this activity are carried out through the offices of various associate directors and appropriate office directors with aid of staff specialists and operating personnel.

Accomplishments in 1971: In this activity, significant accomplishments were: (a) Initiated a study of graduate education and postdoctoral training in the biomedical sciences for the purpose of obtaining information relevant to the evaluation of the NIH training programs. (b) Increased minority employment and expanded the equal employment opportunities program. (c) Established a grants and contracting office. (d) Indirect cost management system became operational. (e) Accounts were converted to the umbrella accounting system.

Objectives for 1972: Program direction and management services will accentuate the following: (a) Completion of the study on the evaluation of the NIH training programs. (b) Strengthen and expand the equal employment opportunities program. (c) Intensify and broaden the NIH program evaluation effort. (d) Achieve greater utilization and potential of the umbrella accounting system. (e) Achieve an overall strengthening of the NIH grants and contracting operations. (f) Redesign the Grants Management Fund to be more effective and responsive to the requirements of the overall DHEW.

New Positions Requested
Fiscal Year 1972

	Grade	Number	Annual Salary
Program direction and management services			
Program Analyst	GS-13	1	$17,761
Program Analyst	GS-12	1	15,040
Total new positions.....		2	32,801

Justification of the Budget Estimates

Payment of Sales Insufficiencies and Interest Losses

Amounts Available for Obligation

	1971	1972
Appropriation	$3,083,000	$4,000,000
Estimated transfer to other accounts 1/	3,083,000	4,000,000
Health Professions Education Fund	(2,035,000)	(2,432,000)
Nurse Training Fund	(1,048,000)	(1,568,000)

1/ Distribution between Health Professions Education Fund and Nurse Training Fund may vary due to changing interest rate.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Health Professions Education Fund

Amounts Available for Obligation

	1971	1972
Receipts and reimbursements from non-Federal sources	$1,912,000	$1,926,000
Transferred from other accounts (est)	2,035,000	2,432,000
Unobligated balance brought forward	1,145,000	971,000
Other unobligated balances carried forward	-971,000	-893,000
Total obligations	4,121,000	4,436,000

Obligations by Activity and Object

	1971	1972	Increase or Decrease
Cancellations	---	$213,000	+$213,000
Interest	$4,121,000	4,223,000	+102,000
Total obligations	4,121,000	4,436,000	+315,000

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Nurse Training Fund

Amounts Available for Obligation

	1971	1972
Receipts and reimbursements from non-Federal sources	$1,448,000	$1,500,000
Transferred from other accounts (est)	1,048,000	1,568,000
Unobligated balance brought forward	2,832,000	1,672,000
Other unobligated balances carried forward	-1,672,000	-2,161,000
Total obligations	3,656,000	2,579,000

Obligations by Activity and Object

	1971	1972	Increase or Decrease
Payment of Participation Certificates	$1,618,000	---	-$1,618,000
Cancellations	---	$540,000	+540,000
Interest	2,038,000	2,039,000	+1,000
Total obligations	3,656,000	2,579,000	-1,077,000

Summary of Changes

1971 Appropriation	$3,083,000
1972 Request	4,000,000
Net change	+917,000

	1971 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Increases:				
A. Built-in:				
Interest to Treasury	---	$2,126,000	---	+$193,000
Cancellations	---	---	---	+753,000
Total, increases	xxx	xxx	---	+946,000
Decreases:				
A. Built-in:				
Payments to GNMA	---	957,000	---	-29,000
Total, decreases	xxx	xxx	---	-29,000
Total, net change	xxx	xxx	---	+917,000

Explanation of Changes

Increases:

The $753,000 is needed for reimbursement to schools for estimated loan repayments cancelled under section 744(b) and 827(b) of the Public Health Service Act in addition to $193,000 in interest to be paid the Treasury Department due to higher interest rates on appropriated funds loaned to schools.

Decreases:

Refinancing of approximately $5,730,000 of Health Professions Education Fund notes in April 1971 is estimated to be at a higher rate of interest than the 6.25 percent paid at the original financing in 1968. This increase is more than offset by lower interest costs incurred by retirement of $1,618,000 of notes in the Nurse Training Fund for a net decrease of $29,000.

Authorizing Legislation

Legislation	1972 Authorization	1972 Appropriation Requested
Public Health Service Act		
Payments to Schools to Cover Certain Costs Incurred in Making Student Loans from Borrowed Funds:		
Section 744(b)--Health Professions Schools.....	Indefinite	$2,432,000
Section 827(b)--Schools of Nursing.....	Indefinite	1,568,000

Appropriation

Section 744. (b) If a school borrows any sums under this section, the Secretary shall agree to pay to the school (1) an amount equal to 90 per centum of the loss to the school from defaults on student loans made from such sums, (2) the amount by which the interest payable by the school on such sums exceeds the interest received by it on student loans made from such sums, (3) an amount equal to the collection expenses authorized by section 740(b) (3) to be paid out of a student loan fund with respect to such sums, and (4) the amount of principal which is cancelled pursuant to section 741(d) or (f) with respect to student loans made from such funds. There are authorized to be appropriated without fiscal year limitation such sums as may be necessary to carry out the purposes of this subsection.

Section 827. (b) If a school of nursing borrows any sums under this section, the Secretary shall agree to pay to the school (1) an amount equal to 90 per centum of the loss to the school from defaults on student loans made from such sums, (2) the amount by which the interest payable by the school on such sums exceeds the interest received by it on student loans made from such sums, (3) an amount equal to the amount of collection expenses authorized by section 822(b) (3) to be paid out of a student loan fund with respect to such sums and (4) the amount of principal which is cancelled pursuant to section 823(b) (3) or (4) with respect to student loans made from such sums. There are authorized to be appropriated without fiscal year limitation such sums as may be necessary to carry out the purposes of this subsection.

Payment of Sales Insufficiencies and Interest Losses

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
1968	$250,000	$250,000	$250,000	$250,000
1969	200,000	200,000	200,000	200,000
1970	957,000	957,000	957,000	957,000
1971	3,083,000	3,083,000	3,083,000	3,083,000
1972	4,000,000			

Payment of Sales Insufficiencies and Interest Losses

	1971		1972		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$3,083,000	---	$4,000,000	---	+$917,000
Total	---	3,083,000	---	4,000,000	---	+917,000

Fiscal Year 1971

The appropriation for fiscal year 1971 for interest losses and sales insufficiencies is $3,083,000. Included is $2,126,000 for payment of interest to the Treasury Department on appropriated funds loaned to schools during fiscal year 1968 through fiscal year 1970 to capitalize their student loan funds. In addition, the appropriation includes $957,000 for interest due to holders of $15 million of participation certificates issued by the Government National Mortgage Association.

Plans, Fiscal Year 1972

In fiscal year 1972, payment of interest to the Treasury and to the Government National Mortgage Association will continue. However, these interest payments are expected to increase for the reasons outlined in the following paragraphs. The assumptions used in arriving at the request of $4 million (an increase of $917,000 over 1971) are:

1. The first involves a change in status (discussed below) of notes held by private investors which were due to be retired in fiscal year 1971. It is anticipated that this change will increase the interest owed on the notes.

One-half of the $15 million ($11.5 million from the Health Professions Education Fund and $3.5 million from the Nurse Training Fund) in notes pledged to the Government National Mortgage Association are due April 8, 1971. The remaining notes are due April 8, 1988. Participation certificates are sold at market demands. There was only a market for sale of participation certificates with 20-year pay-offs totalling $7.5 million of the $15 million offering in April of 1968, when the sale occurred. Consequently, the other one-half of the notes are payable on April 8, 1971.

The original plan was for the GNMA to resell $7.5 million in pledged notes in order to cover the payment due on April 8, 1971. However, the GNMA has now informed the Bureau that any amounts owed but not paid by the Health Professions Education Fund or the Nurse Training Fund, will be financed from unobligated balances available in other Trust accounts of GNMA. There are sufficient funds in the Nurse Training account to pay its share of the note retirement. The Health Professions Education Fund is depleted.

The status of plans relating to the notes due to be retired April 8, 1971, are outlined in the following:

	Health Professions	Nurses	Total
Original notes due to be retired April 8, 1971.....	$5,750,000.00	$1,750,000.00	$7,500,000.00
Less payment of principal already made.....	-20,178.35	-131,821.65	-152,000.00
Actual amount due GNMA on April 8, 1971.....	5,729,821.65	1,618,178.35	7,348,000.00
To be retired by borrowing from other GNMA accounts.....	-5,729,821.65	-0-	-5,729,821.65
To be retired from balance in Nurse Training Fund.....	-0-	-1,618,178.35	-1,618,178.35

As interest rates are considerably higher now than in 1968, we anticipate that this refinancing of the Health Professions notes will increase our interest payments to the Government National Mortgage Association. This will be offset, however, by a reduction of interest resulting from paying off $1,618,000 of notes in the Nurse Training Fund which reduces the total net payments planned to be paid to GNMA by $29,000.

2. Interest owed the Treasury Department on appropriated funds loaned to the schools is expected to increase. The budget for fiscal year 1971 was based on an estimated interest rate to Treasury of 6.25 percent. The currently estimated rate for fiscal year 1972 is 7.5 percent. The increased interest in 1972 amounts to $193,000.

3. $753,000 is requested for forgiveness of loans in the following accounts:

Health Professions Education Fund--Cancellations--Loans made to students for the Health Professions Education Fund are subject to certain forgiveness and cancellation benefits. The Act provides that the unpaid balance of a loan and accrued interest thereon shall be cancelled upon the death of a borrower, or if the Secretary determines that a borrower has become permanently and totally disabled. In addition, cancellation benefits are provided for physicians, dentists, and optometrists if they practice in certain areas with the expectation that such cancellation benefits will help relieve the manpower shortage in such areas. Should a borrower engage in the practice of medicine, dentistry, optometry or osteopathic medicine in an area in a state determined by the state health authority to have a shortage of physicians, dentists, or optometrists he may obtain a ten percent cancellation on his loan for each year of practice in such area up to a total of 50 percent of the amount due plus accrued interest. If the practice is performed in a rural area characterized by low income families then a yearly cancellation of 15 percent per year may be given up to a total cancellation of 100 percent of such total.

The Health Professions Education Fund is required to pay to the schools the amount of principal which is cancelled. It is estimated that cancellations through fiscal year 1971 will be approximately $213,000 which we are requesting in accordance with section 744(b), Title VII of the Public Health Service Act, as amended.

Nurse Training Fund--Cancellations--Loans made to students from the Nurse Training Fund are subject to certain forgiveness and cancellation benefits. The Act provides that the unpaid balance of a loan and accrued interest thereon shall be cancelled upon the death of a borrower, or if the Secretary determines that a borrower has become permanently and totally disabled. In addition, cancellation benefits are provided for employment as a professional nurse in public or other non-profit agencies with the expectation that such cancellation benefits will help relieve the shortage of nurses. Should a nurse become employed, as a full-time professional nurse, in a public or other non-profit agency she may have up to 50 percent of the total loan cancelled for such employment. The cancellations shall be at a rate of ten percent of loan balance outstanding on first day of employment, for each year of such employment. Should such employment be performed in a public or other nonprofit hospital in any area which is designated to be an area which has a substantial shortage of nurses at such hospitals, the annual cancellation shall be at the rate of 15 percent for each year of employment at such hospital up to a total cancellation of 100 percent.

The Nurse Training Fund is required to pay to the schools the amount of principal which is cancelled. It is estimated that cancellations through fiscal year 1971 will be approximately $540,000 which we are requesting in accordance with section 827(b), title VIII of the Public Health Service Act, as amended. The 1972 request of $4,000,000 is distributed among the following categories:

$3,015,000--Payment of Interest Differential to Institutions
(2,004,000)--Health Professions Education Fund
(1,011,000)--Nurse Training Fund

$232,000--Payment of Insufficiencies
(215,000)--Health Professions Education Fund
(17,000)--Nurse Training Fund

$753,000--Payment of Cancellations
(213,000)--Health Professions Education Fund
(540,000)--Nurse Training Fund

Interest Losses (Differential)

Health Professions Education Fund--An appropriation of $2,004,000 for fiscal year 1972 is requested for reimbursement of interest losses of health professions schools capitalizing student loan funds by loans from the Health Professions Education Fund. Section 744(b) of the Public Health Service Act provides for the reimbursement to the schools for the difference between the interest owed to the government on the loans and the amount (interest) collected from student borrowers. By the end of 1972, the losses owed to schools since the fund became operational in 1968 will total about $5,200,000. No significant interest payments will be received from students through 1972.

Only $2,004,000 is needed in 1972 however, to meet the following payments:

1. $604,000 owed to the Government National Mortgage Association in 1972, on $11,500,000 of pledged notes, carrying an interest rate (owed by the schools) of 5.25 percent.

2. $1,400,000 owed to the United States Treasury in 1972, on an estimated $18,671,000 of appropriated funds loaned to schools. Estimated Treasury rate for 1972 is 7.5 percent.

Nurse Training Fund--An appropriation of $1,011,000 for 1972 is requested for reimbursement of interest losses of nursing schools capitalizing student loan funds by loans from the Nurse Training Fund. Section 827(b) of the Public Health Service Act, provides for the reimbursement to the schools for the difference between the interest owed to the government on loans and the amount (interest) collected from student borrowers. By the end of 1972, the losses owed to schools since the fund became operational in 1968 will total about $2,900,000. No significant interest payments will be received from students through 1972.

Only $1,011,000 is needed however to meet the following payments in 1972:

1. $92,000 owed to Government National Mortgage Association in 1972, on $1,750,000 of pledged notes, carrying an interest rate (owed by the schools) of 5.25 percent.

2. $919,000 owed to the United State Treasury in 1972, on an estimated $12,256,000 of appropriated funds loaned to schools. Estimated Treasury rate for 1972 is 7.5 percent.

Insufficiencies

Health Professions Education Fund--The 1972 request for insufficiencies is $215,000. This is based on an estimated $819,000 interest due the Government National Mortgage Association in 1972 on $11,500,000 of pledged notes (half of which are held by private investors) less some $604,000 estimated from interest differential payments to be received through participating health professions schools.

Nurse Training Fund--The 1972 request for insufficiencies is $17,000. The estimate is based on an estimated $109,000 interest due the Government National Mortgage Association in 1972 (6.25 percent on $1,750,000 in notes held by private interests) less some $92,000 (5.25 percent of $1,750,000) estimated from interest differential payments to be received through participating nursing schools.

Cancellations

Health Professions Education Fund--The 1972 request for payment of loan cancellations to participating schools under section 744(b) of the Public Health Service Act is $213,000.

Nurse Training Fund--The 1972 request for payment of loan cancellations to participating schools under section 827(b) of the Public Health Service Act is $540,000.

LIST OF WITNESSES

	Page
Akers, Mrs. E. L.	858
Allison, Linda	1297
Baker, Dr. C. G.	250
Baldwin, C. B., Jr.	250
Baylis, W. G.	562
Beliner, Dr. R. W.	1, 358, 1034, 1095
Bergquist, B. G.	1095
Bowery, Dr. T. G.	1095
Brooks, Dr. G. T.	989
Browning, E. L.	250
Brust, G. A.	220
Burton, Dr. B. T.	562
Chicchirichi, D. L.	1095
Christoferson, H. C.	454
Cooper, Dr. Theodore	358
Corfman, Dr. P. A.	918
Culp, J. G.	989
Cummings, Dr. M. M.	1, 1244
Cyphers, D. F.	562
Davis, Dr. D. J.	784
Eagles, Dr. E. L.	676
Ehrlich, Dr. S. P., Jr.	1297
Endicott, Dr. K. M.	1
Fenninger, Dr. L. D.	1
Gardner, B. F., Jr.	918, 989, 1034, 1095, 1161, 1244, 1331
Gibson, Dr. S. T.	220
Grubbs, Mrs. Elizabeth	220
Heming, Dr. A. E.	858
Hill, J. G.	989
Holliday, Ross	1211
Hubscher, E. M.	918
Kennedy, Dr. T. J., Jr.	1
Kingman, G. M.	1034
Klovdahl, G. J.	858
Kreshover, Dr. S. J.	454
Kupfer, Dr. Carl	989
Langley, Dr. L. L.	1244
LaVeck, Dr. G. D.	918
Leavitt, Dr. M. D., Jr.	1161
MacNichol, Dr. E. F., Jr.	676
Marston, Dr. R. Q.	1, 220, 250, 358, 454, 562, 676, 784, 858, 918, 989, 1244, 1331

Page

May, L. B. 1, 220, 250, 358, 454, 562, 676, 784, 858
Meyer, G. F. 220, 250, 358, 454, 562, 784, 858, 1297
Mider, Dr. G. B. 1244
Miller, Charles 1, 676, 918, 989, 1034, 1095, 1161, 1211, 1244, 1331
Moore, Lyman 358
Morrison, Dr. B. H., III 250
Murray, Dr. Roderick 220
Orringer, B. A. 1034
Payne, Dr. W. W. 1211
Pettinato, Mrs. F. H. 454
Presson, G. E. 1161
Rall, Dr. D. P. 1034
Reeder, J. H. 358
Ringler, Dr. R. L. 358
Russell, G. F. Jr. 918
Seggel, R. L. 1, 1211, 1331
Sharkey, J. E. 1, 220, 250, 454, 562, 676, 858, 918, 989, 1034, 1095, 1161, 1211
Sherman, Dr. J. F. 1, 1095, 1161, 1211, 1331
Sithens, R. L. 676
Smith, K. A. 1244
Stetten, Dr. DeWitt, Jr. 858
Whedon, Dr. G. D. 562
Wipf, Eckart 676

INDEX

B

Page

Buildings and facilities 1211–43
Budget for fiscal year 1972 ..... 1211, 1214
Carryover funds 1234
Heating plant for NIH, modification of 1215, 1219
Justification material 1250
National Institute of Environmental Health, Sciences facility 1215, 1216, 1220, 1238
Coordination with Environmental Protection Agency 1238
Location in North Carolina 1237
Natural gas, shortage of supply of 1219, 1237
Project status by construction category 1236
Repairs and improvements 1216
Rocky Mountain Laboratory 1215, 1238, 1239

D

Description of programs 69–219
Director of National Institutes of Health, testimony of 1
Absorption of salary increases 21
Aging, research into problems of 47, 57
Anemia, sickle-cell 10, 56
Apportionment of funds, effect of delay in 22, 50
Appropriation inadequacies, result of 50
Appropriations and budget requests, 1933–72 64
Appropriations and obligations, 1970–72 36
Appropriations delay 22, 50
Arthritis research 45
Blood products 11
Blood resources, monitoring of 56
Breakthroughs in biomedical research 16
Budget for fiscal year 1972:
Adequacy of 49
Compared with 1970 and 1971 budgets 4
Cancer Conquest Program 5, 33, 51
Breakthrough, time frame for 48
Death rate from cancer 48
Leads in cancer research 54
Cancer research by Dr. Szent-György 42
Cancer research relationship with other institutes 55
Costs of medical schools 29
Description of programs 69–219
Employment, increase in 23
Expenditures for health and medical care 63
Fellowships and training grants 12, 14
Distribution of funds to institutes 15
Predoctoral fellowship program, phasing out of 15, 58
Financial tables 60–68

Director of National Institutes of Health, testimony of—Continued Page
Fort Detrick facilities, use of 17
General research support grant levels, changes in 35
General research support grants, reduction in 34
Genetics research 9, 55
Grant and contracting procedures 32
Grants for research in the private sector 30
Grants to medical schools 23
Health manpower programs 13
Hepatitis, viral 10
Impounding of funds 22
Increases requested 42
Legislation, proposed 32
Management fund, distribution of 18
Medical research, complex nature of 9
Medical researchers and practitioners 30
National Cancer Authority, proposal to create 53
National Library of Medicine 14, 44, 47
Nursing education 33
Obligations 36
Operations budget, decrease in 16
Physician assistant training funds 45
Physician-population ratio 29
Soviet Russia 45
Physicans, foreign, in U.S 46
Research contract funds 31
Research contracting functions, transfer of 20
Research grant budget, level of 16
Research grants since 1967 29
Support for performance of medical and health-related research, by source of funds 60
Training grant program, changes in 43
Transfer of funds out of NIH 21
Division of Biologics Standards 220–249
Enforcing sanitation standards for biological products 232
Hepatitis 224
Incidence in military services 234
Varieties of 236
Influenza vaccine effectiveness 238
Justification material 241
Licensing and enforcement procedures 233
Mononucleosis 232
Overlapping of activities of other agencies 235
Yellow fever vaccine 225, 239

F

Financial tables 60–68

J

John E. Fogarty International Center for Advanced Study in the Health Sciences 1161–1210
Bilateral cooperation 1166
Budget for fiscal year 1972 1161
Building plans 1187
Conferences and seminars 1164, 1173
Foundations engaging in conferences 1191
Genetics 1172
Coordination with World Health Organization and Agency for International Development 1191
Fellowships and training grants 1167
Cutback in 1195

John E. Fogarty International Center—Continued Page
Fogarty scholars-in-residence 1165, 1189
Funds necessary to maintain 1971 level of operations 1193
Gorgas Memorial Laboratory 1167, 1168
Justification material 1196
Oversea offices 1166, 1188
Public Law 480 funds 1190
Preventive medicine 1186
Older citizens 1187
Result of research outside U.S 1191
Special foreign currency program 1167

N

National Cancer Institute 250–357
Advisory councils 289, 299
Aerospace personnel, use in NCI management 303
Agencies other than NCI supporting cancer research 295
Areas of greatest promise in cancer research 268, 275
Budget breakdown by area of research 305
Carcinogens in cigarette smoke 296
Causes and prevention of cancers 276, 301
Ceiling on grants to cooperating groups for chemotherapeutic drugs 286
Chicken tumors, infectiousness of 293
Comprehensive cancer institute administrative plan 279
Conquest of Cancer Program:
Additional funds beyond initial request 309
Advisory groups 299
Background of budget for 271
Budget and time constraints 282
Distribution of funds for 274
Opposition to separate cancer program outside NIH 297
Organizational plan 256, 308, 271
Professional participation in 310
Programing of new funds 280
Rationale against "crash" program 306
Reason for emphasis on cancer cure 272
Suitability of HEW program management for 307
Support for program being in NIH 271, 280
Contagiousness of viral cancers 292
Detection of cancer, progress in early 277
Dr. Lijinsky's research grants 296, 297
Drug curable cancers 300
Employees, increase in 287
Enzymes 258
Drugs to inhibit cancer-causing 259
Evaluation, funds used for 283
Fellowships and training program 273
Foreign research 290
Genetic factors in cancer 268
Grant procedures 309
Immunology and molecular biology, developments in 310
Impounding of funds 308
Incidences of cancer, rise in 255, 290
Justification material 314
Leukemia chemotherapy 305
Lung cancer 256
Magnitude of cancer problem 255
Management and planning requirements 270
Makari intradermal skin test 304
Mary Hitchcock Cancer Research Center 277

	Page
National Cancer Institute—Continued	
Nitrite as possible carcinogen	305
Nitrite preservatives, advisability of limiting use of	296
Obligations	283
Private support of cancer research	296
Public information efforts	303
Reproduction rate of cancer cells	258
Research Center in Southeast U.S	278
Research Centers, new	302
Researchers attracted to cancer field	293
St. Jude's Hospital, funds for	286
Skin cancers	293
State of art of cancer research	257
Structure of cancer cell	259
Sugar consumption and cancer	289
Uterine cancer smear test	255
Vaccines against cancer	276
Viral causes of cancer	257
Virus conversion of cells to cancer	260
National Eye Institute	989–1033
Advances in retina research	993
Budget for fiscal year 1972	990, 1002
Cataracts, cause and treatment of	1000, 1004
Color blindness research	999
Construction of the human eye	996
Diabetic retinopathy, research on	996, 997, 1006
Diagnosis of diseases by fluorescein angiography	993
Detection of tumors	994
Diet, effect on vision	1005
Drug treatment for eye disorders	1006
Fellowships, reduction in	1003
Glaucoma research	1000, 1003
Intramural research	1000
Justification material	1007
Organizational changes	1001
Positions, new	1003
Racial and geographic factors in eye disease	1001
Research grants	1002
Restoration of lost vision	1005
Retinal detachment	998
Retrolental fibroplasia	999
Television broadcasting on eye care	1002
National Heart and Lung Institute	358–453
Acceleration of research	402
Additional funds, use of	405
Ambulances for heart care, equipping of	375
Arteries, use of artificial or transplanted	396
Artificial blood	366
Artificial heart development	377, 395, 406
Birth control pills, clot-producing aspects of	407
Blood clots, dissolution of	407
Blood pressure, low	409
Breakthroughs in research	405
Cardiovascular and pulmonary disease, deaths from	397
Cholesterol, relationship to heart disease	399, 409
Competition for grant awards	410
Contracting procedures	411
Device testing facilities	402
Devices and surgical procedures, beneficiaries of new	414
Drug research, advances in	374
Emphysema	382, 415
Fat, diet and drug reduction of	412
Fat, hereditary tolerance of	409

National Heart and Lung Institute—Continued Page
Grant applications unfunded 401
Grants and fellowships, cutback in 400, 415
Heart and lung transplants 376, 383, 395
Heart attacks:
Caused by blood fat disorders 363, 364
Deaths from 381, 382
Female hormone therapy for 382
Recovery of heart attack victims, monitoring of 413
Variations in incidences between men and women 382
Heart cooperative drug center, cutback in 374
Heart cooperative drug study 403
High blood pressure, control of 363
Hypertension study 412
Inflation, effect on budget 406, 410, 411
Information on heart and lung diseases 378
Justification material 417
Level of program, rationale for maintaining 1971 level 400
Lung diseases, research on 368
Community services for 372
Diseases early in life 407
Funds allocated for 370
Impact of lung problems on heart diseases 371
Liaison with Social Security Administration 372
Lung doctors, shortage of 415
New therapy and prevention activities 371
Priority in 1971 given to 370
Resources for maximum attack on 372
Medical devices application program 365
Fallout effects from 365
Myocardial infarction units 364
Narrowing of blood vessels to heart in early life, research on 406
National blood resource program 366, 405
Obesity and health 408
Pacemakers, cost and demand for 396
Priority of programs 403
Private efforts in heart disease field 403
Sickle cell diseases 366, 373, 404
Smoking, effect of 383
Specialized research centers 369, 402
Storage and distribution of blood 401, 414
Veins, storage for transplant 397
National Institute of Allergy and Infectious Diseases 784
Allergic disease centers 790, 821
Asthma and other respiratory diseases 789
Cromoglycate drug 820
Budget for fiscal year 1972 785, 797
Common cold 793, 796, 800, 823
Vitamin C, effect of 825
Drug resistance 802
Expenditures for respiratory drugs, public 824
Face masks, preventive capabilities of 823
Hepatitis 796, 801, 819
Incidence of infections 793
Incidences of respiratory disease in military services 825
Influenza epidemic recurrence 799
Influenza vaccines 800
Interferon 796, 802
International Centers for Medical Research 797
Justification material 826
Meningitis vaccine 824
Mononucleosis 807
Nuclear medicine 822

Page

National Institute of Allergy and Infectious Diseases—Continued
Organ transplant immunologic studies ... 791, 802
Kidney transplants ... 824
Pneumonia vaccine ... 793, 820, 824
Research findings, recent ... 789
Research grant program ... 816
Respiratory vaccines, successful from ... 795
Statistics on major infectious diseases ... 807
Training grants ... 816
Tuberculosis vaccine ... 801
Vaccines against disease in children ... 794
Venereal diseases, treatment and vaccine for ... 801, 806
Viral respiratory diseases ... 818
Urinary infections, new antibiotic for treating ... 795
National Institute of Arthritis and Metabolic Diseases ... 562
Adjustments in research grant funding ... 614
Arthritis:
Early treatment of ... 624
Progress in ... 597
Research opportunities in ... 624
Spurious cures for ... 623
Clinical research studies of Indians ... 575
Cystic fibrosis and other metabolic diseases ... 567, 615
Dermatologic disorders ... 570
Diabetes ... 566, 604, 624
Digestive and nutritional diseases ... 568
Endocrine disorders ... 569
Gastrointestinal bleeding ... 608
Hematology ... 569
Justification material ... 629
Kidney and urologic diseases ... 567, 587
Advances in kidney transplantation ... 596, 628
Artificial kidney ... 568, 587
Cost of kidney dialysis ... 622, 625
Nutrition research activities ... 576
Pancreas, development of an artificial ... 625
Pay increase costs ... 570, 574
Priority of research versus training ... 622
Reduction in programs ... 573
Research training and fellowships ... 570
Review of research grants ... 621
Sickle cell anemia research ... 569
Transfer of funds to other offices ... 570
Unfunded research grants ... 571
United States-Japan cooperative medical science program ... 575
National Institute of Child Health and Human Development ... 918–988
Adolescent health care ... 946
Adult development and aging ... 927
Aging, research on ... 936, 954
Other institutes' work ... 944
Budget for fiscal year 1972 ... 919, 927
Funds received from Agency for International Development ... 938
Gerontology research center ... 935
Growth and nutrition ... 926
Identification of fetal genetic defects ... 925, 942
Justification material ... 956
Life expectancy ... 935
Maternal health and child development ... 925
Mental retardation ... 926
Research centers:
Coordination of ... 930
Funding of ... 934
Location and work of ... 932
Progress made ... 932

National Institute of Child Health and Human Development—Continued Page
Nutrition research 926, 937, 948
Malnutrition and mental deficiency research 949
Population and reproduction research 927
Abortions 952, 953
Birth control:
Contraceptive methods 923, 929, 939
Contents of pill 950
Experimental oral 951
Medical effects of current methods 924
Long-term effects of 947
Side effects of birth control pills 939
Side effects of IUD's 951
Unwanted children 939
National Fertility Survey 950
Catholic universities, research at 952
Family Planning Act, funds for 928
Family planning service efforts 952
Knowledge of population control methods, inadequacy of 941
Population research center grant program 929
Priority of research versus control with present knowledge 940
Vanderbilt population research center 951
World and U.S. population growth trends 938
Population research in social sciences 924
Priorities in research and training grant programs 944
Tranquilizers for children 945, 947, 953
Use of medical services by the aged 944
National Institute of Dental Research 454
Accessibility of dental services 516, 521
Advancement in research 462
Amalgam fillings, life of 527
Anesthesiology 529
Breakthroughs against tooth decay 458
Budget request 455, 462
Cancer of the mouth 524
Cleft lip and palate 464
Clinical investigators 530
Combatting of tooth decay, collaborative research on 465
Coordination of governmental research 520
Cost of orthodontic services 521
Delegation of responsibility to allied personnel 522
Dental and oral facial anomalies 461
Dental Research Institutes 462, 467
Additional 468
Dental schools 469, 518
Dentists, number of 522
Detection of periodontal disease 528
Expansion of dental research 466, 473
Five-year plan 474, 524
Fluoridated water supply 526, 530
Gold fillings 471
Increased funds, use of 466
Industrial and accident tooth problems 524
Justification material 532
Lag in dental research 473, 520
Oral restorations 459
Pain research 461, 516
Periodontal disease research 460, 528
Preventive dental care 519
Priority of programs 519
Private funds for dental research 474, 519
Public information about dental diseases, dissemination of 472
Research award program 463

	Page
National Institute of Dental Research—Continued	
Researchers and dentists	473
Sealant research	517, 527
Statistics on dentures and false teeth	470
Tooth decay in adults and children	526
Tooth decay, prospects for preventing	520
Tooth transplants	465
Training funds	517
Training needs and training grant level	464
Women in dentistry	523
National Institute of Environmental Health Sciences	1034–1094
Accomplishments of	1038
Animal-holding facilities	1067
Areas of research	1058
Budget for fiscal year 1972	1035, 1044
Increases requested	1049, 1053
Chelating agents, research on	1052
Dissemination of information to the public	1063
Detergents	1039, 1066
Duplication of efforts of other agencies	1049, 1053, 1061, 1064, 1066
Environmental health science centers	1050
Location of	1064
Environmental Protection Agency, relationship with	1049, 1053
Facilities, use of new	1044
Fellowships and training grants	1064
Genetics change in man, studies related to	1053
Grant supported research	1048
Grants unfunded	1063, 1067
High priority programs	1051
Intramural and extramural research	1056
Justification material	1068
Lead and nitrate-nitrite	1042
Lead-Based Paint Poisoning Prevention Act	1059
Limitation on programs due to funding and employment	1065
Mercury intoxication	1040, 1042, 1056, 1066
Mission of	1038
Noise and microwave research	1046
Personnel deficiencies	1065
Personnel increase	1057
Pesticides research progress	1051, 1055
Private investment in pollution control	1063
Smoking, research on	1058
Time limit on research projects	1064
National Institute of General Medical Sciences	858–917
Additional funds added by committee, use of	868
Automating clinical laboratories	872
Budget for fiscal year 1972	859, 867
Chromosomes, research on nature of	866
Collaborative research and development, programs cut by, reduction in	885
Fellowship program, reduction in	868
Reduction in predoctoral fellowships	871
Genetics research	870, 884
Additional projects funded in 1972	884
Advances in	884
Budget for	870
Detection of carriers of faulty genes	866, 884
DNA, research into	866
Major diseases	871
Priority study of	862
Task force on	869
Treatment of genetic diseases	865

National Institute of General Medical Sciences—Continued Page
Glossary of terms 863
Goals and plans 882
Grant award criteria 874
Grant awards, status of 869
Grant staff, increase in 868
Hemophilia 882
Justification material 886
Level of medical service in 2000 A.D. 883
Pediatric pharmacology, studies in 885
Research institutions and contracts 874
Tay-Sachs disease 882
Training for pharmacologists and toxicologists 874
National Institute of Neurological Diseases and Stroke 676–783
Apportionment of 1971 funds, delay in 727
Basic neuroscience research 686
Budget for 1972 677
Reductions from 1971 budget 686, 730, 747
Six percent reduction in 744
Cancer, oral 745
Cerebral palsy 707
Collaborative perinatal project 685, 692, 737, 749
Collaborative research and development contracts 736
Deafness 720
Dystonia 682
Epilepsy 712
Head and spinal cord injuries 683, 691, 729
British competence in spinal injury treatment 746
Centers for spinal cord injury 737
Collaboration with Department of Transportation on head injury 749
Hearing, speech, and language 720
Hereditary metabolic diseases 684
Hogdkin's disease, treatment of 750
Hypertensions 746, 748
Incidence of neurological diseases 747
Justification material 752
Levodopa 686, 739
Multiple sclerosis 740
Muscular dystrophy 730
Neurological research centers 729
Parkinson's disease and other movement disorders 681, 688
Priority of programs 736
Rubella vaccination program 700
Screening tests for infections of newborn 739
Stroke, nature and treatment of 681, 701, 748
Hypertensions and stroke incidence 746
Research centers 738
Training 728, 747
Viruses, research into delayed effects of 684
National Library of Medicine 1244–96
Achievements 1259
Authorizations versus appropriations 1255
Board of Regents 1258
Budget for fiscal year 1972 1244
Adequacy of funding 1269
Compared with prior years 1265
Development of 1262
Increases and decreases 1251
Construction of library and research facilities 1262
Coordination with Agency for International Development 1268
Environmental poisons, information on 1267

	Page
National Library of Medicine—Continued	
Fees on foreign users	1260
Fluctuation in number of grants	1262
Funding level	1255
History of	1259
Information technology	1265
Justification material	1271
Lister Hill National Center for Biomedical Communications	1249, 1253, 1257, 1260, 1268
Medical Library Assistance Act programs	1248
Medical Literature Analysis and Retrieval System, role of	1247
Access of medical schools to	1261
Implementation schedule	1252
Microfilm and microfiche, use of	1264
National Medical Audiovisual Center	1250
Project contracts, reduction in	1251
Public Law 480 funds	1261
Resource grants	1256, 1263
Services discontinued	1257
Toxicology information program	1250, 1254, 1269
Users of services	1265, 1267
O	
Office of the Director	1331, 1333
Cancer program	1336
Grant procedures	1335
Justification material	1339
Organization of National Institutes	2
P	
Payment of sales insufficiencies and interest losses	1332, 1335
Justification material	1345
R	
Research Resources and General Research Support Grants	1095–1160
Animal resources	1101, 1103, 1122
Arteries, diagnosing diseased	1123
Basic programs	1101
Biotechnology resources	1102, 1107
Budget for fiscal year 1972	1096, 1105
Cancer research	1104
Child development	1103
Clinical Research centers	1105
Clinical resource	1102
Computer resources	1111
Dissemination of resources	1108
Division of Research Resources	1100
Electron microscope at University of Colorado	1109
Equipment grant selection methods	1109
Funds required to maintain 1971 level of operations	1113
General research support program	1102, 1103, 1119
Reduction in	1111, 1117
Grants, increase in	1106
Health sciences advancement awards	1114
Heart disease research	1104
Hypopituitary dwarfism	1123
Imbalances in research activities	1121
Justification material	1124
Kidney diseases, research on	1120
Maternal deprivation dwarfism, research on	1106
Narcotic addiction, research related to	1120

Research Resources and General Research Support Grants—Continued Page
Nonprimates used in health research 1118
Outpatient research studies 1117
Pacemakers, new battery for 1123
Primate research centers 1118
Primates, obtaining of 1101
Utilization of research resources by industry and others 1110
Veterinarians, role of 1115

S

Scientific activities overseas (Special Foreign Currency Program) 1297–1331
Abortion, research into effects of 1310
Agency for International Development, coordination with 1315
Breast cancer research project in Bombay 1312
Collaborative study of medical care utilization 1304
Cooperation with other countries 1301
Cost of supporting activities 1313
Delivery of health care, research on 1313
Drug abuse studies 1314
Family planning studies 1314
Historical view of 1307
Israel, project in 1306, 1309
Justification material 1316
Krakow, Poland, children's hospital in 1311
Nutrition, research on 1311
Poland, research opportunities in 1304
Travel, supervision of 1306
United Arab Republic projects 1302
Uranium mining, health effects of 1310
World Health Organization, relationship with 1302, 1311
Yugoslavia, project in 1305

○