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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1998

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTH CONGRESS

FIRST SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

JOHN EDWARD PORTER, Illinois, *Chairman*

C. W. BILL YOUNG, Florida
HENRY BONILLA, Texas
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DAN MILLER, Florida
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NITA M. LOWEY, New York
ROSA L. DELAURO, Connecticut

NOTE: Under Committee Rules, Mr. Livingston, as Chairman of the Full Committee, and Mr. Obey, as Ranking Minority Member of the Full Committee, are authorized to sit as Members of all Subcommittees.

S. ANTHONY MCCANN, ROBERT L. KNISELY, SUSAN E. QUANTIUS, MICHAEL K. MYERS, and FRANCINE MACK, *Subcommittee Staff*

PART 4A

(Pages 1–1307)

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CONTENTS

NATIONAL INSTITUTES OF HEALTH

VOLUME 4

	Page
National Institutes of Health Overview	1
National Cancer Institute	199
National Eye Institute	419
National Center for Human Genome Research	495
National Institute of Allergy and Infectious Diseases	583
National Institute of Environmental Health Sciences	711
National Institute on Deafness and Other Communication Disorders	805
National Heart, Lung, and Blood Institute	865
National Institute on Drug Abuse	983
National Institute on Alcohol Abuse and Alcoholism	1091
National Institute of Diabetes, Digestive and Kidney Diseases	1177
National Library of Medicine	1309
National Institute of Nursing Research	1377
Fogarty International Center	1443
National Institute of Arthritis and Musculoskeletal and Skin Diseases	1491
National Center for Research Resources	1573
National Institute of Child Health and Human Development	1635
National Institute of Dental Research	1737
National Institute of Mental Health	1809
National Institute on Aging	1915
National Institute of Neurological Disorders and Strokes	2001
National Institute of General Medical Sciences	2095
Office of AIDS Research	2155
Office of the Director and National Institutes of Health Buildings and Facilities	2249

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1998

WEDNESDAY, FEBRUARY 26, 1997.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

HAROLD VARMUS M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH
RUTH KIRSCHSTEIN M.D., DEPUTY DIRECTOR
WENDY BALDWIN Ph.D., DEPUTY DIRECTOR FOR EXTRAMURAL RESEARCH
MICHAEL GOTTESMAN M.D., DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH
ANTHONY ITTEILAG, DEPUTY DIRECTOR FOR MANAGEMENT
FRANCINE LITTLE, DIRECTOR, OFFICE OF FINANCIAL MANAGEMENT
DENNIS WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We're very pleased to welcome Dr. Harold Varmus and Dr. Kirschstein and the representatives of the National Institutes of Health this morning for another round of hearings on the NIH. We relish these opportunities to learn about the remarkable scientific advances that your fine institution makes possible.

I have high hopes for NIH this year, because I see increasing recognition in many quarters of the importance of biomedical research, from the designation of the AIDS researcher, Dr. David Ho, as *Time's* man of the year, to news that the *Washington Post* will be sponsoring a public television series on biomedical research, to the repeated mention of research in the President's speeches.

I'm also encouraged that the support of NIH seems to be broadening in the Congress, particularly in the Senate. I have to say, Dr. Varmus, I'm very disappointed, however, that the President's NIH budget does not match the rhetoric of his speeches. I've already expressed my dismay to Secretary Shalala about what I consider to be an inadequate NIH budget request, which is below the rate of biomedical inflation and therefore amounts to a cut in your budget. I sincerely hope that we can do much better.

I would caution everyone in this room, however, that it will not be easy to craft a bill with the kinds of increases NIH deserves and that NIH has had for the last two years, given the competing demands of education and other priorities. We must have a 602(b) allocation with enough room to address all of these priorities so that

we can produce a bill that can be passed by the House of Representatives and signed into law by the President.

Mr. Obey, the ranking minority member on the panel, is at another hearing. I will call on him for opening remarks when he arrives here. And Dr. Varmus, we'd be pleased to hear from you.

INTRODUCTION OF WITNESSES

Dr. VARMUS. Thank you, Mr. Porter.

Before I begin, let me introduce the colleagues who are here at the table with me. Dr. Wendy Baldwin, the Deputy Director for Extramural Research; Mr. Tony Itteilag is the Deputy Director for Administration; Dr. Ruth Kirschstein, well known to you, is my Deputy Director; and Francine Little, who's the Director of the Office of Financial Management; and the indefatigable Mr. Dennis Williams represents the Department on these occasions.

Mr. Porter, this is the fourth time I've had the pleasure and the honor to represent the NIH at appropriations hearings. I had not anticipated the press would be so interested in this anniversary. [Laughter.]

OPENING STATEMENT

Dr. VARMUS. As you know, I very much enjoy on these occasions relating our recent accomplishments and telling you about promising paths our research may take in the immediate future. But before we get into these annualized accounts of our progress and descriptions of promise, we need to remind ourselves of a few stern realities: that the conquest of disease is a formidable challenge; that progress is best measured over many years or decades; that advances against disease require long-term investments in research and training and facilities; and that the benefit of most research is in fact unpredictable, demanding that we institute a broad range of research activities.

CULMINATIONS OF RESEARCH

Now, over the course of the next ten days, you'll hear from the Institute directors who are arrayed behind me about two kinds of recent accomplishments, kinds that I will refer to as "culminations" and "inspirations." Culminations are practical health benefits built upon many years of research in which NIH has had a very significant role. Let me mention just a few examples of such culminations.

The further validation of an effective treatment for stroke with tissue plasminogen activator and of cryotherapy for the retinopathy of premature infants; the evidence that we can reduce disability among the elderly; the first measured real declines in cancer mortality for cancers of the lung, colon, gynecological cancers, prostate cancer and breast cancer; the efficacy of vaccines in nearly eliminating hemophilus influenza meningitis among our children, and more recently, an effective vaccine against rotavirus, which causes diarrhea worldwide; the application of the Visible Human project that you've heard about in previous years to the teaching of medicine and the practice of surgery; the use of antibiotic combinations to treat the common cause of gastric ulcers, *H. pylori*; and the in-

creasing use of recombinant DNA products, growth factors, for the treatment of marrow suppression that occurs during cancer chemotherapy.

INSPIRATIONS OF RESEARCH

Inspirations are more common. They are the important discoveries in basic science that may, we hope, be the foundations for future culminations. They are abundant. Let me give you just a few examples from three areas of recent research. In genetics, the area that has attracted a great deal of press attention, we've all read about the complete sequencing of the genomes, the entire collection of genes, from a number of organisms, yeast and several bacteria. Other genomes have been fully mapped, and some partially mapped, including the human, and all this information has been made miraculously accessible to all investigators and to the public through the GeneBank at the National Library of Medicine.

Many other disease genes have been isolated—disease genes for glaucoma, polycystic kidney disease, for retinitis pigmentosa, for a number of forms of diabetes that are inherited, for basal cell carcinoma in hereditary form, for hemochromatosis. Other disease genes have been identified but not yet isolated in pure form. Those include, most importantly in the past year, the gene for a familial form of Parkinson's disease and one for a familial form of prostate cancer.

Advances in neuroscience continue at a remarkable pace. Imaging technologies are showing us the physiological basis of many important neurological phenomenon, including aspects of behavior, pain, emotion and drug abuse. Animal models have been increasingly useful in the study of neurological disorders, clarifying the causes of disease, for example, Alzheimer's disease, Huntington's disease and spinal cerebellar atrophy. And the animal models are also stimulating new kinds of treatment, for example, the use of growth factors in treatment of spinal cord injury.

Finally, in the area of cell biology, the understanding of blood vessel growth is signalling new strategies for improving blood supply to the heart and the brain; and our understanding of how blood clotting occurs is even giving rise to the new strategies for treatment of cancers. New information about how cells talk to each other is informing research in a wide variety of categories, too numerous to mention.

CULMINATIONS IN HIV RESEARCH

I'd like to give you some sense of how these inspirations and culminations actually work in the pace of research, by telling you about a couple of events that have occurred in the past year in the area of our research on HIV and AIDS.

First, a culmination. We've referred already to the public attention that's been given to recent progress in the treatment of HIV through your mention of the man of the year award by *Time Magazine*.

The demonstrated efficacy of protease inhibitors has been seen as a bombshell by the public, but from our perspective, this is a culmination that depends upon many years of fundamental work. Our work on retroviruses extends back to the early days of this century.

Work on the enzymes that are programmed by retroviruses extends back to the 1970s. Identification of one of those enzymes, the protease; and the determination of how it works biochemically; its three dimensional structure; studies of other proteases made by cells; and the development of inhibitors that are used in the treatment of hypertension. All this was followed by drug development, largely by the pharmaceutical industry, whose strengths also depend upon NIH-sponsored training and research.

INSPIRATION IN HIV RESEARCH

Inspiration in HIV research has come from the long-awaited discovery of a class of cell proteins that is required to allow HIV to enter cells, proteins known as the co-receptors. These co-receptors, which are essential for establishing HIV infection, turn out to be proteins we already knew, proteins that recognize molecules called chemokines, proteins that are important in inflammation. We already know, even in the span of a few months, that chemokines can block infection with HIV, and that some people lack, medically lack, the co-receptors and can't be infected, even though they're otherwise healthy. What this means is that there is inspiration here for new strategies to prevent infection through vaccines and to control infection when it occurs.

OVERSIGHT AND ADMINISTRATIVE ACTIVITIES

Well, so much for science. Let me say a few words about oversight and administrative activities. Last year in our hearings, we focused on problems that beset clinical research and the need to build a new clinical research center at the NIH and to reorganize the existing clinical center. I'm happy to report that due to the generosity of this committee and your Senate counterparts, funding for the clinical research center has begun.

The design is underway. We have carried out many of the improvements we talked about last year in the functioning of the clinical center. A board of governors has been established. We've been devising new ways to recruit clinical investigators. We've expanded our training in clinical research. We've just instituted a new program that brings medical students to the NIH campus for training in clinical research—a specific response to a recommendation made by my panel on clinical research that's staffed by mostly extramural investigators.

We have responded to a variety of other administrative directives and concerns that we discussed last year. We have held our research management and support dollars steady, and we have initiated a more extensive study of all our administrative activities as a result of consultations with you and your colleagues in recent months. We have made increased use of our competitive service centers at NIH to allow institutes to carry out administrative tasks conjointly and to thereby effect some reductions in our FTEs. We have developed a search for a chief information officer and mounted a number of other strategies to improve our information systems, which could represent large cost savings over the next several years.

I have instituted a number of new reviews in conformity with earlier patterns of behavior—reviews of institute directors, of sev-

eral intramural programs, and of a variety of research areas, including AIDS, clinical research, and gene therapy.

THE PRESIDENT'S BUDGET PROPOSAL

Finally, a few comments about the budget. As you know, the President is requesting $13.078 billion for the NIH. This is $337 million more than was in the 1997 budget, a 2.6 percent increase. That request includes $90 million for the Mark O. Hatfield Clinical Research Center. That $90 million is not, however, part of the increase, because it equals the amount that was in the 1997 appropriation. And we should also say that we expect to ask for $90 million in 1999, and another $40 million in the year 2000 to finish the construction project.

Most of the increased monies will be devoted to research project grants, our traditional strength and pride. There is a 3.9 percent increase in that category. We recognize the constraints upon the Federal budget that restrict our ability to pursue every inspiration. So we believe that the increase requested by the President—built on the very strong appropriations we've received due to the generosity of the Congress and the Administration the last two years—will allow us to maintain our momentum and achieve the largest number of grants in the history of NIH, nearly 27,000 grants total.

We can do this because the rates of inflation in biomedical research have been lower in the last couple of years, because we are concentrating the increased dollars on our research project grant pool, and because we plan to limit increases in awards to 2 percent per year.

In summary, the Institute and center directors and I are proud of what has been done with the generous appropriations we've received in the past. We are optimistic about our future prospects to use science for the advances in human health and relief of human suffering. They and I look forward to answering any questions you may have over the next ten days.

[The prepared statement follows:]

Department of Health and Human Services
National Institutes of Health
Statement of the Director

I am pleased to present the President's budget request for the National Institutes of Health for Fiscal Year 1998, a sum of $13.078 billion, an increase of $337 million (or 2.6%) above the FY1997 appropriation.

The pace of medical research: Retrospective

This is the fourth year that I have been privileged to represent the NIH at this Committee's proceedings. As on previous occasions, the Institute Directors and I will soon provide you with a summary of remarkable scientific accomplishments from the past year and a description of some exciting paths our research is likely to take in the coming year. This annual process of recounting our performance and predicting future productivity is important, stimulating, and necessary. But it should not obscure some essential features of our activities: that our ultimate task, the conquest of disease, is formidable; that the course of progress is best measured over many years or decades, rather than over a single year; that scientific advances require a long-term investment in training and facilities, as well as research projects; and that the benefits of research are unpredictable, demanding work on a broad range of topics to achieve success with even a single problem.

Some of these features are dramatically illustrated by recent events in our battle against the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS). In the past year, the world has learned that many people with AIDS can experience dramatic improvement after treatment with a new class of anti-HIV drugs, called protease inhibitors, especially when combined with another class of drugs, called reverse transcriptase inhibitors. Although far from perfect, such potent anti-viral agents are unprecedented in the history of virology, and the achievements have been appropriately heralded in many news stories, including New Year cover stories in the lay press (Time magazine) and the science press (Science magazine).

But the history of these accomplishments encompasses much more than a single year; it reaches back over many years and in many directions. It extends to the early isolation of retroviruses from birds and rodents, as long ago as 1910. To the identification in the 1970's of retroviral enzymes---reverse transcriptase and protease---that now serve as targets for the anti-viral drugs. To the determination of the three-dimensional structure of these enzymes a few years ago. To the development of inhibitors of cellular proteases over twenty years ago for the treatment of hypertension. To the lengthy training of investigators competent to pursue basic science, drug discovery and development, and clinical testing. And to the strength of our nation's laboratories, developed over decades, in governmental, academic, and industrial sectors.

The pace of medical research: Prospective

The breadth and depth of the investments required for the success of protease inhibitors underscore the importance of the strong bipartisan support that the NIH has

received for the past fifty years. It is our responsibility to bring here each year new signs that such continued confidence is warranted and likely to produce future dividends. Thus, while we can take pride in end products, such as protease inhibitors, it is even more important to showcase recent discoveries, especially those findings from which many lines of investigation are likely to grow and measures to combat disease are likely to develop.

To illustrate this point, I would like to refer again to the field of HIV research, this time to describe a recent, long-awaited finding that holds special promise. Soon after the discovery of HIV in the early 1980's, investigators found that CD4, a well-known protein on the surface of certain T lymphocytes, was required for HIV to attach to and infect target cells. But it was also learned that at least one other protein was required, and those proteins---the so-called co-receptors---remained elusive for many years.

About one year ago, a research group in the NIH intramural program used an ingenious detection method to unveil co-receptors as members of a class of cell-surface proteins we already knew a great deal about---proteins that normally allow cells to detect secreted signaling molecules called chemokines. This discovery was especially exciting because another group of NIH intramural scientists had shown that certain chemokines could interfere with infection by HIV. Now we recognize that the interference is due to blockade of a co-receptor. Recently, some individuals were found to carry mutations that prevent production of a co-receptor. Because these people are actually resistant to infection by HIV, yet otherwise normal, co-receptors have emerged as prime targets for therapeutic and preventive strategies against HIV, stimulating a frenzy of experimental activity towards those goals.

Recent culminations and inspirations

For dramatic purposes, I have chosen to present in detail two paradigms of success---one representing culmination, another inspiration---from the domains of AIDS research. But other examples abound.

The culminations are visible as practical health benefits, often accompanied by economic benefits:

- The first successful treatment for stroke, using recombinant tissue plasminogen activator (tPA).
- Increasing use of cell growth factors to protect patients against the bone marrow toxicities of cancer and AIDS therapies.
- Declining mortality rates for many cancers, including some common ones.
- Reduction in disability rates among the elderly.
- The virtual elimination of Hemophilus influenza as a cause of childhood meningitis, due to widespread use of a new vaccine.

Recent inspirational discoveries are also legion, especially in the fields of genetics, molecular biology, and neurosciences:

- The genomes of baker's yeast and several bacteria (including the experimental warhorse, Escherichia coli) have been fully sequenced; a detailed map of the human

genome as been assembled and posted on the Internet; and innovative technologies are being harnessed to understand this genetic cornucopia.

- The locations of still unknown genes implicated in Parkinson's disease, prostate cancer, and other diseases, have been narrowed to small chromosomal regions, implying imminent isolation; and genes involved in many other disorders (such as retinitis pigmentosa, polycystic kidney disease, many birth defects, basal cell carcinoma, hemochromatosis, and some forms of diabetes) have been isolated and characterized.
- The precise changes that occur in genes during our lifetimes are telling us how environmental agents, like tobacco and sunlight, cause cancer by inducing mutations, and how normal mechanisms for correction of DNA can fail, allowing harmful mistakes to persist in our genetic material.
- Experimental manipulation of genes in mice has produced new animal models for studying many diseases (including Alzheimer's Disease, cardiac and vascular diseases, developmental defects, drug abuse, cancers, and others).
- New imaging methods are informing our understanding of the central nervous system during early development, behavioral change, learning, pain, and emotion, and in a variety of disease states, including drug addiction.
- Recently-identified molecules that govern the behavior of nerve and muscle cells are providing new prospects for repairing injury and degeneration in the brain and spinal cord.

Such advances inspire further work and support our request for appropriated funds for FY1998. To help you see what these funds are likely to accomplish in the immediate future, the Institute Directors and I have identified many of the most exciting topics of on-going and anticipated research and grouped them within six broad Areas of Research Emphasis: the biology of brain disorders, new approaches to pathogenesis, preventive strategies against disease, therapeutics and drug development, genetics of medicine, and advanced instrumentation and computers. These categories of research reach beyond Institute boundaries to highlight the disciplines that we judge to show special promise for further discovery and practical application. You will be hearing from individual Institute Directors during the next two weeks about many specific examples that illustrate why we believe these topics warrant such high priority.

Clinical research and the new Clinical Research Center

In my appearance before this Committee last year, I emphasized my concerns about several aspects of clinical research, especially the need to reinvigorate, reorganize, and rebuild the Clinical Center at the NIH. Since then, we have received $90 million in FY1997 appropriated funds that allow us to proceed with the detailed planning and initial construction of what will be the Mark O. Hatfield Clinical Research Center. We have established a Board of Governors to oversee management of the Clinical Center, in accord with the recommendations of last year's report by Dr. Helen Smits and her colleagues to the Secretary of HHS, and we have initiated plans to collect third party payment for care at the Clinical Center. We have continued to recruit outstanding clinical scientists, improve instruction in clinical research, toughen the review of protocols for clinical experiments, expand outreach to extramural clinical investigators, and forge stronger ties with nearby academic health centers. In the past few months, we have also developed a program to bring medical students to the NIH campus for one or

two years to participate in patient-oriented research, in accord with a recommendation by the NIH Director's Panel for Clinical Research. (This important training program, to begin this Fall, is our first collaborative effort with the newly-constituted Board of the National Foundation for Biomedical Research, which received its first appropriated funds, $200 thousand, in FY1997.)

The prospect of a new Clinical Research Center has re-energized clinical investigators at the NIH. Two weeks ago, we held a full-day celebration of our clinical research activities, with many presentations of past, present, and future projects on metabolic, infectious, and genetic diseases; diagnostic methods developed with molecular and novel imaging tools; therapies involving immune manipulation and gene transfer; and various approaches to disorders of the nervous system. For this occasion, Institute Directors prepared statements of their goals for patient-oriented research for the next several years; post-doctoral fellows showed posters outlining recent work; and architects and administrators described plans for the form and function of the new facility. In addition, the intramural clinical research community has proposed measures to strengthen our ability to recruit clinical investigators and to ensure a nurturing environment for them at the NIH.

Other aspects of administrative oversight

Clinical research is only one of many areas that have benefitted from increased administrative oversight during the past few years. The Institutes have recently pledged to develop more interactive information systems, and the NIH is in the process of hiring a Chief Information Officer. Directives from both this Committee and the Administration to limit administrative costs have stimulated the adoption of streamlined methods for peer review, accounting, and other activities; more widespread use of electronic communication; sharing of resources through service centers; and reduced use of FTE positions. In response to your request, Mr. Chairman, we are currently undertaking an extensive study of all of our administrative functions, looking for opportunities to achieve even greater efficiency, without impairing support of the research enterprise and our traditional stewardship of Federal funds.

We have also been vigilant about oversight of our research activities. In the spirit of the 1994 report on intramural research by the Marks-Cassell Committee and the 1995 Bishop-Calabresi report on the NCI, we have continued to review individual intramural research programs; a report on the NIMH program was recently completed, and four others are in progress. Complex activities--- gene therapy, the AIDS program, and clinical research---have been subjected to detailed review, and many trans-Institute areas of investigation---nutrition, pain, sleep, and several specific diseases---are being monitored by special coordinating committees. In addition, we have initiated a process for evaluating the performance of Institute and Center Directors every five years; panels are currently reviewing the activities of the seven Directors with the longest terms of service.

Plans for the proposed budget for FY1998

The President's FY1998 budget for the NIH provides an increase of $337 million over the current NIH appropriation. In line with our traditional priorities, we plan to allocate about 80% of the additional funds ($271 million) to research project grants (RPGs), increasing support for these awards by nearly 4% over FY1997. We expect to increase the average size of both continuing and new awards by 2%, allowing us to support about 7,100 new and competing grants and to achieve an all-time high total of nearly 27,000 research grant awards. (Note that the Department of Commerce has determined the Biomedical Research Development and Price Index [BRDPI] to have been 2.6% in 1996, the lowest rate in many years, consistent with the recent decline in the consumer price index; we project BRDPI values of about 3% for 1997 and 1998.) The budget also includes a $30 million increase for the National Institute for Drug Abuse as part of the Administration's efforts to address the problem of drug use.

We request $90 million to support continued construction of the Mark O. Hatfield Clinical Research Center in FY1998, along with advanced appropriations of $90 million for FY1999 and $40 million for FY2000, for a total of $310 million, which is required to complete the project by 2002.

I will be pleased to answer any questions you and your colleagues might have.

BUDGET ESTIMATES

Mr. PORTER. Dr. Varmus, thank you for your opening statement.

Let me spend just a minute looking into the budget figures. Because NIH two years ago was increased by 5.7 percent, last year by 6.9 percent. At the Democratic convention, the President had Christopher Reeve talk to the American people about the importance of biomedical research and has mentioned it very prominently, both in his acceptance speech and in his State of the Union speech this year.

And yet, the budgetary increase that the President suggests is 2.6 percent. I believe that is below the rate of biomedical inflation. I would first like to ask you, because there are really three filters here, one is your own in preparing your budget with your Institute directors, the second is the Department's and Secretary Shalala's, and the third of OMB and the White House. I would like to ask you first what request you made of Secretary Shalala in the beginning of this process. What was the budget that you developed within NIH?

Dr. VARMUS. Mr. Porter, we had a professional judgment budget that was in the range of $13.88 billion. And what we were allowed by the Department was $12.865 billion. The OMB returned to——

Mr. PORTER. A billion dollars less than what you asked for or would suggest in your professional judgment budget?

Dr. VARMUS. We didn't submit a direct request at that stage. The numbers returned to us by OMB were $12.667 billion.

Mr. PORTER. So OMB initially suggested a cut from last year's appropriation?

Dr. VARMUS. That's correct.

Mr. PORTER. A cut in nominal terms as well as real terms?

Dr. VARMUS. Correct.

Mr. PORTER. And what happened then?

Dr. VARMUS. There was a series of discussions involving OMB and the White House and the Department and NIH. And the final agreement was the budget request that you've heard, $13.078 billion.

[CLERK'S NOTE.—The following was submitted by Dr. Varmus to clarify his remarks:]

The NIH budget request to the Department for 1998 was for $12.865 billion, a 3.9 percent increase over the 1997 President's budget of $12.377 billion. Prior to final 1997 Congressional appropriations action, the Department submitted a 1998 budget request to OMB for NIH of $12.667 billion, representing a 2.3 percent increase over the 1997 President's budget. The Congress then appropriated $12.741 billion for NIH for 1997, which established a new base for discussions of the 1998 proposals. Finally, the 1998 President's budget request for NIH of $13.078 billion was developed, a 2.6 percent increase over the 1997 appropriations level.

PROFESSIONAL JUDGMENT BUDGET

Mr. PORTER. I realize that you and NIH have to be good soldiers and all this, but our job is to determine priorities for the country and where the money can best be spent. And if your professional judgment budget is $13.88 billion, that means you believe that you can wisely spend that amount of money in the next fiscal year. And I would like for you to give us some idea of what has to be foregone between the $13.88 billion that you've suggested in your profes-

sional judgment budget, and the $13.1 that is suggested by OMB and the President.

Dr. VARMUS. Let me first point out, Mr. Porter, that we make that professional judgment in an intellectual framework in which we don't worry about the other demands on the budget process.

Mr. PORTER. Yes.

Dr. VARMUS. We recognize that's a number that represents a starting point in a dialogue that will lead to some kind of compromise with the realities of balancing the budget and meeting other important demands upon the economy and upon the budget.

Mr. PORTER. Absolutely.

Dr. VARMUS. It's very difficult to say that there is one thing we cannot do. Because obviously we're going to continue to work on all fronts with the budget that's below our professional judgment. But what will happen is that some projects will not get funded. And many things that could go quickly will go less quickly.

In some areas, it's possible to say that certain fairly predictable milestones will be met less quickly. For example, in a process like the sequencing of the human genome, where we can say that given a certain amount of money and equipment and personnel, we can do the sequencing so much more quickly, we can actually make some very clear predictions about how many fewer nucleotide sequences will be determined.

In other areas of less predictable, discovery type science, we simply have to say that we will fund fewer grants.

ESTABLISHING PRIORITIES

During the process of putting together the 1998 budget, I met individually with every institute director and asked them to tell me about areas of priority that they would like to receive allocations for in the context of the NIH areas of emphasis. These are, as you recall, broad areas of research promise that we put together in a way that emphasizes the interactions among the institutes, the broad themes of biological research that we think are useful in the advancement of health.

And I received, during the course of the several weeks in which we deliberated, long lists of research projects, research areas that institute directors felt were particularly promising, and warranted my assigning to them amounts of money that might range from an additional $1 million to an additional $10 million. I put together a series of budget possibilities based on various levels of increment in our budget that might be anticipated. And as I reviewed that list, I can see that the institute directors and I worked out a list of priorities that now reflects the conviction we have that progress could be made with varying limits on our budget.

So I could give you some sense in detail, if you like, but I think it's better to say that some of these initiatives that we would like to undertake will not be undertaken, or will be undertaken with fewer dollars, instead of putting $2 million into a project to work on asthma in the Heart Institute, maybe we'll put in $1 million.

SUCCESS RATES

Mr. PORTER. Let me raise this in a different way. Isn't it true that in most institutes, if not all, the percentage of competing

grants, that is science that has been peer reviewed and thought to be very promising, that we can fund, even with the increases we've had recently, is going down rather than up?

Dr. VARMUS. The success rate actually varies among the institutes. But of course, in the last two years, because we've had good appropriations from the Congress, our success rate is currently, we estimate, about 28 percent for 1997. And we expect it will be fairly similar in 1998.

Mr. PORTER. So we're funding three out of every ten?

Dr. VARMUS. A little less than that. It's important to point out, Mr. Porter, that that number is an aggregate number and it is slightly misleading in the sense that there are, first of all, lower rates for new grants as opposed to renewal grants, lower rates for new investigators. We find it's very important to bring new investigators who are just out of training into the process early, otherwise they become discouraged and leave science. It may be lower in some of the most competitive areas, in areas where the demand upon NIH monies is particularly tight.

So it's an aggregate number, it's somewhat misleading about the——

Mr. PORTER. Well, we're very concerned that we maintain the momentum that NIH has had and that we don't lose a young, promising scientist because they can't get their promising projects funded and become discouraged. And our job, as you know, is to choose priorities. We may end up seeing it a little differently than the President.

I sincerely hope that we do, because I believe that this is among the best money that we ever spend, that it pays for itself many times over, that there is so much promising science there that to delay and put NIH on hold is unwise policy. And I believe that this Congress can do that, to put NIH at a high priority within the context of bringing the budget into balance. That, after all, is our job.

CLONING

Let me now raise another question that has come up in the news over the weekend, that I think shocked many in the scientific community, because they said it couldn't be done. But we've read of experiments in Great Britain by Dr. Wilmot where they have used adult DNA to clone a sheep. And I would like to ask you if you will tell us whether this is valid science, whether it would lead to cloning of adult human beings, what the implications are, both positive and negative, for science itself, and what the ethical implications are for all of society.

Dr. VARMUS. How much time do I have, Mr. Porter? [Laughter.]

Mr. PORTER. As much as you'd like.

Dr. VARMUS. Let me begin by telling you something about these experiments and perhaps describing them slightly more precisely and give you some idea of the intellectual context in which they arise. These experiments have strong antecedents in research that dates back quite a long time, to work by Gurdon and his colleagues in England who showed some years ago that it was possible to take the nucleus of a frog skin cell that had been grown in culture and to transfer that into the egg of a frog that had been relieved of its own nucleus.

By appropriate stimulation, it was possible to allow that egg, now supplied with the nucleus from the skin cell, to grow to the tadpole stage. Never to the full adult, but nevertheless, this was the first indication that one could do something that has a deep scientific meaning that I will come back to, and that is, you can take a cell which has undergone the process of differentiation—the process by which certain genes are turned off and others are turned on—to make a cell with a defined function and demonstrate that the nucleus of that cell—the nucleus being the compartment of the cell surrounded by a membrane, containing all the genes of the organism—could undergo some kind of still not fully understood process that would allow the cell to be able to generate all the components of a tadpole.

AN EARLIER CLONING EXPERIMENT

The report you refer to is not the first report that's been published from the Roslyn Institute in Edinburgh. About a year ago, the same group of investigators, headed by Ian Wilmot, published a paper in *Nature* in which they had done the following kind of experiment with sheep. That experiment had followed the clue from frogs, starting with an oocyte that had been relieved of its own nucleus and adding to that enucleated egg the genetic material from a very, very young sheep embryo, this actually was an embryo at the 8 to 16 cell stage. And the DNA, or the genes of the organism, were introduced by fusing an entire cell, including the nucleus after growth of the embryo cells in culture into the enucleated egg.

At this very early stage in embryogenesis, the cells are still believed to have all the potential for making all of the tissues of the organism. So it wasn't as electrifying as the current experiment when it turned out that by fusing cultured cells to the enucleated egg and returning the reconstituted egg with its nucleus from a cultured cell to a potential surrogate mother, that sheep were born. As I said, this work was published about a year ago.

The investigators in Edinburgh then took the next step of using other sources of genetic material—namely whole cells at other stages of development—and fusing them to the enucleated egg. Those additional sources of cells included older embryos, embryos that had been allowed to proceed to a much more complicated multi-cell stage; cells from a fetus representing a partly-developed sheep; and most dramatically, a cell that had been taken from the udder, from the mammary gland, of a six year old female sheep.

In each case, the cells were manipulated in an interesting way. After they had been grown in culture, the cells were returned to a resting state by slowly reducing the nutrients supplied to the cells. Normally when cells are grown in a petri dish in culture, they are grown in serum obtained from animal sources. By reducing the level of serum, it was possible to make the cells quiescent, so they weren't undergoing growth. That appears to be quite important in the success of these experiments.

In any event, with all three new sources of genetic material—that is, older embryos, fetal cells, or, in one case, mammary cells—a reconstituted egg, now carrying the nucleus from each of those three cell types, was returned to a prepared uterus and the investigators waited for a sheep to develop. In all three cases, they did.

Only one succeeded out of 277 reconstituted eggs, in the case of the cells derived from the adult female sheep. It was inefficient, nevertheless, it was successful.

Now, as you know, public attention has been focused initially on the most sensational aspects of this. And that's only natural. Because it is quite clear that this experiment opens the possibility of being able to do the same experiment with virtually any other mammal. And naturally, given the imaginations and novelistic inclinations of all of us, the idea of generating human clones of mature individuals has been much discussed.

SCIENTIFIC SIGNIFICANCE OF CLONING

In my view, this makes interesting movies, but poor science and poor ethics.

Let me speak a little bit to the scientific importance of the experiments that were described, and then come back to some of the ethical issues. The first level of significance of the experiments that are described is very much in the tradition of agricultural husbandry. Both in the area of agriculture and in animal husbandry, there is a strong tradition of trying to recapitulate strains that are particularly productive for food production.

So whether it's the selfing of corn, or the generation of in-bred strains of animals, or the twinning of cattle, there is tremendous interest in trying to enlarge a population that appears to be very productive. And in that sense, there are practical applications of what we've read about, with respect to agriculture.

MEDICAL USES OF CLONING

The second application has to do with the medical research uses of animals. There are a number of possible experimental routes that are opened by the experiments we've read about. In one case, the interest would be in the production of medically useful products. Proteins that are produced in animals, for example, in milk, could be made in large amounts in a more convenient way that is currently possible through recombinant DNA technology. Another product that might be possible is to make organs for transplantation that have been made more like human organs because they are programmed to make antigenic proteins on their surface that would lead to less problem with rejection in transplantation procedures.

Equally important is the possibility of using animal models other than the mouse or the rat for certain disease states. I'm sure you're aware that in recent years scientists have made increasing use of our ability to manipulate the genetic constitution of mice. We can add genes to the mouse, we can change the genes that exist, and we can make use of our increasing knowledge of disease genes of humans to attempt to generate models for disease that can be used for developing novel therapies that may be applicable to man.

In not all cases, however, have those disease models reproduced faithfully and instructively the kinds of pathology that are seen in human beings. One good example of that is in the case of cystic fibrosis, where we know the human gene and the mutations that exist in the gene have been identified. We can make the same mutations in the mouse, but the disease is different. Using an ani-

mal like the sheep might open the way to make better disease models that could be instruments for developing and testing more useful therapies for some of these disorders.

HOW GENES TURN ON AND OFF

The third area of importance is one that has been neglected for the most part in discussions today, but to my mind is the most important. And that is that these experiments open the door to a much deeper understanding of how genes are turned off and turned on. I remind you that we as human beings have roughly 80,000 genes, that all of those genes are useful in some of our many different kinds of cells. We have perhaps 200 different types of cells in our bodies. Each expresses a different subset of those 80,000 genes.

During the course of our development to produce an organism that has a liver and skin and brain and many other organs, our bodies are programmed to turn such genes on and off. And it's generally been considered difficult, if not impossible, to redirect a cell of one type to behave like a cell of another type.

In the sheep experiments we've been discussing, a cell derived from an adult mammary gland has been reprogrammed to become a fully potent cell to make every component of a sheep. That's a remarkable achievement. We know very little about what that process entails, save for the fact that it seems to be fostered by moving a growing cell into a quiescent state, as I mentioned before, by reducing the serum in the medium used for growth of the cell.

There are many applications that could be imagined for greater knowledge of how genes are turned off and on. Let me begin with the simplest. We already use such a strategy for the treatment of sickle cell disease. In sickle cell disease, one of the globin genes is impaired. We know that we can overcome that impairment by expressing another form of globin gene that's normally expressed only in the fetus. Hydroxyusea is a drug therapy that's currently in use and shown to be quite effective; it turns on the fetal globin gene in the adult and reduces the morbidity of sickle cell disease by about 50 percent.

We still have an imperfect notion of how to turn that gene back on. So anything further to help in our ability to control that process would be very useful.

USE IN BONE MARROW TRANSPLANTS

Let me give you some other examples. We know that when persons undergo chemotherapy for cancer that their bone marrows are frequently severely affected, and it's been increasingly common to treat such individuals with bone marrow transplants. Those transplants are difficult because of rejection of the donated marrow, because of protein incompatibility between the donor and the recipient. So one long-term goal has been to use, in such transplantation experiments, marrow that's compatible with the recipient. Sometimes that's done by using the marrow from the individual who's undergoing treatment. But that's obviously less than ideal, because those cells may include cancer cells.

The prospect of being able to take the nucleus from a skin cell and put it into some other, cell, to produce bone marrow cells in

culture, and return those to cancer patients is made real by the experiments with the sheep—far off, but nevertheless possible. One could imagine, and if you'd like an inversion of that experiment, where you consider somebody who's been incapacitated by massive burns and needs skin transplantations, one can imagine taking the nucleus from a liver cell, for example, putting it into another enucleated cell as a recipient, and making skin cells that could then be used for a non-rejectable transplant to the burned individual.

One could imagine similar kinds of experiments in neurodegenerative diseases. There are instruments for remodeling cells to behave as mature nerve cells with the antigenic properties, of the recipient. So there are some remarkable possibilities here that definitely require exploration and will be fired by the sheep experiments.

ETHICAL IMPLICATIONS

Let me say a few words about some of the ethical issues. We have been aware of the possibility of doing such experiments for some time. In 1994, I convened a panel headed by Dr. Steven Muller to look at the ethical issues that surround many forms of human embryo research, including this form. And in that year, that panel brought back to me recommendations about which kinds of experiments involving the human embryo would be suitable for Federal funding, unsuitable for Federal funding, or fall in between.

And with respect to carrying out experiments of the sort described for the sheep in the human being, that is, human cloning, the committee designated such experiments as not suitable for Federal support, for reasons that I think perhaps are worth reading very briefly. The panel said, "the notion of cloning an existing human being or of making carbon copies of an existing embryo, appears repugnant to members of the public. Many members of the panel share this view, and see no justification for Federal funding of research involving nuclei transplantation for this purpose."

I agree with that point of view. Frankly, as an experimental strategy, it doesn't offer anything. We have a much better experiment carried out in nature. We have identical twins who are sometimes reared together, sometimes reared apart. That to my mind, if one wants to look at the effects of environment on human development, using genetically identical subjects, that experiment has already been done. It occurs done very commonly in human populations.

Secondly, our sense of ourselves as human beings is very closely linked to our diversity. And the notion of carrying out cloning of the human population, to my mind, is not consistent with the traditional ideas of human individuality and diversity. This does not mean that cloning strategies should not be used in other animals for purposes of agriculture or for purposes of medical research. But in the case of human beings, the NIH panel rejected it, as it happens, these experiments would also be forbidden by the amendment that's attached to our appropriation bill, the so-called Dickey–Wicker amendment.

That's a long speech, Mr. Porter. I'd be happy to answer any more questions.

Mr. PORTER. Thank you, Dr. Varmus. I might say to my colleagues that I'm not going to charge myself with that question or answer, because all of us wanted to ask the question. And I also would say, Dr. Varmus, that's probably the longest answer ever not interrupted by a member of Congress.

[Laughter.]

Dr. VARMUS. I appreciate your indulgence.

Mr. PORTER. Mrs. Lowey.

LEGISLATING CLONING

Mrs. LOWEY. Thank you very much, Mr. Chairman.

And again, Dr. Varmus, it truly is an honor to have you here before us. We feel honored to be on this committee to somehow have some role in this great Nation's investment in biomedical research. So I want to thank you personally for your leadership.

Just briefly, and I guess this will be counted against my time, or maybe not, I just wanted to have a few comments about your response. Because thus far, the sheep cloning has raised a great deal of justifiable anxiety across the Nation. In my own State of New York, a bill has already been introduced in the State senate to ban scientists from cloning humans. And we are clearly at the dawn of a new era in the history of mankind. Fifty-two years ago, the world changed forever at Alamagordo, New Mexico, when we exploded the first atomic bomb. This past week, as we know, and I appreciate your asking this question, the world has changed again.

Cloning raises the most profound questions about man's humanity, about God, about religion, about life and death. These are sensitive issues, and they must be dealt with seriously and thoughtfully. And I want to say, I applaud the President's decision this week to appoint a high level panel to examine the issue. And I look forward to reading their report.

As you stated, we have to ensure that science does not outrace our values. But we must also recognize that once the genie is out of the bottle, it cannot easily be put back in. And history demonstrates that if the technology exists, it will be applied. So the question before us then is whether or not we will be able to harness this scientific advance, this miracle, in fact, to work for us and improve the human condition.

Will advances in cloning be able to cure diseases like breast cancer and Alzheimer's? You referred to the great possibilities of medical research. Can we utilize this technology to provide hope to tens of millions of people with genetic disorders across the Nation and around the world? Perhaps so. And I certainly hope so. And while I know that cloning technology is fraught with peril, it also contains real opportunity and promise.

The future of cloning can look like our worst nightmare, like all this Huxley's Brave New World or the Island of Dr. Moreau, a world where freakish experiments know no bounds. Or cloning technology can cure diseases and improve our lives. And it's really up to all of us to decide. And as members of the Congressional panel that funds biomedical research, we have a special responsibility to engage this issue in all its complexity. And I certainly look forward to the discussion.

There is clearly a need for regulation. But regulation, I hope, that is consistent both with our human values and our support of biomedical advances.

I was going to ask you to discuss it, but I think perhaps we've taken a good deal of time, and I hope that in a rational, reasonable way, we can engage in this discussion if you have additional comments.

Dr. VARMUS. I'd like to make one comment, Mrs. Lowey, because your point reminds me of something that I was hoping to say at some point, which is that I'm concerned about the rush to legislation in this arena. We have a new finding. It needs to be absorbed and discussed.

I, too, applaud the President's referral of this matter to his National Bioethics Advisory Commission, which as you know was established about a year ago to consider questions of just this kind. The Commission is very well suited, in the light of the personnel who have been appointed to that commission, to discuss these issues and to make some recommendations.

I am worried, as my comments reflected, about the possibility that in rejecting the one aspect of these experiments that all of us find repugnant—that is, the idea of cloning adult human beings—that we end up with legislation, be it state or Federal, that restricts the experimental possibilities that will be beneficial to all.

Mrs. LOWEY. I thank you.

I assume I can go on. I'm not sure if I was charged for that comment. But I have a little time left.

Mr. PORTER. Yes, you were charged. [Laughter.]

IOM RECOMMENDATION ON CLINICAL RESEARCH

Mrs. LOWEY. Then I'll ask one of my questions. Thank you.

Dr. Varmus, this subcommittee supports the construction, as you know, of a new clinical research center on the NIH campus which you are undertaking. And I'm pleased that the new center will surely strengthen the clinical research conducted on the NIH campus.

However, we continue to hear from clinical researchers at academic medical centers across the country that they face major obstacles in obtaining Federal funding and retaining talented researchers. Last year, this committee did urge NIH to respond to the recommendations of the 1994 Institute of Medicine report on clinical research as well as to accelerate the work of the NIH panel formed to deal with the problems faced by clinical researchers.

As you know, last Congress I introduced legislation with three colleagues on this subcommittee to implement the IOM recommendation. This legislation was included in the Senate NIH authorization bill. However, NIH has the authority to implement most of the recommendations without legislation. And I need your help in responding to the frustrations, frankly, of the extramural clinical research community.

Can you provide to this subcommittee, by perhaps the end of March, what specific extramural initiatives NIH will undertake in the next six months to reinvigorate clinical research in this country? We'd be most appreciative.

[The information follows:]

The National Cancer Institute (NCI) and the Department of Defense (DoD) signed an agreement to allow DoD medical beneficiaries to participate in various NCI sponsored clinical trials of new cancer treatments. Participants may receive treatment either through the medical treatment facilities that have been approved to conduct NCI trials or through medical care arrangements reimbursed through TRICARE/CHAMPUS, the DoD's health program. This partnership allows DoD beneficiaries throughout the country to receive state-of-the-art care through NCI sponsored clinical activities by participating in emerging new approaches that have significant promise for the successful treatment of cancers.

NCI will continue to provide a user-friendly, active information system through an expansion of the Physician Data Query. This allows physicians quick access to information about open available protocols at the nearest or most appropriate institution or to physician participating in the suitable protocols.

In the training area, the NCI has developed a new program, the Career Transition Award, to provide support to outstanding newly trained basic or clinical investigators to develop their independent research skills through a two phase program; an initial period involving an intramural appointment at the NIH and a final period of support at an extramural institution. The award is intended to facilitate the establishment of a record of independent research by the clinical investigator in order to sustain or promote a successful research career. It is anticipated that this new program will be announced in the NIH GUIDE in the next few months.

In addition, the NCI has recently implemented an Accelerated Executive Review (AER) that targets new competing research grant applications that are within 4 percentile points of the payline for basic research or 10 percentile points for "patient oriented research". This AER is designed to encourage clinical projects by allowing a broader range of eligible applications, 10 percentile beyond the payline for funding. In FY 96, the NCI Executive Committee reviewed 51 applications under the AER (31 basic research and 20 patient oriented research). The committee recommended 26 of these for awards, for a total cost of $6.7 million. Nine of these were for "patient oriented research".

The National Heart, Lung and Blood Institute, in collaboration with the Health Care Financing Administration, is sponsoring a randomized trial, Lung Volume Reduction Clinical Trial, to determine the benefits and risks of this operation to patients with end-stage emphysema. Currently, hundreds of patients are being subjected to this operation despite the fact that its effectiveness had never been established. Furthermore, there are no data on long-term outcome, and no evidence is available to indicate which patients might benefit from the operation. This trial will provide patients with the information they need to make informed, intelligent decisions about their health care.

Within the next six months, the National Institute of Allergy and Infectious Diseases (NIAID) will fund ten new clinical research initiatives in FY 1997 and announce an intent to fund 12 additional ones that will be funded in FY 98. These initiatives span the range of clinical research activities from small pilot studies to large clinical studies and phase II and III clinical trials. New career development activities for clinical investigators are included in the goals of the initiatives on emerging and re-emerging diseases. The clinical research needs and opportunities addressed by these 22 new clinical research initiatives include AIDS, vaccine development and testing, chronic fatigue syndrome, immunological effects of aging, women's health issues, sexually transmitted diseases in adolescents, transplantation, and emerging and re-emerging infectious diseases, including malaria. A list of the titles of these initiatives is attached. The NIAID is also conducting a review of its infectious diseases research training programs to ensure that these programs are producing investigators with the capacity to carry out independent research in clinical investigation.

Beyond its specific initiatives and activities, the NIAID is also applying newly developed, streamlined grants management procedures to expedite the evaluation and funding of clinical research grant applications. These streamlined procedures consist of selective payment of applications that are identified as having important clinical research goals; electronic peer review and early Council review to expedite the award of grants to clinical investigators.

In FY 97, The National Center for Research Resources (NCRR) will support the network of GCRC and other related activities with a total of $157 million. The NCRR funded one new GCRC in FY 96 and depending on available funds, may consider funding an additional new center in FY 97. The FY 96 award was made to Howard University which is particularly significant in that it related to research on diseases that affect African Americans and for Historically Black Colleges and Universities. In addition, NCRR funded a new satellite site at Children's Hospital, Seattle, WA.

The NIH loan repayment program is currently limited to scientists in the intramural program and is being implemented. The NIH may seek a legislative change to broaden the eligibility for the loan repayment program to include clinical researchers at academic health centers throughout the country, a situation under legislative restrictions now.

Mrs. LOWEY. I know that NIH is currently working with certain health plans such as the military's CHAMPUS plans, to arrange for their subscribers to participate in NIH research protocols. This is an important development. I know you share that opinion. Could you explain to us the prospects for similar arrangements with private insurers and more broadly speaking, can NIH help to encourage managed care companies to support academic research?

Dr. VARMUS. Mrs. Lowey, you've given me a large task. I'd be happy to provide more written details. We're going to be out of time if I don't do that.

Mrs. LOWEY. Right.

[The information follows:]

SUBSCRIBERS PARTICIPATION IN NIH PROTOCOLS

I and my staff recognize the importance of new partnerships to enhance clinical research in the coming century. These partnerships must include the NIH, academic health centers (AHCs), foundations, the pharmaceutical industry, managed care organizations (MCOs) and private insurers. I believe NIH can help to encourage MCOs to support academic research in the context of such partnerships. Heartened by NCI's successes in working with the Department of Defense/CHAMPUS and the Veteran's Administration to obtain coverage for the routine clinical care component of clinical trials, NIH's Institutes and Centers, including the Clinical Center, will work with MCOs to ensure the nation's clinical research endeavors.

In November 1996, some Institute Directors and I met with representatives of managed care organizations, including Aetna/US Healthcare, Group Health Cooperative of Puget Sound, Harvard Pilgrim Health Plan, HealthPartners, Kaiser Permanente, Prudential and the United Healthcare Corporation. Many of these organizations already maintain extensive research portfolios and receive NIH funding for some of their research projects. We agreed to work together to address our mutual interests in clinical research and identified significant research areas where NIH and others can cooperate.

This dialogue will be enhanced by a recently-developed NIH Fellowship in Managed Care. We have identified a senior MCO manager of research to serve as liaison to enhance communication among NIH, AHCs and MCOs. NIH's goals are to develop proposals to advance clinical research through greater involvement of health plans and their patients in peer-reviewed research studies; to determine what is known about participation of MCO beneficiaries in NIH-approved protocols; to assess health plan policies regarding enrollment in NIH studies; and to explore models of health plan collaboration with AHCs.

Other NIH initiatives include the convening of an NIH-wide Managed Care Workgroup made up of representatives from each Institute and Center to serve as a central source for discussing and coordinating approaches for collaborating with the managed care community. The Workgroup will share strategies advanced by individual Institutes and Centers, develop proposals for grass-roots experiments, design innovative approaches for linking AHCs with managed care partnerships, enhance NIH research information dissemination, and communicate widely about what has been learned in the process.

The effects of changes in the financing and delivery of health care on the research infrastructure, the nation's capacity to sustain medical progress and the quality of health care are issues of particular concern to NIH. I remain committed to our traditional venues of support for clinical research, but at the same time I am ready to explore new opportunities for collaborative research partnerships. As managed care organizations become responsible for the health care of greater numbers of Americans, their support of patient-oriented studies will be increasingly critical to the NIH as it seeks to develop new mechanisms to enhance and stimulate clinical research.

PROGRESS IN SUPPORT FOR CLINICAL RESEARCH

Dr. VARMUS. But as you know, first of all, we're working very closely with the clinical research panel that I established about a year and a half ago. Many of their recommendations are already being implemented. And I think you'll find that clinical researchers around the country are appreciative of the changes we've made. In some cases, we're limited by authorization, for example, we're attempting to develop a loan repayment program for clinical investigators, but we simply don't have the authorization to institute it. But we do have such a program on the NIH campus.

We have had very productive conversations with representatives of the managed care industry to explore our common interest in research, for example, in clinical trials and epidemiology, in health services research, we are dealing with some of the most enlightened members of what is obviously a very heterogeneous group of organizations, but they represent many millions of patients.

We are finding common ground, and I am hopeful we'll be able to work very productively with them. But I think in view of the time constraints, I'd rather give you a more detailed account of the very considerable progress I think we've made in the last year in the clinical research arena for your perusal.

Mrs. LOWEY. Given the time, I will close. And I just want to thank you again. We're aware of the progress, but I'm sure you're aware of the frustrations as well. So I look forward to that response and I thank you again.

Mr. PORTER. Thank you, Mrs. Lowey.

Mr. Wicker.

IMPACT OF 7.5 PERCENT INCREASE

Mr. WICKER. Thank you, Mr. Chairman.

Dr. Varmus, we're always glad to have you before our subcommittee. Let me ask you about money. I understand you've commented about the funding level briefly in your opening statement. But particularly, we have here that Senator Specter has suggested a 7.5 percent increase in your budget, as opposed to a rather modest 2.6 percent Administration request. I wonder if you could comment on the difference in programs that impact the health of Americans between those two levels of funding.

And also, in the out years, are you making plans at NIH for the very modest level of growth proposed by the Administration?

Dr. VARMUS. Mr. Wicker, as the numbers you've given me to work with in answering this question indicate, we would have over $500 million more under the proposal made by Senator Specter compared to the President's request. And obviously, with that money, we could support a large number of additional grants that otherwise might not be funded because of the constraints of the budget that's being proposed.

Mr. WICKER. What would be your priorities there?

Dr. VARMUS. Well, as I mentioned earlier, we've established, during a reiterative process during the past year, a long list of new efforts we'd like to undertake. And I have tried to look at those initiatives in the context of an inflationary increase, an increase of perhaps 5 percent, 7 percent, and 9 percent. And there are some

initiatives we wouldn't undertake and there are some we would undertake with less money if we were to receive a smaller budget.

So it's not as though we would not do genetics research with one budget but would with another. But in general, things would go more slowly. And fewer investigators would be working on the problem, or certain areas, certain narrowly defined initiatives might not be undertaken with the smaller budget appropriation.

So it's difficult to say that there is one thing that we will not be working on, because we will continue to work, albeit less rapidly than we might be able to with a larger budget, on a broad range of research activities.

As far as the out-years are concerned, I have developed a mind set over the last few years of concentrating on the year at hand. So right now, I'm concentrating on 1998. The President and OMB, in making the out-year projections for NIH, have proposed very modest increases. But those modest increases are indications that we are a Presidential priority, and we take that as a sign that when the budget is formulated for 1999, that there will be a solid budget for the NIH. We are planning around 1998 and not making specific plans based on the budget projections for 1999 and 2000.

CONSENSUS DEVELOPMENT PANELS

Mr. WICKER. Let me ask you, Dr. Varmus, what is a consensus development panel?

Dr. VARMUS. We have a tradition dating back over 20 years of bringing together, and we have done so over 100 times, groups of speakers who are informed about a certain medical topic, for example, a new treatment for a disease, to present their findings to a panel of informed but impartial individuals who then, after listening to the speakers, puts together a statement that hopefully represents consensus in the scientific community about the state of the art in a certain area.

Let me give you one particularly useful example. About two years ago, we had a conference on ulcers and an organism known as *Helicobactor pylori.* For many years, it was thought that stress and gastric acidity were the major causes of gastric and duodenal ulcer. It wasn't appreciated until more recently that there was a bacterial cause. And the consensus conference allowed a number of investigators to present the findings and to have a public airing of this new view about the cause and treatment of gastric and duodenal ulcer. The effect of the consensus was to diffuse through the medical community these new ideas, to establish their credibility, and make anti-bacterials more widely used.

Mr. WICKER. The witnesses are people outside.

Dr. VARMUS. They are outside, they are experts brought to the NIH to present their findings to a panel, which is also from the outside. But the panelists have no declared views on this topic. They have not published opinions about that area of research. They listen to the experts then come up with a statement.

Mr. WICKER. Let me just ask you, because we are short on time, I understand there was recently such a consensus development panel focused in part on needle exchange programs.

Dr. VARMUS. That's correct.

PANEL ON POTENTIAL RESEARCH ON MARIJUANA

Mr. WICKER. Perhaps another one on legalization of marijuana.

Dr. VARMUS. No, let me correct you on that. The marijuana discussion was not a consensus development conference.

Mr. WICKER. It was a different type of panel?

Dr. VARMUS. Yes. We can discuss that if you like. It had a very different intention in mind. If you like, I can expand on that.

Mr. WICKER. Please, yes.

Dr. VARMUS. As you know, due to the passage of referendums in Arizona and California, the use of marijuana for medical purposes has become an important public health issue. There is very limited evidence available on the issue of whether there's any appropriate use for marijuana in the treatment of a number of conditions, including the anorexia and wasting syndromes that occur in AIDS, nausea in cancer chemotherapy, glaucoma, multiple sclerosis and so forth. And we felt that it was incumbent on us to ask whether there was enough evidence to suggest that there should be more clinical trials in this area. And equally importantly, whether methodology existed for doing a credible clinical trial on a smoked product.

So we brought experts in clinical trial design, in the pharmacology of marijuana, and in the treatment of the various conditions for which marijuana has been recommended in the past, to come together and discuss these issues. The outcome of the meeting, for which a formal report has not yet been written, is that there is very limited evidence on the efficacy of smoked marijuana in these conditions. There are some indications that it may be useful in certain limited contexts and that it would be possible to design credible clinical trials. And the NIH has been open to applications for clinical trials in this area. We've funded very few because we've had very few applications that passed peer review. But we are prepared to do such studies if they are properly designed and pass peer review.

NEEDLE EXCHANGE

Mr. WICKER. Let me back up then to the needle exchange programs. As you are aware, section 505 of our appropriation bill specifically states that no such funds should be used for needle exchanges. In light of that, why is it appropriate for a consensus development panel to be focusing in on this issue, and to conclude, among other things, that significant policy and legal barriers must be removed in order for this powerful weapon to be effective?

Dr. VARMUS. Two points, Mr. Wicker. First of all, the consensus conference was not about needle exchange solely. It was about behavioral modalities that might be used to restrict the spread of HIV, which as you know is the cause of a lethal disease. Second, section 505 does not simply prevent the use of Federal money for needle exchange. It prevents such use unless the Secretary can certify that needle exchange programs would reduce the spread of infection without increasing the use of intravenous drugs.

We are continually asking whether those conditions can be met, because we are seeking, in the light of the threat posed by HIV, any means that can be used to reduce the spread of infection.

Now, we all acknowledge that, first of all, drug abuse is a major avenue for the spread of infection. We believe that at present, perhaps half of the new infections that occur in the U.S. each year, half of between 40,000 and 80,000 new infections that occur each year, can be directly attributable to drug use or to sexual encounters with drug users, or to being the offspring of somebody who uses drugs. Those are troubling numbers.

There have been many studies of the use of needle exchange programs in a variety of communities in this country and elsewhere. And there is increasing evidence in favor of the idea that needle exchange programs can reduce the spread of blood-borne infections with hepatitis viruses and with HIV. There is also evidence—less compelling because of the nature of the evidence, but nevertheless evidence—that the use of needle exchange programs does not increase the use of intravenous drugs. Therefore, it seemed to those who listened to the consensus conference that good could be achieved by needle exchange programs—namely, a reduction in transmission of these lethal infections—without apparent harm, that is, increase in drug use.

Mr. WICKER. A quick follow-up. Do you believe, based on the evidence that you now have, that the Secretary should make a finding that the use of needle exchanges is appropriate?

Dr. VARMUS. It is a difficult issue. Because the nature of the evidence for the absence of increased use of drugs is less compelling than the direct evidence of measuring virus in the blood for demonstration of efficacy. Nevertheless, my own personal view is that the evidence is supportive of that conclusion.

Mr. PORTER. Thank you, Mr. Wicker.

Our ranking member, who was required to be at his hearing on Armed Services, is here and I would like to call Mr. Obey for any opening statement that he might wish to make, and then he can proceed with his questions.

MAMMOGRAPHY POLICY

Mr. OBEY. Mr. Chairman, thank you. I don't have any opening statement. It's just that I've recently had hernia surgery, so I ask you to please don't say anything that makes me laugh or sneeze.

I just want to raise one question. I note that while I was at home, the Senate gave its advice and directed its wisdom on the subject of mammograms to NIH. And I guess I would simply say that I would like to question what appears to be conventional wisdom in the Senate that either House or Senate ought to start telling NIH exactly what it ought to be recommending in these areas.

That is not a totally accurate characterization of what the Senate did. But I can recall in the 1970s, when we used to have a lot of pressure to see to it that women were told to have mammograms at earlier ages than had been the case in the past. And very frankly, at that time, it seemed to me, and certainly to a lot of people who knew a lot more about it than I did, that given the state of imaging technology it was an open question as to whether or not mammographies at an early age caused more harm than good.

We've now had an improvement in the technology. But it seems to me that there are still legitimate questions about exactly how much emphasis should be given to advising women in their 40s

that they ought to have mammographies. And so I guess I would just say that I would urge you, despite the Senate's resolution, to call them as you see them. Because it would seem to me that in the end, we would do the most good by seeing to it that we have a lot of emphasis on having women above 50 certainly obtain mammographies, because there is no question that you can save a lot of lives if they do. It seems to me that the greatest emphasis ought to be there. And that science, rather than conventional wisdom in the political field, ought to drive what happens with respect to other age groups. I don't know if you have a comment or not.

Dr. VARMUS. Well, I appreciate your comment, Mr. Obey. Yesterday, I attended the National Cancer Advisory Board meeting at which this topic was discussed. And I'm sure it will be further aired this afternoon, when Richard Klausner from the NCI testifies. In the course of the deliberations of the NCAB, the points that you were just making right now were emphasized in a very useful way, trying to place into context the much greater importance of getting women in the age range of 50 to 70 in for mammography. Currently less than half take advantage of what is clearly an effective means of detecting early cancer in that age group. And also, it is important to get those who are positive into treatment.

Also emphasized during the course of the discussion was the importance of educating caretakers and patients who are in their 40s of the benefits and risks of mammography in the 40s, and to teach people that there's nothing magical about turning 40 or turning 50, that throughout the 40s, the benefits increase as one ages. And given one's attitude toward screening, given one's apprehension about a false positive diagnosis, which is fairly common in the 40s, given one's genetic family history and given the changing nature of the technology, people may make different decisions at different times in their 40s to begin mammographic screening.

I believe this is a much more sensible approach than mandating one or the other. I think much of this is driven by concerns about reimbursement and perhaps that might be where some of the emphasis is placed in the discussion of this issue.

CLONING OF HUMANS

Mr. OBEY. Thank you. With respect to the marijuana question, again, I would hope that NIH would proceed to try to, as much as possible, provide the scientific answers. It seems to me that what is most important is not the opinion of Arizona or California activists, or for that matter, the President's drug czar. What's important is what the facts are. And it seems to me that we would in the end benefit from having NIH proceed to provide as much information as they can by way of whatever trials they can put together.

I understand that you made some comments about the recent events in Scotland with respect to animal cloning. I guess I just have one question on that score. I am concerned about the long-term implications of that in terms of research on human beings. But I have a dark Irish soul which has taught me a long time ago that if anything bad can happen, it eventually will. Where are we in terms of the possibilities with respect to human cloning? What is the state of the science on that? And how in fact can we discourage going down that road, given the fact that as long as possibili-

ties are there, I'm convinced that people are going to try to go down that road.

Dr. VARMUS. Well, to answer your question of where we are with respect to human cloning experiments, at the moment, the evidence that such experiments can be done depends entirely on what you've read about the sheep. There are similar efforts being made with other organisms, mice, for example, and experiments are being done with embryo cells from a variety of organisms.

But nothing is being done with humans for a number of reasons. First, there is a prohibition, as you know, on human embryo research. As I mentioned earlier, the panel I commissioned in 1994 to look at the prospects for Federal funding of experiments that involve the human embryo had expressly indicated that experiments that would involve nuclear transplant for human cloning would not be recommended for Federal funding for a variety of reasons that I elaborated on earlier.

Mr. OBEY. I understand that. I know there's a prohibition on Federal funding. But not everything that happens in the world happens with Federal funds.

Dr. VARMUS. If you're asking whether I know that such experiments are being done in the private sector, I essentially can't comment.

Mr. OBEY. No, I mean, how likely do you think it is that over the next 30 or 40 years the scientific community is going to be totally dissuaded from trying to go down that road as far as the knowledge?

Dr. VARMUS. Well, the scientific community, I think, will not find that experiment something worth doing. It doesn't have any particular scientific objectives, and it is repugnant to the scientific community in general for a variety of reasons having to do with our belief in human diversity and individuality.

That is not to say there isn't a renegade who would want to do such experiments. As the papers have repeatedly pointed out, the experimental design for the work that was done on the sheep is surprisingly simple, and doesn't require a cyclotron. It requires fairly limited scientific instrumentation. And it would be very difficult for anyone to say that there is not anybody who is trying to do such an experiment.

So it's hard for me to answer you in a very direct fashion, except to say that such work done in animals has a variety of uses. The extrapolations of such work to an understanding of how genes are turned off and on, and how we can make different kinds of cell types—not whole human beings, but different kinds of human tissues—for transplantation and treatment of disease. I think it offers tremendous prospects, which is why I'm very concerned about a rush to put into place some restriction on this whole area of research, which I think could severely limit our ability to capitalize on the most interesting, important, and medically useful aspects of the work.

Mr. OBEY. Thank you.

Mr. PORTER. Thank you, Mr. Obey.

Ms. Pelosi.

Ms. PELOSI. Thank you, Mr. Chairman. Thank you for your leadership on this NIH issue.

And welcome, Dr. Varmus. I was very thrilled, really, to hear your explanation of what we are calling an "experiment," in Scotland. Mr. Obey, when I had to run out of the room to testify in Transportation, I used up my time re-explaining it to them. [Laughter.]

I didn't have as much time as you had, Dr. Varmus. I didn't do it justice. [Laughter.]

I don't know whether I succeeded in my mission of getting more money for rapid transit for San Francisco. [Laughter.]

But I think that the members of the committee are scratching their heads, wondering what a sheep in Scotland has to do with the price of rapid transit in California.

But in any event, it was very interesting, and it takes me to the question that Mr. Obey was pursuing, are you satisfied that in our educational institutions the curriculum is inclusive enough of the ethics courses that we need, or the leadership in this arena to match the science as it marches ahead?

Dr. VARMUS. Are you referring to graduate training in science?

Ms. PELOSI. Yes, graduate training in science, and then also just, for example, I'm very pleased, too, that the President has this National Bioethics Advisory Commission. I'm not completely familiar with it. If you want to say more about it.

Dr. VARMUS. Yes, I'd be happy to.

Ms. PELOSI. What kind of people are they? Mostly scientists? Are they philosophers?

Dr. VARMUS. Perhaps I should address that first. The National Bioethics Advisory Commission did exist, initially I think in 1978. It was in place for a couple of years, and then was simply not constituted for many years. The President reconvened it under the leadership of Dr. Harold Shapiro, who's an economist and the president of Princeton University, about a year and a half ago.

There are 18 members of the Commission. Some are scientists who work in the areas of genetics, embryology, and development. Others are ethicists. Some are lawyers. They represent a diversity of occupations. A very well balanced committee with very well-known people who have made significant contributions in the areas of the relevant science.

And their charge is not simply to look at issues that surround human development or embryo research. Their mission is much broader. Indeed, some of the things they have talked about focusing on include a number of issues relating to human genetics, including issues of privacy and genetic testing. They've also been interested in informed consent and the conduct of clinical trials. So there are many issues to which they might be assigned.

The President was very wise in referring this issue to them and giving them three months to begin deliberations and to make some proposals about things that might be done. As I said earlier, I am a little concerned that in the frenzy of the excitement about the novelistic possibilities here that something more limiting of the research possibilities generated by these new findings would be done

precipitously. Nothing is going to happen immediately in the scientific arena. It's worth exploring some of the deeper aspects of these experiments with respect to gene regulation before we throw the baby out with the bath water.

ETHICS TRAINING

With respect to ethics training, we have made it a part of NIH graduate training programs for the last several years that there be a component devoted to the conduct of science. That encompasses a large number of topics ranging from issues of how you work with your colleagues to scientific misconduct, to how you apply for grants, and what to consider as career possibilities after training in these fields.

But it would also include ethical issues of the sort that we're describing today. We don't prescribe a program narrowly, but we do require that all of our training programs have such a component.

Ms. PELOSI. And do you think that in the educational institutions, the institutions of higher learning in our country, that there is sufficient attention paid to the ethical challenges that we will be facing?

Dr. VARMUS. Well, Ms. Pelosi, I actually think that these issues grab such attention that they should be used as vehicles for interesting people in science. All too few folks are able to appreciate the deeper significance of the purported experiments, because they know too little about genes and nuclei and eggs and how fertilization normally occurs, and how a human being or any other animal develops from a single fertilized egg.

What I'd like to see is institutions at all levels, from the grade school level on up, take this news account and use it as a lasso to bring people into thinking about biology. We have tremendous opportunities generated by the genome project or by use of recombinant DNA products in generating food to attract the attention of young folks who frequently see science as tedious, because their textbooks are full of terms they have to memorize instead of being brought into the scientific arena through public issues such as the one we're discussing today, that could be the vehicles for driving people to a greater appreciation of science and how its principles underlie many public issues that we have to worry about.

HIV VACCINE

Ms. PELOSI. Thank you. I was pleased with what you had to say earlier about your work being to promote human health and reduce human suffering. If this research is in furtherance of that, the research that you said, that you don't want to cut off because of the possibility of developing the tissue for transplantation, etc.

You talked also about culminations and inspiration. And I was pleased that the new AIDS therapies were part of the culmination. I guess they're part of the inspiration as well.

I wanted to ask you about, I don't know if Dr. Fauci would call it a breakthrough——

Dr. VARMUS. He never calls anything a breakthrough. He's very conservative. [Laughter.]

Ms. PELOSI. But I wanted to ask you about the possibility of an HIV vaccine that the President referenced in his State of the Union

speech. Under your leadership, NIH has made a commitment to give a higher priority to developing a vaccine. As we all know, a vaccine is needed to end the global threat and domestic threat of HIV/AIDS. What is the status of that research?

Dr. VARMUS. Ms. Pelosi, as you know, about a year ago, a very broad review of all our AIDS research programs was carried out under the leadership of Arnold Levine from Princeton University, joined by 100 colleagues. One of the major recommendations of that review was that we devote greater attention to the possibility of developing a vaccine against HIV. HIV has been a difficult combatant in the development of vaccines for a variety of reasons I won't go into here. But it's been increasingly appreciated that we have not understood our failures, nor have we exploited all the potential for developing a vaccine.

We are excited about protease inhibitors as treatment devices, but we know they're terribly expensive. They don't work for everybody in this country. And they're really not accessible to the parts of the world where HIV infection has its most devastating and widespread effects, because of the cost of the drugs and because of the difficulty in administering them and monitoring the response to the drugs.

So we need something more decisive to control the epidemic that's occurring worldwide. A vaccine is that answer.

In response to the recommendations of the Levine Committee, we have increased the amount of money that's available in our AIDS program for vaccines. We have put together an AIDS advisory group headed by David Baltimore of MIT, one of the world's leading immunologists and virologists, who with the advice of a number of people who have already met, are putting together an important program to move our vaccine program forward on a variety of fronts.

Ms. PELOSI. I appreciate that. Thank you.

I have some other questions about brain research and child abuse, etc., but my time is up, and I'll submit those for the record if we don't have another round.

Mr. PORTER. Thank you, Ms. Pelosi.

Mr. Hoyer.

Mr. HOYER. I'll pass.

Mr. PORTER. Mr. Bonilla.

COMMITMENT TO DIABETES RESEARCH

Mr. BONILLA. Thank you, Chairman.

Good morning, Dr. Varmus. It's always good to see you, and I apologize for not being here for the beginning of your testimony. We were in the midst of a hearing questioning the Secretary of Defense this morning on the Defense Appropriations Subcommittee and it ran a little long. But again, welcome. I appreciate any time you call me or visit with me, because I hope you always remember that I've got that open door policy, that if you ever want to talk about anything, just pick up the phone, like you always have.

I'd like to start, Dr. Varmus, by talking about why you concur with others on this committee who believe strongly that science and not politics are the direct medical research funds in this country, and you've done a great job at the NIH since day one. Exam-

ple, last December, scientists at the University of Chicago were conducting research unrelated to diabetes, and made a new discovery of two genes linked to causing the disease. And prior to this surprise discovery, neither gene had been a suspect in diabetes. But this now opens the door for more research and understanding of the disease. It was a big breakthrough.

Obviously, in this case, a broad approach to research served diabetes well. But with significant momentum, it concerns me that NIH has assigned a low 2.23 percent increase at NIDDK, a percentage which does not keep pace with biomedical inflation which is expected to be at 3 percent for the next two years.

As you know, diabetes is extremely prevalent in Texas, and a major concern to me and other members of this committee. I especially have worked closely with Mr. Stokes on this issue. One in every 15 Texans has been diagnosed with this disease. In light of the fact that 27 percent of the entire Medicare budget is spent on caring for persons with diabetes, my concern is that if it's not given a high priority, we will lose the momentum needed to prevent and cure this disease.

So if you would, Dr. Varmus, explain the NIDDK's low priority at NIH, especially when it is truly on the brink of pivotal breakthroughs in this area.

Dr. VARMUS. Mr. Bonilla, I agree entirely with your assessment of the discovery of the two genes that are involved in maturity onset diabetes of the young. But I would take issue with you about our lack of commitment to diabetes research. I don't believe that the NIDDK is unfairly penalized. Secondly, it's not the only venue in which diabetes research is conducted. Thirdly, that institute of course conducts research on a wide variety of topics.

Let's look at the example you provided. Much of the work, that you described, of course, emerges from a study of gene regulation and from the genome project, as well as from initiatives in diabetes. What we're dealing with here is a problem in the coding of disease and the numbers which we look at, which tend to differ by fairly small percentage points, are the result of a frankly imperfect attempt to assign dollars to various categories. They are very inaccurate assignments.

What really counts here is the way in which we exploit discoveries of the sort that you mentioned. And I will guarantee you that those discoveries will be very vigorously pursued, because they represent very important avenues of new discovery. Having new genes that clearly are involved in the pathogenesis of diabetes offers that most miraculous of things, a scientific opportunity that people are going to leap to. People who didn't work on diabetes before are going to be jumping on these topics, and we will be pursuing them as vigorously as possible.

DIAGNOIS AND DETECTION OF DIABETES

Mr. BONILLA. I'm sensing a lot more attention being paid to the prevention and education among those who have not yet been affected by diabetes but are in a high risk category. Are you feeling that as well? When I'm visiting with researchers and even the Speaker talks about it all the time now. He thinks it would be a great way to combat the higher projected Medicare costs in the fu-

ture. Are you sensing that as well, that we really need to get on the horse here?

Dr. VARMUS. Yes. I think we have a responsibility in three areas. One, the area we just discussed, doing more research to advance our ability to diagnose and treat diabetes, secondly, better methods of detection. Very importantly, as was demonstrated by a long-term study of the treatment of diabetes by the NIDDK, we have a major responsibility to take those findings which show that careful control of metabolism in patients affected with diabetes has an important outcome on the complications of diabetes, reducing heart disease, renal disease, and neurological disease.

And the careful control has to be instituted. The Eye Institute, which has a major role in diabetes research, has shown conclusively that early detection of the retinopathy of diabetes is incredibly important, because we can treat the retinopathy and prevent blindness. And yet, all too many individuals with diabetes fail to see an ophthalmologist regularly.

So we have initiatives for discovery, initiatives to identify those who are at risk, and very importantly, initiatives to develop a sense in the physician community and among patients of the need for careful surveillance of their disorder. Because the complications in very large measure can be prevented.

Mr. BONILLA. So just to sum up this area of questioning, even though I mentioned this 2.23 percent, you're not concerned that we're neglecting diabetes research at this time?

Dr. VARMUS. I do not believe we're neglecting diabetes research.

IMAGING RESEARCH

Mr. BONILLA. I want to turn now to the subject of imaging, which we've discussed before. I'm interested in knowing how much of a priority imaging research is at the NIH. And as you know, some people would like to see an imaging institute created at the NIH. They suggest that current funding which is dispersed throughout NIH for imaging should be combined to create this institute.

Tell us specifically how you intend to address imaging research, Dr. Varmus.

Dr. VARMUS. Well, as I mentioned in my introductory remarks, imaging is playing an increasingly important role in the study of neurological disorders and in the study of many other disorders as well, for example, in cardiology and in the study of the vascular system. Imaging is fundamental to both research and to clinical practice. Virtually every institute has some involvement in imaging technology and the use of new imaging devices, be it advanced x-ray procedures or magnetic resonance imaging or PET scanning to further their understanding of the body and the diseases that afflict it.

I know there is an interest in an imaging institute. My personal attitude is, this will not occur on my watch. That's true for many reasons. Administrative expenses will be increased if we do that, it will remove from the place where imaging should be practiced, namely the institutes looking at various diseases, the incentive to advance instrumentation in the areas of special interest to that institute.

And right now, we coordinate our activities in imaging extremely well. We've had a recent review of our imaging activities in the intramural program. And we are developing new programs that are well coordinated among the institutes. We have the existing mechanisms for coordinating our efforts in imaging. We don't need another administrative structure.

Mr. BONILLA. Thank you, Dr. Varmus.

Mr. PORTER. Thank you, Mr. Bonilla.

Ms. DeLauro.

Ms. DELAURO. Thank you for being here, Dr. Varmus. I'm sorry I won't be in New Haven to listen to your lecture. I would be delighted to do it, but I know the city will treat you well while you're there.

I think the questions of this morning have shown that the experiment in Edinburgh really was truly the "baa" that was heard around the world. [Laughter.]

Ms. DELAURO. So I think we have covered the topic, so I'm not going to ask a question in this area, and, at the risk of my colleagues throwing something at me, I feel a little sheepish about doing one. [Laughter.]

OVARIAN CANCER

Ms. DELAURO. But I did want to ask a couple questions. First, in 1997, the NIH spent $41 million out of the $12.7 billion budget on ovarian cancer research. And over the past few years, increases in ovarian cancer research funding have been extremely incremental. We know through the studies that if it's properly diagnosed, treated early, that the survival rate for women is 92 percent. But to date, we have no simple diagnostic test to detect ovarian cancer.

My questions are, how much does the NIH plan to spend this year on ovarian cancer research? What types of initiatives does this include? And will the research be done primarily through the extramural or the intramural programs?

Dr. VARMUS. While my valued colleagues are digging up the exact number for 1998—it will be in the range of $40 million—let me say a few things about what's going on. First of all, there is activity in ovarian cancer research, both intramurally and extramurally. We have clinical activities and basic science activities within the intramural program and of course, many activities outside. I agree with you that we have yet to achieve the ideal diagnostic procedure in the case of ovarian cancer. And that actually is true for many internal cancers, unfortunately.

The number for 1998, I'm told, is going to be $41 million.

But there are at least a couple of things that are being explored in a large scale study attempting to evaluate both trans-vaginal ultrasound and an existing immunological marker, CA–125, that I'm sure you're familiar with, that attempts to evaluate their usefulness.

One major source of activity in ovarian cancer research in the last year that's given us a lot of optimism is the large number of clinical trials, approximately 60. Importantly, almost half of those are phase one trials that involve new drugs. We're also extremely encouraged by the efficacy of certain combination therapies, particularly those that use taxol and cis-platin, often in combination

with a third agent. And as you know, that has had a dramatic effect on our ability to control mortality from this disease.

ADVANCES IN OVARIAN CANCER RESEARCH

I'm also pleased to say that one of the initiatives that I'm sure Dr. Klausner will discuss this afternoon, involving our efforts to understand the genetic anatomy of cancers, includes ovarian cancer as one of the five target sites for initial investigation. As you know, one of the major discoveries of the last few years, the isolation of the BRCA–1 and BRCA–2 genes, which was initially an initiative mainly seen in the context of breast cancer, has had dividends in the area of ovarian cancer. Because individuals who are born with mutations in either of these two genes are at higher risk for ovarian cancer. It's also possible to predict from the nature of the mutation the likelihood the individual will have ovarian cancer.

So there have been advances. They're not as far along as I would like. When you were here three years ago, we discussed the role of telomerase in the treatment of ovarian cancer. That has not yielded the benefits that some anticipated at the time. But you can be assured that we recognize the great significance of ovarian cancer and are pursuing it as actively as possible.

Ms. DELAURO. I would call on you, and I will say the same thing to Dr. Klausner this afternoon, that 27,000 women will be diagnosed with ovarian cancer, 15,000 will die. When we can find this in the early stages, and when it's treated, it's 92 percent survival.

Dr. VARMUS. This year, two of those diagnosed individuals are friends of mine. So I'm with you on this one.

CHILD DEVELOPMENT AND THE BRAIN

Ms. DELAURO. Thank you. Can you please discuss the NIH's research in the area of child development and the work that's being done on the brain, how children learn? How has the NIH coordinated or are you coordinating with the Department of Education programs like Head Start and others that ensure that the results that you are uncovering in a brilliant way, this research, is applicable to public policy and the classroom?

Dr. VARMUS. Well, there is a great deal of activity in this arena. And I'm sure you'll be hearing a great deal more about it, both from Duane Alexander, when he speaks to you about the activities of the NICHD, and from Steve Hyman, when he talks about NIMH. And of course, a lot of this is yet further inspired by the President's interest in studying early brain development to ensure that all Americans can read by the third grade.

One important development has been our deeper understanding of the mental processes that go on during the efforts to learn how to read, the ability to recognize phonemes, the components of words that represent a special kind of thinking that we are beginning to understand, using imaging devices and tools of behavioral research. Investigators supported by NICHD have developed methods for diagnosing difficulties in appreciating phonemes, and have developed interventions that are useful in being able to correct the reading abilities of individuals, if they are detected early.

We are working closely with the Department of Education, trying to put some of these principles into effect. The evidence to date

shows that the interventions are effective, and we hope that through the White House initiatives in early development and the emphasis being placed on education in the current Administration that some of the principles that we're uncovering by these studies in fundamental neurobiology will have outcomes of the most practical kind, namely a public that consists only of those who can read.

IMPACT OF THIRD PARTY PAYMENTS

Ms. DELAURO. The point, and the wonder of this committee is, that the work that you do is under our purview, at the same time the work that's done with Head Start is, too. Now we're uncovering information that says, we have a successful model in Head Start, and we will continue to work to make it better. We now understand that if you can have an impact with children in the zero to three years, which also is part of the work of this committee, that we need to really work those together among departments in order for us to get the best of both worlds.

In your budget, Dr. Varmus, there's a request for $15 million in savings through third party payments for the cost of patient care at the NIH clinical center. Can you explain the proposal, and what it would mean for those who are receiving the care at the clinical center, and would these payments affect NIH's ability to attract patients for clinical trials?

Dr. VARMUS. Well, I thank you for the question. We obviously are concerned about the possibility that requesting third party payment might impede referral of patients to the clinical center or the ability of, or the willingness of, our patients to come there. So we've been working with potential third party payors to gauge what the impact would be. We recognize our fiscal responsibility to collect for medical care delivered in the course of research, in view of the stringencies in our budget. And yet we are also sensitive to the possibility that we would impede access to the kind of research that we do.

So, at the moment, we have no third party payment procedures in place. We have never collected, and we are obviously being urged by many to do so. We're moving toward that in a cautious manner. And we hope to have some payment processes that don't impede patient access.

Ms. DELAURO. That would defeat our purposes. So I really do ask you to proceed cautiously.

Dr. VARMUS. We are doing so.

Ms. DELAURO. Finally, I'd like to associate myself with the comments of my colleague Mrs. Lowey on clinical research. We're always in awe of the discoveries, and what happens with regard to patients in doctors' offices. So I look forward to seeing your response.

Thank you. And thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. DeLauro.

Mr. Istook.

COMPARISON OF MEDICARE COSTS AND DISEASE RESEARCH COSTS

Mr. ISTOOK. Thank you, Mr. Chairman.

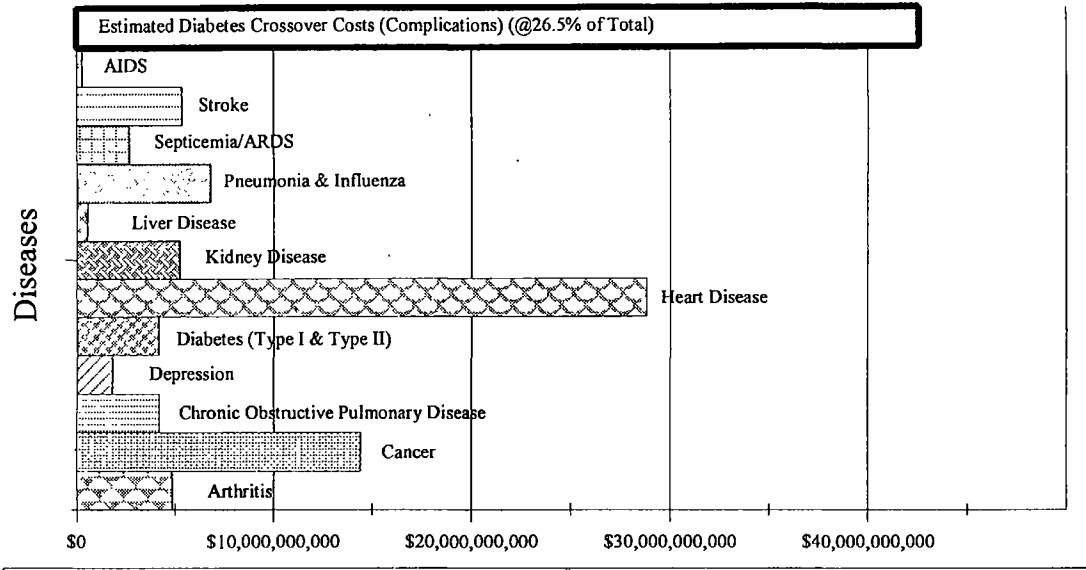
Dr. Varmus, good morning. We spoke yesterday and also some last year, of course, about allocation of research dollars within NIH. And you're well aware of my concerns of whether we are putting the resources where they can be most significantly used.

I don't know if you've had a chance to look at the graph.

[See figures 1 and 2.]

FIGURE I

Medicare Spending by Disease: 1995



Arthritis	$4,858,605,246
Cancer	$14,394,300,819
Chronic Obstructive Pulmonary Disease	$4,171,478,382
Depression	$1,802,490,398
Diabetes (Type I & Type II)	$4,158,388,268
Heart Disease	$28,811,590,496
Kidney Disease	$5,239,066,021
Liver Disease	$546,498,048
Pneumonia & Influenza	$6,836,991,894
Septicemia/ARDS	$2,667,495,504
Stroke	$5,342,235,096
AIDS	$271,339,601
Estimated Diabetes Crossover Costs (Complications) (@26.5% of Total)	$42,551,923,175

FIGURE 2

Medicare Expenditures by Disease (Fee for Service) for Calendar Year 1995 Disease	Medicare Payment	% of Total	Beneficiaries	Cost/ Beneficiary	% of Total Medicare Beneficiaries	NIH Support ($millions) FY97	% of NIH FY97 Total	% of NIH (43%) Disease Spending
Estimated Diabetes Crossover Costs (Complications) (@26.5% of Total)	$42,551,923,175	26.5%	(Source: CDC)					
Arthritis	$4,858,605,246	3.0%	6,166,660	$788	18.4%	$231.925	1.8%	4.2%
Cancer	$14,394,300,819	9.0%	7,028,300	$2,048	21.0%	$2,712.590	21.4%	49.7%
Chronic Obstructive Pulmonary Disease	$4,171,478,382	2.6%	2,935,620	$1,421	8.8%	$66.127	0.5%	1.2%
Depression	$1,802,490,398	1.1%	1,628,240	$1,107	4.9%			
Diabetes (Type I & Type II)(Complications cost $42.5 billion)	$4,158,388,268	2.6%	4,688,920	$887	14.0%	$316.292	2.5%	5.8%
Heart Disease	$28,811,590,496	17.9%	17,935,380	$1,606	53.5%	$902.862	7.1%	16.5%
Kidney Disease	$5,239,066,021	3.3%	1,561,360	$3,355	4.7%	$343.812	2.7%	6.3%
Liver Disease	$546,498,048	0.3%	502,420	$1,088	1.5%	$178.620	1.4%	3.3%
Pneumonia & Influenza	$6,836,991,894	4.3%	13,276,680	$515	39.6%	$64.661	0.5%	1.2%
Septicemia/ARDS	$2,667,495,504	1.7%	924,440	$2,886	2.8%	$11.412	0.1%	0.2%
Stroke	$5,342,235,096	3.3%	2,220,180	$2,406	6.6%	$127.489	1.0%	2.3%
AIDS	$271,339,601	0.2%	46,380	$5,850	0.1%	$1,501.073	11.8%	27.5%
Total Expenditures for Above Diseases	$79,100,479,774	49.3%	58,914,580				50.8%	118.2%
Total Other Expenditures	$81,472,815,226	50.7%						
Total Spent on All Fee-for-Service beneficiaries	$160,573,295,000	100.0%	33,539,429 (27,267,960 Unique Beneficiaries)					

Source: Health Care Financing Authority [Pat Clifford (410) 786 0156]
April 7, 1997
10:46 a.m.

Study involved taking a 5% sample of all claims and estimating total expenditures for each disease treatment

Dr. VARMUS. Just out of the corner of my eye.

Mr. ISTOOK. Of course. Let me tell you, the document provided to you and committee members, we've spoken before about the ratio of funding of different diseases compared to the frequency of their occurrence in a population and the national cost of it.

We obtained from HCFA the report of how much it is costing taxpayers through Medicare to treat patients with certain diseases. Now we were told they were not able to give us a breakdown on Medicaid. But this chart is to represent the ratio at which the taxpayers are paying for treatment of different diseases. And because it's Medicare it includes not only an aged population but also those that are disabled by their disease. Certainly there are a number of debilitating diseases, AIDS, we've talked about, is certainly one of them. So you will have people, regardless of their age, that are reflected in this chart if they're disabled.

The point that I'd like to focus on is the difference in the amounts that Medicare is paying and the proportion of Medicare payments compared to the proportion of disease-specific funding by NIH. For example, if you look at cancer, you see that 9 percent of the taxpayers' money that's going for Medicare treatment is going to care for cancer patients. But only 5 percent of the NIH research is going to cancer patients. That's of the disease-specific research.

[CLERK'S NOTE.—Later corrected to "49.7%".]

Mr. ISTOOK. If you also look through, you'll find, for example, chronic obstructive pulmonary disease, again, Medicare, 2.6 percent of its payments are to take care of patients with that difficulty. Whereas 1 percent of the disease-specific research is going to it.

[CLERK'S NOTE.—Later specified at "1.2%".]

Mr. ISTOOK. Diabetes, if you look there, type 1 and type 2 diabetes, 2.6 percent of Medicare outlays compared to 6 percent of disease-specific NIH. However, if you drop down to the bottom of the chart and you look at the complications of diabetes, the complications are more than one-fourth of the total Medicare payments for those treatments. And again, this compares to a research allocation of about 6 percent.

[CLERK'S NOTE.—Later specified at "5.8%".]

Mr. ISTOOK. Again, just finishing up on a couple of other examples, pneumonia and influenza is 4.3 percent of the cost to taxpayers through Medicare, whereas it's 1 percent of the disease-specific NIH research. AIDS is two-tenths of 1 percent of the outlay for Medicare. But it's 27 percent of the NIH research dollars. So that AIDS has 100 percent greater proportion of research dollars than what it's costing taxpayers through Medicare.

[CLERK'S NOTE.—Later specified at "1.2%".]

[CLERK'S NOTE.—Later specified at "27.5%".]

Mr. ISTOOK. I might mention also that the figure of the number of AIDS patients of some 46,000 that are being, having their expenses paid through Medicare, compares to the CDC report of just over 80,000 AIDS patients in 1994. It's a very significant proportion of the AIDS patients. In fact, the Government outlays, unique on AIDS, $1.5 billion for research, $270 million for treatment. No other disease has anywhere near that ratio, where the research outstrips the cost of care.

[CLERK'S NOTE.—"New AIDS patients" later added.]

ALLOCATION OF RESEARCH DOLLARS

Mr. ISTOOK. Now, this is part of the concern that I've expressed to you before about the priorities, are we putting our research dollar where it benefits a greater amount of the population, where it benefits the taxpayers and links up with the extraordinary expense to the taxpayers of providing health care. I would appreciate your comments on that, especially if there is any formal consultation process in allocating the funding for NIH disease research, any formal consultation process with HCFA, which administers the Government Medicare and Medicaid outlays, Centers for Disease Control, private insurance companies and hospital administrators, and anyone else that may be in the private sector as well.

Is there any formal process for them to have input on how we are allocating our research dollars?

Dr. VARMUS. Mr. Istook, there are a number of ways in which I would like to respond to your comments.

Mr. ISTOOK. Sure.

Dr. VARMUS. As far as the formal consultation process is concerned, there isn't any formal process that we go through. However, the data of the sort that you're presenting—I haven't seen this table before—but other kinds of information, of course, is not only accessible to us, but we look at it quite closely. As you know, in the past we provided to the Congress cost of illness reports, and we're of course following the epidemiology of disease throughout the Nation very, very closely, because we are concerned about these figures. They do feed into the overall priority setting process.

I haven't seen this table before, and I'd have to question some of the numbers that you're quoting. Because——

Mr. ISTOOK. These are from HCFA, by the way.

Dr. VARMUS. The HCFA numbers, I'm sure are correct, but the numbers that relate to percentage of disease spending are somewhat perplexing to me, and I'm sure perplexing to Dr. Klausner, since he previously was receiving almost 20 percent of the NIH budget and is now only receiving 5 percent.

Mr. ISTOOK. Certainly any errors we want to rectify.

Dr. VARMUS. There may be some corrective——

CRITERIA FOR FUNDING ALLOCATIONS

Mr. ISTOOK. Sure, we may correct information. But the ratios, of course, still indicate that a significant question of at least $1.5 billion of the application.

Dr. VARMUS. I think we would be remiss if we were allocating our dollars solely on the basis of Medicare payment. Obviously, the economic burden of disease is one of the things that we take into consideration when we think about how our appropriations are spent. If there were a major disease we were not studying, we'd be quite troubled.

But as you know, there are many other criteria that we have to consider in putting together our budget. One is the other kinds of burdens posed by the disease, because they're not all financial. The age at which the disease occurs—disease of children, disease of middle age, disease of adults, of aged adults—makes a difference. The degree of morbidity, the longevity of the illness.

But then we have to consider many things other than the illness itself, because, of course, much of our money is spent in research that's very difficult to categorize as belonging to one disease or another. And one of the places we always run into trouble in these discussions, and it's a trouble that's inherent in the process of setting priorities and explaining what we do, is that much of our research is an effort to understand the workings of cells and organisms that may not apply to any single disease, yet of course, the public has a right to expect us to be able to categorize what we spend in understandable terms.

Mr. ISTOOK. Which calls into question why even allocate among any disease at all if research is just going to be of such general application?

Dr. VARMUS. Well, because some research is, classifable. If we do a clinical trial to treat a certain condition, we can say we're spending money on that disease in that case without appreciable ambiguity, even though as you know, sometimes such clinical trials do lead to developments that affect other illnesses as well. But that's a by-product.

I think we end up with the difficulty we've been in before: that, for us, scientific opportunity and the submission of applications to study certain questions end up being a very significant driver of where our money is spent. We don't expect there to be a one to one relationship between any cost accounting and the place where we spend our monies. I find myself more responsive to a complaint that there is a promising opportunity that we're not seizing than I am to the notion that there is a less than uniform correspondence of one component of our priority making to the way we spend our money.

REDUCING HEALTH CARE COSTS

Mr. ISTOOK. Of course when you have, it's hard to find any other disease that has a one to one ratio. And yet you've got one disease that has a 100 to 1 percentage or priority ratio. I'm concerned, especially, we're spending tremendous amounts, of course, through NIH on research.

But it doesn't seem to me that one of the purposes is to try to reduce not only the burdens, but the cost of health care, to patients, to their families, to citizens, to taxpayers, to all the people that are being hit with tremendous health care costs. And our research doesn't seem to take into account that national priority of trying to reduce the burden of health care costs by making sure that research is focused on the diseases that are costing so many people so much. Instead it is grossly focused on a disease that, although terrible, is not more terrible than many other diseases, and certainly does not represent the same degree of threat to nearly as many people in this country as other diseases, such as cancer and diabetes.

Dr. VARMUS. Well, let me take issue with a couple of things you've said. One is that the goal of our research is not solely to reduce health care costs. In fact, sometimes the outcome of our research is to increase costs. In some areas that does happen. We like to point to advances that in fact do save money, but they don't all

save money. Sometimes we have an advance that decreases human suffering, but does so at the cost of increased medical expenses.

Secondly, I would take issue with the question of the populations at risk. And let's talk specifically about AIDS, because that's obviously what's on your mind. AIDS is currently the leading cause of death for individuals between the age of 25 and 44. It's a disease which has tremendous impact worldwide. Every child growing up in America, every parent is concerned about HIV. Peoples' attitude toward life is affected by it. It's a new disease. It's a disease which continues to spread in certain populations here, even though the infection rate has begun to stabilize.

We do have some therapies for it. It represents an enormous challenge, which we have already seen pays dividends in thinking about other ailments. We discussed this before, and I understand that money we spent on other diseases also has ramifications beyond the narrow disease confines to which the monies are classified.

But I think the pervasive nature of infection with HIV, its involvement of every organ system, has produced for us challenges that have had particularly broad ramifications in all of medical science.

Mr. ISTOOK. Thank you, Dr. Varmus. I will work with you and try to get more information from you on how many people and how much input actually goes into deciding the allocation of the research dollars within NIH, and whether we need a much broader and more inclusive process to make those determinations.

NIH PRIORITY SETTING PROCESS

Dr. VARMUS. I would like to make just one very brief comment if I can.

Mr. ISTOOK. Sure.

Dr. VARMUS. We are preparing, for the public and for the Congress, a booklet that describes how we go about the priority setting process. As you'll see, many, many constituencies are involved in that process, and my response to your request for information about formal interactions was accurate. But those influences are felt, just not through a formal process——

Mr. ISTOOK. Sure. You'll give us the information on the informal part.

Mr. PORTER. I might say to my colleagues that everyone, except Mr. Stokes, who had to leave, has had an opportunity to ask questions this morning. Dr. Varmus will be here with each of the Institute directors for seven full days of additional hearings. And would be available to answer any questions, as well as the directors themselves.

Dr. Varmus, we'd like to thank you very much for your testimony this morning. You've enlightened us a great deal. We appreciate the wonderful job you do at NIH. You and the Institutes are truly national treasures, and we appreciate your strong leadership there.

The subcommittee will stand in recess until 1:30 p.m.

[The following questions were submitted to be answered for the record.]

FISCAL YEAR 1998 BUDGET REQUEST

Mr. Porter: Provide NIH's FY 1998 request by ICD at each stage of the process: submission to the Department, the Department's submission to OMB, and the passback from OMB. Identify the percent of total funding allocated to each ICD at each step.

Dr. Varmus: The following table identifies the FY 1998 request at each stage of the budget formulation process. The percent of the total funding allocated to each ICD is also shown. The NIH submission to DHHS was provided in the NIH aggregate. OMB's funding level is provided back to NIH in the aggregate, although the attached table shows the President's Budget broken down by institute.

National Institutes of Health
Chronology of FY 1998 President's Budget
(Dollars in thousands)

			Fiscal Year 1998				
	FY 1997 Estimate	Percent of Total	NIH to DHHS 1/	DHHS to OMB 1/	Percent of Total	President's Budget	Percent of Total
NCI	$2,156,416	16.93%	This level	$2,156,953	17.03%	$2,217,482	16.96%
NHLBI	1,370,952	10.76%	was not	1,382,416	10.91%	1,404,770	10.74%
NIDR	182,893	1.44%	developed	182,493	1.44%	190,081	1.45%
NIDDK	802,889	6.30%	by ICD	807,978	6.38%	821,164	6.28%
NINDS	701,582	5.51%		702,673	5.55%	722,712	5.53%
NIAID	608,950	4.78%		611,636	4.83%	634,272	4.85%
NIGMS	970,749	7.62%		979,512	7.73%	992,032	7.59%
NICHD	566,996	4.45%		568,268	4.49%	582,032	4.45%
NEI	323,147	2.54%		324,151	2.56%	330,955	2.53%
NIEHS	301,998	2.37%		302,279	2.39%	313,583	2.40%
NIA	483,952	3.80%		482,672	3.81%	495,202	3.79%
NIAMS	252,730	1.98%		254,377	2.01%	258,932	1.98%
NIDCD	186,525	1.46%		187,267	1.48%	192,447	1.47%
NIMH	604,144	4.74%		604,476	4.77%	629,739	4.82%
NIDA	328,286	2.58%		326,155	2.57%	358,475	2.74%
NIAAA	200,819	1.58%		201,175	1.59%	208,112	1.59%
NINR	54,221	0.43%		54,348	0.43%	55,692	0.43%
NHGRI	186,528	1.46%		192,424	1.52%	202,197	1.55%
NCRR	340,994	2.68%		324,650	2.56%	333,868	2.55%
FIC	16,245	0.13%		16,291	0.13%	16,755	0.13%
NLM	147,463	1.16%		151,810	1.20%	152,689	1.17%
OD	251,291	1.97%		234,106	1.85%	234,247	1.79%
OAR	1,501,073	11.78%		1,498,890	11.83%	1,540,765	11.78%
Subtotal	12,540,843	98.43%		12,547,000	99.05%	12,888,203	98.55%
B&F	200,000	1.57%		120,000	0.95%	190,000	1.45%
Total, NIH	12,740,843	100.00%	$12,865,333	12,667,000	100.00%	13,078,203	100.00%

1/ The base for this level was the FY 1997 President's Budget of $12,376,561.

FISCAL YEAR 1996 and 1997 DIRECTOR'S DISCRETIONARY FUND REQUEST

Mr. Porter: Identify the uses for the Director's Discretionary fund for FY ' 96. Have any funds been committed from the FY '97 discretionary fund at this time?

Dr. Varmus: The following table identifies the FY 1996 distribution of the Director's Discretionary Fund. No decision has been made on how the FY 1997 funds will be allocated.

National Institutes of Health
Director's Discretionary Fund
Expenditures for FY 1996
(Dollars in thousands)

ICD	Shannon Awards	Spinal Cord Grants	Mouse EST Project	Dr. Slavkin's	Mouse Genome Wkshp	Nat'l Bioethics Advisory Comm.	Cancer Genome Anatomy Project	Animal Models Cancer	Neuroden Res. Grants	Other Grants	World Lecture Series	Total
NCI	$400						$158	$158				$716
NHLBI	150									150		300
NIDR	50											50
NIDDK	500									138		638
NINDS	150	2,380							1,005			3,535
NIAID	200											200
NIGMS	750		227									977
NICHD	350									200		550
NEI	150	210										360
NIEHS	100											100
NIA	150	96							675			921
NIAMS	300	225		150								675
NIDCD	220											220
NIMH	50									532		582
NIDA	150								180	158		488
NIAAA	100								150			250
NINR	50											50
NHGRI	50				3							53
NCRR	82									113		195
FIC	0											0
NLM	50									145		195
OD	0					295					12	307
Total	4,002	$2,911	$227	$150	$3	$295	$158	$158	$2,010	$1,436	$12	$11,362

FULL TIME EQUIVALENT
FY 1990-FY 1997

Mr. Porter: Provide two charts of National Institutes of Health (NIH) Full Time Equivalent (FTE) for FY 1990-1997, one broken down by each ICD and central services, the other broken down by intramural, RMS, and other FTE.

Dr. Varmus: The following tables identifies NIH FTEs for FY 1990-1997.

National Institutes of Health
Total by Institute

ICD	FY 90[1/]	FY91 [1/]	FY92	FY93	FY94	FY95	FY96	FY97
NCI	2,192	2,345	2,525	2,601	2,382	2,218	2,180	2,180
NHLBI	845	881	912	911	852	822	834	834
NIDR	327	330	352	362	342	314	301	301
NIDDK	599	603	629	638	597	570	545	545
NINDS	662	721	723	709	669	649	620	620
NIAID	919	1,005	1,091	1,136	1,102	1,039	1,006	1,006
NIGMS	172	183	190	191	179	172	169	169
NICHD	448	502	550	562	504	481	485	485
NEI	213	229	260	272	253	240	233	233
NIEHS	667	701	721	750	702	650	640	640
NIA	365	402	439	472	448	426	411	411
NIAMS	118	138	162	166	150	147	157	157
NIDCD	58	97	122	133	125	125	126	126
NIMH	868	903	934	948	900	843	828	828
NIDA	313	356	399	424	386	360	363	363
NIAAA	227	232	241	254	234	220	225	225
NINR	28	38	46	52	53	44	40	40
NHGRI	26	37	44	55	139	173	187	187
NCRR	90	98	104	108	98	97	93	93
FIC	59	67	72	75	68	68	72	72
Subtotal ICDs	9,196	9,868	10,516	10,819	10,183	9,658	9,515	9,515
NLM	550	585	602	625	596	575	575	575
OD	626	685	699	716	700	732	690	690
Central Services	4,571	4,734	4,951	4,945	4,756	4,392	4,359	4,359
Undistrib.	0	0	0	0	0	4	14	14
Total NIH	14,943	15,872	16,768	17,105	16,235	15,361	15,153	15,153

National Institutes of Health
Total by Mechanism

	FY 1990 1/	FY 1991 1/	FY 1992	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997
Intramural	9,560	10,038	10,523	10,734	10,109	9,450	9,270	9,290
RMS	5,245	5,688	6,081	6,190	5,957	5,742	5,695	5,675
Cancer Control	138	146	164	181	169	169	188	188
Total	14,943	15,872	16,768	17,105	16,235	15,361	15,153	15,153

1/ Includes comparable ADAMHA FTEs

ONE-PERCENT EVALUATION FUNDING IN RMS

Mr. Porter: Identify the dollar amounts for RMS for FY 90 - FY 98, with the portion of RMS used for the one percent evaluation set-aside identified, as well as a separate line indicating the amount of non-RMS dollars used for the one percent set-aside in each year.

Dr. Varmus: The table below reflects the dollar amounts for RMS for FY 1990 - FY 1998. Also shown are the RMS, non-RMS and total dollars used for the one percent set-aside in each year.

National Institutes of Health
Research Management and Support
FY 1990 - FY 1998
(dollars in thousands)

	Total RMS	Program Evaluation RMS	Program Evaluation Non-RMS	Program Evaluation Total
FY 1990	$405,358	$50,527	$ 564	$51,091
FY 1991	434,706	31,970	370	32,340
FY 1992	484,327	39,093	4,181	43,274
FY 1993	493,200	39,765	3,750	43,515
FY 1994	497,886	40,892	9,893	50,785
FY 1995	506,415	36,315	19,085	55,400
FY 1996	479,746	15,103	79,395	94,498
FY 1997 Estimate	479,368	12,591	77,811	90,402
FY 1998 Estimate*	479,368	TBD	TBD	TBD

1/Includes up to $6.1 million of one percent Evaluation Funds which may be used by NIH.
2/FY 1998 assessments have not yet been determined by the Department. However, NIH's share of one percent evaluation set-aside funding is expected to increase by about 40 percent over FY 1997 based on the President's budget proposals to increase resources for the Agency for Health Care Policy Research and the CDC National Center for Health Statistics.

PUBLIC EDUCATION

Mr. Porter: Identify the percent of the NIH budget in total and by Institute that is allocated to public education efforts.

Dr. Varmus: The table on the next page reflects the percent of the NIH budget in total and by Institute that is allocated to public health education efforts from FY 1996 through FY 1998. Also shown is the total dollar amount allocated for public health education efforts. These efforts include, but are not limited to Back to Sleep, the National Diabetes Education Program, the Alzheimer's Disease Education and Referral Center, Prevention of Traumatic Brain Injury in Adolescents, and Drug Abuse Materials for Minority Audiences.

National Institutes of Health
Percent of Public Health Education to Total Budget
FY 1996 - FY 1998
(dollars in thousands)

	FY 1996		FY 1997		FY 1998	
	Amount	%	Amount	%	Amount	%
NCI	$21,403	0.95%	$21,350	0.90%	$21,425	0.88%
NHLBI	7,657	0.57	7,040	0.49	6,700	0.46
NIDR	300	0.16	300	0.15	300	0.15
NIDDK	1,275	0.17	1,216	0.15	1,233	0.15
NINDS	300	0.04	300	0.04	300	0.04
NIAID	0	0.00	0	0.00	0	0.00
NIGMS	0	0.00	0	0.00	0	0.00
NICHD	665	0.11	1,000	0.16	1,000	0.15
NEI	835	0.27	887	0.27	908	0.27
NIEHS	0	0.00	0	0.00	0	0.00
NIA	1,000	0.22	900	0.19	900	0.18
NIAMS	0	0.00	0	0.00	0	0.00
NIDCD	94	0.05	88	0.05	91	0.05
NIMH	2,309	0.35	2,308	0.33	2,338	0.32
NIDA	585	0.13	508	0.10	691	0.13
NIAAA	0	0.00	50	0.02	100	0.05
NINR	0	0.00	0	0.00	0	0.00
NHGRI	0	0.00	0	0.00	0	0.00
NCRR	400	0.10	400	0.10	400	0.10
FIC	0	0.00	0	0.00	0	0.00
NLM	0	0.00	0	0.00	0	0.00
OD	0	0.00	0	0.00	0	0.00
Total	$36,823	0.31%	$36,347	0.29%	$36,386	0.28%

NUMBER OF APPLICATIONS

Mr. Porter: Identify the number of applications received in each of the past ten fiscal years. For FY 96, how many of the total applications received were amended applications that have been previously submitted?

Dr. Varmus: The following table reflects the number of research project grant (RPG) applications received (success rate base) in each of the past ten fiscal years as well as the estimates for FY 1997 and FY 1998. Of 23,819 competing RPG applications received in FY 1996, 8,151 were amended applications. Amended applications replace any original applications received during a fiscal year; only one application for the same project is counted as a competing application.

NATIONAL INSTITUTES OF HEALTH
Total Applications Received
FY 1987 - FY 1998

Fiscal Year	Applications Received
1987	20,487
1988	21,889
1989	22,021
1990	22,875
1991	22,197
1992	22,832
1993	25,140
1994	25,508
1995	25,225
1996	23,819
1997 Estimate	25,780
1998 Estimate	25,842

NATIONAL CENTER ON SLEEP DISORDERS RESEARCH

Mr. Porter: What steps has the Office of the Director taken to facilitate the implementation of the National Sleep Disorders Research Plan and cross-Institute collaboration?

Dr. Varmus: The Office of the Director, NIH strongly supports the recommendations in the Sleep Disorders Research Plan. Last September, I met with the Sleep Disorders Research Advisory Board and discussed a variety of topics including strengthening sleep research and collaboration among Institutes. One message was that the Plan serves as an excellent vehicle to alert the broad scientific community of the numerous sleep research opportunities; NIH can facilitate this research by pointing to areas that require further investigation. At the same time, I urged Institute representatives on the Advisory Board to continue to collaborate in crosscutting areas.

To date, I am pleased with NIH-wide collaborative activities initiated by the National Center on Sleep Disorders Research (NCSDR). For example, in FY 1996 the NCSDR released a new initiative on the molecular biology and genetics of sleep and sleep disorders, which is sponsored by NHLBI, NIMH, NICHD, and NIAMS. This initiative addresses one of the primary recommendations in the Research Plan, and applications responding to this announcement will strengthen and expand ongoing sleep

research at NIH. Several trans-NIH sleep related workshops have been conducted over the past few years addressing important areas such as melatonin and the interaction between the circadian and sleep/wake systems. These meetings should stimulate investigators to submit more sleep related research applications to NIH. The NCSDR is currently developing a trans-NIH sleep training grant program announcement, which will target another critical recommendation in the Plan.

I am regularly given updates on the activities of the NCSDR and will work with the Sleep Disorders Research Advisory Board, the Trans-NIH Sleep Research Coordinating Committee, and the NHLBI to achieve the goals identified in the Sleep Disorders Research Plan. Also, I will continue to monitor progress and encourage collaboration among the Institutes.

ADMINISTRATIVE COSTS

Mr. Porter: Provide a table identifying administrative costs NIH-wide for FY97-98 using the definition of administrative costs outlined in the 1997 House report.

Dr. Varmus: The House Report accompanying the FY 1997 appropriation recommended that NIH report administrative costs consistent with the P.L. 99-158 definition of such costs, including costs for the previously excluded institutes and centers: the National Institute of Nursing Research, the John E. Fogarty International Center, the National Library of Medicine, and the Clinical Center.

In response to P.L. 99-158, NIH collaborated with staff of the General Accounting Office (GAO), to develop a methodology to calculate these costs. These include obligations in the Research Management and Support (RMS) budget activity and those directly related to the Office of the Scientific Director in the Intramural budget line of an Institute. As the Scientific Director also has program responsibilities and is usually a researcher as well, a percentage of these costs has been excluded. Obligations directly associated with the Intramural Administrative Office are also included; while direct program costs in the Office of the Director (those for AREA Awards, the Director's Discretionary Fund, AIDS research, the Minority and Women's Health Programs and Initiatives, the Office of Education, Extramural Facilities Construction, and the Intramural Radiology Program) have been excluded.

The table below shows NIH administrative costs under this definition for FY 1997-1998:

National Institutes of Health
FY 1997 and FY 1998 Administrative Costs
(dollars in thousands)

	FY 1997	FY 1998
Total Administrative Costs	$ 572,452	$ 572,452
Total Appropriation	12,740,843	13,078,203
Percent of Total	4.49%	4.38%

TOLL-FREE NUMBERS

Mr. Porter: Provide a listing of all the toll-free numbers for public information programs that NIH supports.

Dr. Varmus: The following table provides a listing of the toll-free telephone numbers for public information supported by the NIH.

Institute	Toll-Free Number	Information Program
National Cancer Institute	1-800-4 CANCER	Cancer information services
National Heart, Lung, and Blood Institute	1-800-575-WELL	Recorded message for requesting NHLBI publications.
National Institute of Diabetes and Digestive and Kidney Diseases	1-800-GET-LEVEL	National Diabetes Outreach Program
	1-800-891-5388	Bladder Control for Women Awareness
	1-800-946-8098	Weight-Control Information Network
National Institute of Neurological Disorders and Stroke	1-800-352-9424	Information on neurological conditions and referrals to health and government agencies

National Institute of Allergy and Infectious Diseases	1-800-874-2572	AIDS Clinical Trials Information Service
	1-800-448-0440	AIDS Treatment Information Service
National Institute of Child Health and Human Development	1-800-505-CRIB	Sudden Infant Death Back to Sleep campaign
National Institute of Environmental Health Sciences	1-800-NIEHS94	Environmental information from NIEHS to the general public.
National Institute on Aging	1-800-438-4380	Alzheimer's Disease and Referral Center
	1-800-222-2225 1-800-222-4225 (TTY)	NIA Information Center
National Institute of Arthritis, Musculosketal and Skin Diseases	1-800-624-BONE	Osteoporosis and related bone diseases - National Resource Center
National Institute on Deafness and Other Communication Disorders	1-800-241-1044 1-800-241-1055 (TTY)	Clearinghouse for information on 7 mission areas of NIDCD
National Institute of Mental Health	1-800-421-4211	Depression information
	1-800-64-PANIC	Panic Disorder Information
	1-888-8-ANXIETY	Anxiety Disorders Information
National Library of Medicine	1-800-272-4787	Access to professionals for NLM information and services.

Office of the Director	1-800-528-7689 1-888-352-3001(TTY)	Intramural research training opportunities
		NIH's educational loan repayment and undergraduate scholarship programs
		Link to Office of Education, OIR
	1-800-549-6636	Women's Health Initiative
	1-888-644-2667	Office of Medical Research of Applications - Technology Consensus
	1-800-633-3425	Audio Visual Branch Radio news service
	1-888-644-6226	Office of Alternative Medicine information line

RESEARCH ON SPECIFIC DISEASES

Mr. Porter: Provide the traditional one-pager identifying estimated spending by disease for FY '96-98. Separately identify direct and related spending for FY '98.

Dr. Varmus: The attached table provides the funding amounts for specific and diseases and research areas that are most often requested. The only disease on this list for which we collect funding by direct and related is Parkinson's disease. This is shown on the table.

Mr. Porter: Also identify the amount of research funding that cannot be attributed to a specific disease or condition for FY 96-98.

Dr. Varmus: Nearly sixty percent, or approximately $7.0 billion in FY 98, of NIH funding supports basic research, that is, research that may not be targeted directly to a specific disease or condition.

		DHHS-National Institutes of Health			
		Research Initiatives/Programs of Interest			
		(Dollars in thousands)			
		FY 1996	FY 1997	FY 1998	%Chg
	Research/Disease Area	Actual	Estimate	Estimate	97/98
1	Advanced Instrumentation	$297,182	$325,883	$348,895	7.1%
2	Aging	855,401	910,147	931,185	2.3%
3	Alzheimer's Disease	304,411	322,502	330,399	2.4%
4	*AIDS Research	1,410,925	1,501,073	1,540,765	2.6%
	Minority AIDS Research	265,716	278,004	282,957	1.8%
	Pediatric AIDS Research	156,641	163,327	165,762	1.5%
5	Biology of Brain Disorders	1,994,464	2,103,464	2,181,495	3.7%
6	Biotechnology Research	4,901,828	5,130,729	5,292,875	3.2%
7	Brain Disorders	2,329,923	2,459,550	2,543,484	3.4%
8	Cancer Research	2,570,566	2,712,590	2,780,543	2.5%
	Breast Cancer	381,880	401,148	408,248	1.8%
	(Breast Cancer Genetic)	98,844	110,061	114,185	3.7%
	Cervical Cancer	60,180	62,938	65,358	3.8%
	Lung Cancer	127,796	132,122	137,214	3.9%
	Ovarian Cancer	42,168	44,858	46,536	3.7%
	Prostate Cancer	92,661	96,198	100,047	4.0%
	Colo-Rectal Cancer	105,525	106,848	107,988	1.1%
	Uterine Cancer	13,956	14,771	15,290	3.5%
9	Cardiovascular Research	985,736	1,044,874	1,069,440	2.4%
	Contraception/Reproduction Research	194,186	204,180	208,592	2.2%
10	Cystic Fibrosis	64,130	67,498	68,813	1.9%
11	Decade of the Brain	2,317,597	2,448,697	2,535,469	3.5%
12	Diabetes	298,920	316,292	322,683	2.0%
13	Diagnostic Radiology	220,559	228,875	231,617	1.2%
14	Diethylstilbestrol (DES)	5,097	5,332	5,488	2.9%
15	Emerging Infectious Diseases	77,744	82,811	87,548	5.7%
16	Epstein Barr Virus	20,928	22,210	23,239	4.6%
	(Chronic Fatigue)	7,085	7,950	7,882	-0.9%
17	Gene Mapping	679,738	729,886	768,601	5.3%
18	Gene Therapy	203,474	215,566	220,409	2.2%
19	Genetics of Medicine	936,701	997,104	1,056,853	6.0%
20	Health & Behavioral Research	840,784	882,949	912,708	3.4%
21	Human Fetal Tissue Research	20,048	20,988	21,455	2.2%
22	Hypertension	174,395	184,195	187,933	2.0%

23	Immunology	1,169,156	1,222,972	1,245,351	1.8%
24	Infant Mortality/(Low Birth Weight)	316,695	334,888	344,738	2.9%
25	Kidney Disease	190,706	202,587	206,810	2.1%
26	Lupus	32,872	34,745	35,547	2.3%
27	New Approaches to Pathogenesis	1,563,060	1,624,829	1,674,877	3.1%
28	Nutrition Research	412,927	433,568	445,203	2.7%
	Obesity	85,449	90,252	92,409	2.4%
29	Osteoporosis	99,643	104,975	107,302	2.2%
30	Parkinsons	77,158	81,441	83,611	2.7%
	Parkinsons (DIRECT)	32,353	34,218	35,117	2.6%
	Parkinsons.(RELATED)	44,805	47,223	48,494	2.7%
31	Prevention	3,017,789	3,181,258	3,264,509	2.6%
	(NCI Primary Prev.)	442,052	450,000	457,000	1.6%
32	Preventive Strategies	1,885,476	1,958,604	2,031,437	3.7%
33	Rehabilitation	173,243	182,563	187,947	2.9%
34	Rural Health	98,553	104,142	107,729	3.4%
35	Schizophrenia	111,479	119,425	124,796	4.5%
36	Sexually Trans. Diseases/Herpes	102,583	106,591	110,033	3.2%
37	Sickle Cell Disease	48,570	51,725	52,956	2.4%
38	Smoking and Health	137,338	142,478	146,408	2.8%
39	Spinal Cord Injury	56,277	59,647	61,481	3.1%
40	Stroke	120,280	127,489	130,866	2.6%
41	Sudden Infant Death Syndrome	45,887	48,813	49,985	2.4%
42	Therapeutics/Drug Development	646,159	679,525	725,913	6.8%
43	Topical Microbicides	20,124	22,335	25,535	14.3%
44	Tropical Diseases	108,509	113,174	115,522	2.1%
45	Tuberculosis Research	64,125	67,235	68,852	2.4%
46	Vaccine Development	273,081	294,983	316,148	7.2%
47	Vaccine Related	303,954	325,745	346,050	6.2%
48	Women's Health Research	1,831,749	1,924,889	1,974,381	2.6%
Prepared by the Office of Financial Management					
*Represents Budget Authority for AIDS					
	February 19, 1997				

DETAIL OF FULL TIME PERMANENT EMPLOYEES

Mr. Porter: Provide a chart showing the distribution of full-time permanent positions by grade level throughout the NIH.

Dr. Varmus: The table on the following page identifies the distribution of full-time permanent staff by grade level throughout NIH as of 9/30/96.

National Institutes of Health
Detail of Full Time Permanent Staff

	FY 1996
Senior Executive Service	189
GS/GM-15	959
GS/GM-14	1,355
GS/GM-13	1,367
GS-12	1,676
GS-11	1,433
GS-10	434
GS-9	875
GS-8	677
GS-7	1,421
GS-6	605
GS-5	401
GS-4	114
GS-3	29
GS-2	10
GS-1	3
Subtotal	11,359
Commissioned Corps:	
CC-1	4
CC-2	13
CC-3	66
CC-4	214
CC-5	201
CC-6	335
CC-7	4
CC-8	6
Subtotal	843
Wage Grade (all levels)	824
Ungraded	16
Sub Total, permanent positions	13,231
SBRS	37
Other Than Full Time Permanent	2,437
Total positions, end of year	15,705

INSTRUMENTATION

Mr. Porter: How much funding is provided for instrumentation and equipment through the direct costs of research project grants?

Dr. Varmus: In FY 1996, the NIH provided $62,865,383 in funding for equipment and instrumentation under research project grants. An additional $66,124,042 in equipment and instrumentation was provided to grants other than research projects grants.

FULL TIME EQUIVALENT CEILING

Mr. Porter: How do you plan to reach your FTE ceiling of 14,903 in FY 99?

Dr. Varmus: The NIH has undertaken a variety of strategies, beginning with "buyouts", primarily in positions that had been identified for reductions, such as employees in administrative positions. With the ending of the buyout program, we used early retirement and attrition to meet FTE reductions. We are continuing our streamlining efforts, such as the establishment of Competitive Service Centers and reengineering efforts that will reduce staff effort. The NIH is also exploring the use of other, more flexible hiring mechanisms, such as the Intramural Research Training Associates (IRTA) program. This program allows NIH to hire short-term staff for particular research projects. Fiscal Year 1999 FTE targets are available at the HHS level only. The FY 1999 FTE target for NIH has not yet been determined.

SHANNON AWARDS

Mr. Porter: Will Shannon awards be funded in FY '97 and FY '98, and from what source?

Dr. Varmus: No definite plans have been made as yet for the James A. Shannon award program in FY 1997 or in FY 1998. The NIH does not formulate its Shannon funding policy until after institutes have conducted the final round of grant reviews in May, in order to accumulate data on all grants eligible for such funding.

ONE-PERCENT EVALUATION SET-ASIDE

Mr. Porter: Identify the one percent evaluation set-aside tap by Institute for FY '97 and FY '98. Also identify all the various taps on the National Institutes of Health (NIH) budget in FY '97 and FY '98.

Dr. Varmus: The first table displays the statutorily required one percent set-aside for Program Evaluation. The second table reflects the taps and assessments.

National Institutes of Health
Program Evaluation
FY 1997 and FY 1998 Estimates
(dollars in thousands)

ICD	FY 1997[1] Estimate	FY 1998 Estimate
NCI	$17,566	
NHLBI	10,568	
NIDR	1,446	
NIDDK	6,020	
NINDS	5,361	
NIAID	9,267	
NIGMS	7,359	
NICHD	4,656	
NEI	2,450	
NIEHS	2,278	
NIA	3,579	
NIAMS	1,899	
NIDCD	1,392	
NIMH	5,172	
NIDA	3,608	
NIAAA	1,564	
NINR	443	
NHGRI	1,401	
NCRR	3,064	
FIC	198	
NLM	1,111	
Total	$90,402	TBD[2]

1/Includes up to $6.1 million of one percent Evaluation Funds which may be used by NIH.

2/FY 1998 assessments have not yet been determined by the Department. However, NIH's share of one percent evaluation set-aside funding is expected to increase by about 40 percent over FY 1997 based on the President's budget proposals to increase resources for the Agency for Health Care Policy Research and the CDC National Center for Health Statistics.

National Institutes of Health
Taps and Assessments
FY 1997 and FY 1998 Estimates
(dollars in thousands)

	FY 1997 Estimate	FY 1998** Estimate
Program Evaluation:		
Agency for Health Care Policy & Research	$ 35,884	$TBD
National Center for Health Statistics Surveys	35,151	TBD
Assistant Secretary for Planning and Evaluation	11,802	TBD
Office of Public Health and Science	2,933	TBD
Subtotal*	85,770	
National Research Service Awards: Primary Care (Health Resources & Services Administration)	4,179	4,267
Agency for Health Care Policy & Research	4,179	4,267
DHHS Special Projects	3,066	3,149

*Excludes up to $6.1 million of one percent evaluation funds which may be used by NIH.

**FY 1998 assessments have not yet been determined by the Department. However, NIH's share of one-percent evaluation set-aside funding is expected to increase by about 40 percent over FY 1997 based on the President's budget proposals to increase resources for the Agency for Health Care Policy Research and the CDC National Center for Health Statistics.

NIH-WIDE DIABETES RESEARCH EFFORTS

Mr. Bonilla: Since diabetes, like AIDS, impacts a number of different body systems, and as we just discussed a broad approach is effective, it seems logical to me that there is a need for multi-disciplinary approach to diabetes research which cuts across many of NIH institutes.

Is there a coordinated plan to attack diabetes similar to the plan developed last year by the NIH AIDS Research Program Evaluation Task Force, chaired by Dr. Arnold Levine?

Dr. Varmus: The National Institutes of Health (NIH) does indeed use a multi-disciplinary research approach for the prevention, control, and treatment of diabetes. Because of the systemic impact of diabetes, and the multiple potential causes, research in Type 1 and Type 2 diabetes is funded by many Institutes at NIH. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funds basic research on both types of diabetes, as well as large multicenter prevention trials. The National Heart, Lung and Blood Institute (NHLBI) funds research to learn how diabetes of both types causes vascular disease. The National Eye Institute (NEI) supports research on diabetes-related diseases of the eye, such as diabetic retinopathy, which can lead to blindness. Because Type 2 diabetes is a complicating factor in many chronic diseases of the elderly, the National Institute on Aging (NIA) funds research on several aspects of its causes and effects. Type 1 diabetes begins early in life and is thought to result from an autoimmune response brought on, perhaps by viral infection, and the National Institute of Child Health and Development (NICHD) is supporting research into how to predict and to halt this process. The National Center for Research Resources (NCRR), through its support of general clinical research centers, also is responsible for a large share of diabetes treatment and prevention trials.

NIH also periodically reviews its diabetes research portfolio. In 1996, the Office of the Director prepared a listing of NIH-wide diabetes research that is being used by the Institutes in planning and evaluating their research programs. Diabetes research is also coordinated across the Institutes through the development of Requests for Applications and Program Announcements. When an Institute develops such a request, it is reviewed by other NIH Institutes, resulting in an informal, but powerful, means of coordinating research and sometimes leading to co-funding of grants. Also, several ongoing multicenter clinical prevention trials serve as dynamic environments in which scientists pool case materials and resources, and develop new ideas and protocols for preventing or stabilizing diabetes when it is detected in any of several stages.

Mr. Bonilla: If not, do you think there is a need for a similar type of examination of NIH-wide diabetes research efforts?

Dr. Varmus: Recently, the Director of NIDDK in conjunction with the Director, NIH, announced plans for a conference on diabetes. This conference will be a step toward developing an NIH-wide agenda for diabetes research. The conference, which is being planned for the summer of 1997, will bring together experts in separate but related fields to generate ideas and stimulate collaboration. It is hoped that the conference will produce recommendations for coordinating research efforts between the Institutes, and identify opportunities for new research and treatment approaches.

NEW APPROACHES TO PATHOGENESIS

Mr. Bonilla: Please explain your proposed "new approaches to pathogenesis" as it relates to diabetes.

Dr. Varmus: Special Emphasis Areas reflect areas of research which show promise for addressing public health needs and for yielding medical advances that will lead to improvements in human health. One of these areas, "New Approaches to Pathogenesis," encourages novel scientific approaches to understanding the fundamentals of a given disease process. This emphasis is especially important for diabetes, since Type 1 and Type 2 diabetes results from multiple factors which are not yet completely understood, and may differ among patients.

An example of a new approach to understanding diabetes has been developed through obesity research. Scientists have discovered two genetic mutations which cause diabetes in animal models and have learned that these mutations are in the gene for leptin and the leptin receptor. Leptin is a hormone that functions in regulating food intake by signaling the appetite-control area of the brain as to the levels of body fat. These experiments, along with others which tested the effects of leptin on the liver, have shown that leptin, which is present in high levels in obese individuals, can change glucose metabolism in the liver, and through this path, play a role in the onset of Type 2 diabetes.

A promising approach to understanding Type 1 diabetes is research into the defects in the immune system which lead to the autoimmune attack on the insulin-producing islet cells of the pancreas. Research is planned to determine why a particular set of immune system cells begin to attack the islet cells, to study signaling proteins that are involved in the attack on the immune system and to develop antagonists (blocking agents) to these proteins. Insulin itself is often a target of the autoimmune attack, and since the administration of insulin can deflect the destruction of islet cells in prediabetic patients, research is being directed at discovering how the exogenous insulin skews the repertoire of autoantibodies being expressed.

Genetic research is also yielding advances in the understanding of both types of diabetes. For example, susceptibility genes for Type 1 diabetes have been found recently. Scientists have learned that these genes play a role in how cells identify themselves and communicate with the immune system. This knowledge has led to ways to block the autoimmune attack by preventing the immune system from recognizing these proteins on

the islet cells. Type 2 diabetes is a "polygenic" disease, meaning that defects in multiple genes are involved in its development. Genes involved in glucose regulation, lipid regulation, obesity, and insulin stimulation have been identified as contributors to development of this type of diabetes. When a specific defect is discovered, it greatly advances the understanding of disease mechanisms and opens new research avenues.

New understanding of diabetes has also led to new studies to develop drugs for the treatment of diabetes. For example, the sulfonylurea drugs which are used to stimulate insulin secretion in patients with Type 2 diabetes have been found to exert their effect through changing the function of "potassium channels" in the islet cells, and this system is being studied in hopes of producing improved drugs to stimulate insulin secretion.

INDIRECT COST CAP

Mr. Bonilla: Last year, I asked you about indirect costs and you indicated that if you capped those costs at 65 percent it would yield a relatively small amount of savings, about $40 million of the $2.5 billion that you spend on facilities plus administrative costs. It seems to me that $40 million would be a substantial amount if targeted to a disease on the brink of a breakthrough such as cancer or diabetes.

Has there been any effort at NIH to examine capping indirect costs since we talked about this last year?

Dr. Varmus: National Institutes of Health (NIH) staff are participating in efforts aimed at improving methods for charging indirect costs, now referred to as facility and administrative (F&A) costs, through the Office of Management and Budget (OMB). The circular (A-21) that governs F&A costs for colleges and universities was revised by OMB on May 8, 1996. It contained quite a few improvements to the procedures for determining F&A costs and allocating those costs for reimbursement from Federal sponsoring agencies. The revision included the application of common accounting standards to university expenditures; maintenance of the F&A rate in effect at the time of award through the life of the award; elimination of tuition benefits for dependant children; elimination of special studies for the determination of utility and library costs; and standardization of the calculation of interest costs on equipment and facilities. These revisions are a product of efforts by NIH staff and that of all of the other research agencies to further standardize and contain F&A costs.

When Circular A-21 was revised on May 8, 1996, OMB also announced its intent to publish additional guidelines on the calculation of facility costs and utility costs. NIH staff participated in a Federal-wide committee that was chaired by OMB to develop alternative guidelines for the calculation of facility costs. OMB intends to publish the guidelines that emerged from that review and a similar review of utility costs on July 1,

1997, for public comment. These new guidelines would bring additional standardization and stabilization to this important area of cost reimbursement. NIH staff have had an opportunity to provide input into this process. However, it is essential that it remain a Federal-wide effort under the leadership of OMB.

RESEARCH SPENDING PER DEATH FOR SELECTED DISEASES

Mr. Bonilla: I ask you the following each year: In FY 96 how much did the NIH spend on research funding per death for each of the following diseases: cancer, diabetes, heart disease, HIV/AIDS and stroke?

Dr. Varmus: The NIH research funding per death shown below for HIV/AIDS, diabetes, cancer, heart disease, and stroke is based on the National Center for Health Statistics Provisional Vital Statistics Data Monthly Vital Statistics Report, Vol. 45, No. 3(S)2 as of October 4, 1996. The National Center for Health Statistics Provisional Vital Statistics can only provide FY 1995 data at this time and will have FY 1996 data available in October 1997.

NIH - RESEARCH SPENDING PER DEATH FOR SELECTED DISEASES
(Dollars in thousands)

Selected Diseases	FY 1995 Spending	FY 1995 Number of Deaths	FY 1995 Total per Death
HIV/AIDS.....	$1,410,925	42,508	33.192
Diabetes.....	295,142	69,085	4.327
Cancer.....	2,434,304	537,969	4.778
Heart Disease.....	833,787	738,781	1.153
Stroke.....	114,296	158,061	.761

AWARENESS RELATING TO BIOMEDICAL RESEARCH

Mr. Bonilla: Currently only three cents of every health care dollar is to medical research. But like you, I believe federal investment in the NIH more than pays for itself by the lives saved and hardships prevented not to mention the jobs it creates and its contribution to the economy.

According to a survey conducted by the Charlton Research company, a majority of Texans agree it is important to be spending money on biomedical research. Unfortunately, the survey also indicated that NIH has low recognition in Texas. In addition, it shows that Texans don't know that business and industry invest more annually on biomedical research than the government does. This raises questions about the amount of awareness and education on issues relating to biomedical research.

Everyone should be aware of the crucial role business, industry, and the NIH have played in prolonging and improving the quality of our lives. Do you see this as a problem? If so, what efforts are underway to improve the NIH's recognition and awareness on issues relating to biomedical research?

Dr. Varmus: Yes, helping the public understand the National Institutes of Health's (NIH) role in medical research and linking those research results to applications that improve the public's health is a difficult task. However, information dissemination has long been an integral part of NIH's mission, and our institutes, centers, divisions, and offices continue to make every effort to inform the public of new and developing health advances from the NIH. We know through public opinion polls and focus groups that the public supports the crucial role of medical research, but that it does not understand the research process. New activities aimed at increasing the public's understanding of medical research issues and NIH include:

Continued use of the public television medium. In FY 1996, NIH joined with Maryland Public Television to produce two pilot television programs, titled *HealthWeek*, in an effort to inform the public of new and developing health advances from the NIH. We believe the success of those pilots enabled Maryland Public Television (MPT) and the Washington Post Company (WPC) to form a partnership to produce what we expect will be a successful half-hour weekly series on public health and environmental issues. NIH expects to work closely with WPC and MPT.

Regular distribution of *HealthWise*, a new publication primarily aimed at smaller media markets around the country. *HealthWise* contains stories that provide practical health news and information, based on research conducted or supported by NIH, to reporters and editors.

- Enlisting grantees and advisory panel members in efforts to promote public understanding of NIH and its mission around the country. Information kits, entitled *Talking About NIH*, have been developed to aid individuals in giving talks to public groups or conducting media interviews.

- Helping grantees and their home institutions identify actions that will enhance the public's understanding of the impact of NIH's support. Encouraging grantees and their institutions to credit NIH support of their research in public speeches, media interviews, press releases and other documents and activities will help to highlight

NIH's national role and will help grantees be responsive to legislative mandates directing them to acknowledge federal contributions when they publicize their research findings. Recently, various NIH institute directors have written to grantees reminding them of these responsibilities and suggesting various actions they might take to fulfill them.

Developing new communications programs that can be used as models for increasing public awareness of medical research, its benefits, and the research process. For example, the National Cancer Institute has created a multi-year, multi-faceted communications program, called the *Science Awareness Program*, in an effort to change the way the public views science and medical research. While the *Science Awareness Program* is focused on cancer research, the methods used to enhance its partnerships and develop new materials and modes of outreach may prove to be useful models for other institute and center initiatives.

POPULATION RESEARCH

Mr. Istook: Please provide a list of the FY 96 recipients of federal funds (grants and contracts) for "population research".

i. List the amount of federal funds for grant or contract
ii. A brief description of each grant or contract
iii. The Institute supporting that research
iv. The name, zip code, and Employer Identification or Tax Identification number for each recipient (where known)
v. Provide this list on paper and electronically, either in "DBF", "WK1", or ASCII text with delimiters and an explanation of the structure of the file.

Dr. Varmus: In FY 1996, the NIH spent a total of $274.1 million in grants and contracts for population research. The list of projects are provided on paper and as a .WK1 file under separate cover.

[Clerk's Note: Information too voluminous to print.Available in Comm. files]

Mr. Istook: Also, please provide the total amount of funds spent by NIH each fiscal year over the past 6 years FYs (1992-1997) on population research.

Dr. Varmus: This information is summarized on the table below.

National Institutes of Health
Funding for Population Research, FY 1992-FY 1997
(Dollars in thousands)

	FY 92	FY 93	FY 94	FY 95	FY 96	FY 97 Est.
Population Research	$272,656	$278,312	$297,248	$291,115	$299,819	$317,145

CONTRACEPTIVE RESEARCH

Mr. Istook: Please provide a list of the FY 96 recipients of federal funds (grants and contracts) for "Contraceptive Research"(exclusive of population research above):

i. List the amount of federal funds for grant or contract
ii. A brief description of each grant or contract
iii. The Institute supporting that research
iv. The name, zip code, and Employer Identification or Tax Identification number for each recipient (where known)
v. Provide this list on paper and electronically, either in "DBF", "WK1", or ASCII text with delimiters and an explanation of the structure of the file.

Dr. Varmus: In FY 1996, the NIH spent a total of $53.3 million in grants and contracts for Contraceptive Research. The list of projects are provided on paper and as a .WK1 file under separate cover.
(Clerk's Note: Information too voluminous to print. Available in Comm. files.)

Mr. Istook: Also, please provide the total amount of funds spent by NIH each fiscal year over the past 6 years FYs (1992-1997) on Contraceptive Research.

Dr. Varmus: This information is summarized on the table below.

National Institutes of Health
Funding for Contraceptive Research, FY 1992-FY 1997
(Dollars in thousands)

	FY 92	FY 93	FY 94	FY 95	FY 96	FY 97 Est.
Contraceptive Res.	$28,342	$30,525	$40,211	$57,884	$53,325	$55,536

PRENATAL RESEARCH

Mr. Istook: Please provide information on research supported or conducted by NIH on prenatal care to enhance outcomes for children, both physically and psychologically. Please provide a list of the FY 96 recipients of federal funds (grants and contracts) for "prenatal research":

i. List the amount of federal funds for grant or contract
ii. A brief description of each grant or contract
iii. The Institutes supporting that research
iv. The name, zip code for each recipient (where known)
v. Provide this list on paper and electronically, either in "DBF", "WK1", or ASCII text with delimiters and an explanation of the structure of the file.

Dr. Varmus: In FY 1996, the NIH spent a total of $129.7 million in grants and contracts for Prenatal Research. The list of projects are provided on paper and as a .WK1 file under separate cover.
(Clerk's Note: Information too voluminous to print. Available in Comm. files.)

Mr. Istook: Also, please provide the total amount of funds spent by NIH each fiscal year over the past 6 years FYs (1992-1997) on Prenatal Research.

Dr. Varmus: This information is summarized on the table below.

National Institutes of Health
Funding for Prenatal Research, FY 1992-FY 1997
(Dollars in thousands)

	FY 92	FY 93	FY 94	FY 95	FY 96	FY 97 Est.
Prenatal Research	$117,975	$128,525	$125,830	$125,495	$137,342	$144,598

DIRECT AND INDIRECT COSTS

Mr. Istook: Please provide articles from trade publications, correspondence or telephone conversation notes about direct and indirect Administrative costs. Include discussions, correspondence (paper and electronic) with OMB or other interested parties, plus internal NIH memos regarding direct and indirect costs.

Dr. Varmus: Our conversations with OMB, both in person and by telephone, on the subject of Facility and Administrative costs (indirect costs) are captured in two studies in which NIH had a lead role. Attached is a copy of *Report on Indirect Costs* issued Nov. 4, 1994, by the National Science and Technology Council, committee on Fundamental Science, subcommittee on Research and a copy of *Management of Research Costs: Indirect Costs*, May, 1992, from the HHS Working Group on the Costs of research. These two studies include analysis of current practices and proposed improvements in the process of determination of Facility Administrative costs and are attached. I believe that both of these studies have had considerable impact on subsequent revisions to OMB Circular A-21. In addition, a set of suggestions were offered by NIH staff in a meeting at OMB on November 15, 1996. (See Recommendations for Improvements in the Process of Determining Facilities and Administrative Costs dated November 15, 1996, attached). These suggestions were made during the development of alternatives that could be studied as potential future improvements in the process of determining Facility and Administrative costs. Correspondence between NIH and the OMB regarding the implementation of Circular A-21 is also attached.

The most recent publication of the Circular on May 8 1996, included many of the recommendations from these studies and also proposed future modifications in the determination of facility costs and utility costs. Staff have confirmed with OMB that they do intend to publish proposed modifications by July 1, 1997, for public comment with the intent to finalize those changes by July 1998. We do not routinely keep trade publications, although indirect costs are certainly a topic of interest within the science press.

(Clerk's Note: Information provided was too lengthy to be printed and is available in Committee files.)

NIH PRIORITY SETTING

Mr. Istook: Since Dr. Varmus has stated in the hearing that there is no "formal" process by which allocations are made between institutes, or for research on diseases, please describe the informal process by which this is done, and the parties involved in this process and the differing scopes and manner of that involvement.

Dr. Varmus: I am pleased to provide the following overview on priority setting at National Institutes of Health (NIH) for the record:

Priority Setting at The NIH

The ultimate goal of all NIH research is to improve human health. This research, whether conducted in academic institutions, research foundations or hospitals in all 50 States or on the NIH campus, is made possible by a system which fosters both independent thought and collaborative efforts.

For NIH, the process of setting strategic priorities entails examining a broad constellation of public health needs, scientific opportunities, Executive and Congressional interests, and other factors that bear on the course of the Nation's investment in medical research. Although the process is not reducible to a simple flow chart or time line, it takes place at several distinct levels and is occurring all of the time. There are two pivotal levels at which priorities are set: the first is the Institute and Center (IC) Directors and the second, the Director of NIH, with whom ultimate responsibility lies for the course of federally-funded medical research.

Office of the Director, NIH

With a unique and critical perspective on the whole of NIH, the NIH Director is responsible for providing overall leadership to the institutes. This responsibility entails attention to individual institute research programs, with particular emphasis on needs and opportunities for crosscutting efforts. The Director is apprised of each institute's priorities and accomplishments through a well-established system of regular senior staff meetings, NIH interest groups, and briefing sessions with IC Directors. The annual NIH Leadership Forum is a central element of the NIH strategic planning process. This Forum consists of an annual meeting of the NIH Director, ICD Directors, and NIH administrators who review and address major trans-NIH research and management issues.

Advice is also sought from special panels of experts convened to advise the Director on "trans-NIH" issues (for example, gene therapy; the NIH investment in clinical research; the role of NIH's intramural research program; and the effectiveness/efficiency of NIH peer review procedures:) At the NIH Director's level, this bottom-up information

flow converges with top-down discussions with the Department of Health and Human Services (DHHS) and Congress. Because NIH is committed to input from the public, and since Congress is, first and foremost, representative of the public, this dialogue is particularly important.

The Director also assures cross-Institute priority setting by encouraging and expanding inter-Institute collaborations in both planning and research activities. In only a few instances is a single Institute the sole supporter of research into the causes and consequences of a given disease or into potential treatment and prevention strategies. When appropriate, an individual institute will act as the lead Institute for research on a particular disease, disorder, or system, acting to assure NIH-wide coordination and collaboration. Program offices in the Office of the Director are also responsible for some cross-Institute coordination, including research on women's health and minority health, AIDS research, disease prevention and behavioral and social science research. Because there are also many government-wide interagency groups dealing with specific research areas, the institutes co-fund research programs with agencies outside the NIH when the opportunity is available and the need is a high priority for each agency. Examples include the National Cancer Institute collaboration with the Department of Defense on breast cancer studies and the National Heart, Lung and Blood Institute's work with the Health Care Financing Agency to conduct clinical trials of lung reduction surgery in the late stages of emphysema. The NIH is strongly committed to an integrated approach to developing and implementing research priorities which reflect and anticipate broad conceptualizations of illness and health.

Each year, the NIH Director, in partnership with Institute Directors, identifies Areas of Emphasis which show the most promise for addressing public health needs and yielding medical advances that will lead to improvements in human health. Prior to receiving the proposed fiscal year 1998 appropriation level, the NIH Director held a series of one-on-one meetings with Institute Directors to review scientific opportunities. Accordingly, six Areas of Research Emphasis were identified for FY 1998. Five of these were also used in the development of the FY 1997 budget—The Biology of Brain Disorders, New Approaches to Pathogenesis, New Preventive Strategies Against Disease, Genetic Medicine, and Instrumentation and Computers. A new area of emphasis, "New Avenues for Development of Therapeutics" emerged from consideration of Institutes' and Centers' proposals for new initiatives.

The Director holds primary responsibility within NIH for formulating the Agency's annual budget on the basis of extensive interactions with the institutes, DHHS, and the OMB. The Director also works closely with institute program Directors in articulating and justifying priorities through the Congressional Appropriations process. This annual activity allows for ongoing clarification, justification and discussion of NIH priorities with members of Congress. Thus, the budget provides an established framework within which priorities are continually identified, reviewed and justified.

Beyond the process of advice and consultation, and the formulation of the budget request, the NIH Director has access to several more concrete approaches to highlight and supplement priority areas of scientific opportunity and public health need. These include the Director's Discretionary Fund, and the Director's authority to transfer up to one percent of the total NIH budget, both of which are used to start particularly exciting or urgent areas of research during a particular Fiscal Year for which the budget has already been set. Use of these mechanisms typically follows extensive discussions between the NIH Director and the institutes to identify particular research initiatives which reflect NIH-wide priorities.

Institute Planning and Priority Setting

In order to set priorities, the Institute Director seeks the advice of a number of individuals, including institute program staff and the scientific and public members of the institute's National Advisory Council. The Director engages in ongoing discussions with extramural grantees, intramural investigators and the public in order to prioritize research efforts. Staff from the institutes attend working groups with representatives from all over the government and outside to identify common concerns and interests, and to solve problems. Institutes deliberately seek a wide variety of inputs so that many views are heard as priorities for research are established. Advice is specifically sought regarding the urgency, from a public health perspective, of an area of research; the top scientific opportunities; gaps in knowledge which merit special effort; the costs of doing the research assessed against its benefits; economic issues, including the potential effects of the research on quality of life; the scientifically and programmatically appropriate balance between intramural and extramural research; the balance between laboratory research and clinical research; and the selection of mechanisms by which to support research, including regular research grants, program projects, research and development contracts, and centers.

The advice an IC Director receives provides much of the information needed to set research priorities. This advice alone, however, is not sufficient to sustain a dynamic research program. A successful research program depends upon the NIH funding the most meritorious scientific proposals.

The cornerstone of NIH-funded research remains the investigator-initiated research project. These projects emerge from the creativity and expertise of extramural (usually academic) scientists who submit grant applications or intramural scientists who develop projects to be supported. All projects funded by grants undergo stringent review by scientific experts primarily chosen from outside the government. Intramural projects also undergo peer review by a Board of Scientific Counselors. It is these projects that form the backbone of science funded by the institutes and it is the outstanding ideas of scientists that drive the priorities of the NIH.

Ultimate responsibility for the allocation of financial and other resources of the institute rests with the IC Director. After careful consideration of all the factors described above, the IC Director sets the priorities for the institute's activities. A booklet on NIH priority-setting is nearly completed; I will be pleased to forward copies to the Committee.

PRIORITY SETTING AT NCI

Mr. Istook: Please describe the way the National Cancer Institute conducts its formal and informal processes to allocate dollars between the various types of cancer research.

Dr. Varmus: I am pleased to provide the following paper from the NCI addressing this issue:

Priority Setting for the National Cancer Institute

You're asking an important but of course, very difficult question. It is a question we deal with every day. We need to make sure that we're covering all of the areas of cancer research. We shouldn't choose between prevention or detection and treatment and understanding the basic biology. It's a constant juggling, a constant balance that relates to opportunities. When a new opportunity surfaces, researchers propose or initiate new ideas to close in on an opportunity to get a definitive answer. We believe that to be a very good use of funds.

Priority setting is a very dynamic process. We depend upon the larger community to come up with their ideas. The cancer research community across the nation produces proposals that then are reviewed for their quality and for their importance, for what they can achieve. Our approach is to permit the distributed wisdom of the entire scientific community to interact with us, so that we maintain a balanced portfolio. We need to approach this and all of these problems from all possible angles since often we don't know exactly where a new advance is going to originate.

Cancer funds are allocated among many mechanisms of support and are based on the results of significant input regarding current and future plans by the many advisory bodies to the NCI Director.

The NCI's principal advisory body is the *National Cancer Advisory Board* (NCAB). This Presidentially-appointed group works directly with the Institute, advising the NCI Director on issues related to the entire National Cancer Program, including a review of institute programs and scientific initiatives and funds allocated. The NCAB also provides a second level of review for grant applications referred to NCI and assesses the applications with regard to the NCP's priorities.

The NCI also has advisory groups for both the intramural and extramural programs that provide guidance for specific components or functions of the NCI. A *Board of Scientific Counselors* (BSC) reviews and advises Institute leadership on intramural research activities including funding and priority setting for initiatives. The *Board of Scientific Advisors* (BSA) were established last year by the NCI Director to assist him appraising and making recommendations for both the clinical and basic extramural programs and initiatives. To assure that all facets of the community are heard by NCI regarding program priorities and funding, the lay community is represented in addition to leading scientists.

A pair of unique advisory groups to the NCI are the *Intramural Advisory Board & Extramural Advisory Board.* In order to solicit advice from the community of NCI intramural scientists and the scientific and administrative staff responsible for the review, award, and scientific management of the grant programs, the internal Intramural Advisory Board (IAB) and Extramural Advisory Board (EAB) meet regularly to advise on policy and process and serve as information conduits back to the staffs they represent.

The primary decision body of the NCI is the *NCI Executive Committee.* It meets weekly to make major policy and operating decisions for the Institute including funding allocations. The Executive Committee includes the chairs of the IAB, EAB, BSC, and BSA, as well as division directors and other key advisors to the Director. In this way, the extramural community and the internal working scientists and scientific administrators inform and influence NCI policies and actions.

A new family of planning groups and processes will allow the Institute to draw on expertise from outside NCI, involving the cancer community to a greater degree in setting and articulating priorities, and facilitating information exchange.

NCI Director's Working Groups are ad hoc "think tanks" appointed to address key issues in science. Their members include leaders in laboratory, clinical, and population-based research drawn from the extramural and intramural research community, staff of the NIH and other government agencies, members of professional organizations, and interested consumers and patient advocates. Recommendations will provide a framework for Institute strategic planning and for the development of operational plans by NCI divisions.

The initial quartet of Working Groups examines the four scientific areas identified as extraordinary opportunities for investment in the NCI's 1997/1998 Bypass Budget: cancer genetics, preclinical models of cancer, detection technologies, and developmental diagnostics. These four Working Groups have convened to identify strategies for transforming the broad goals articulated in the Bypass Budget into a realistic plan with short and long-term scientific aims and objectives, including implementation strategies and milestones for measuring progress. An additional working group in AIDS-related malignancies, established by the Division of Cancer Treatment, Diagnosis, and Centers, has a similar mission and charge.

Program Review Groups draw on the expertise of the external cancer community to provide in-depth, overarching reviews of broad organizational or trans-organizational programs. Composed of outside experts, the Program Review Groups focus on the effectiveness of a given program, soliciting testimony from NCI staff and representatives of the scientific community. Based on their findings, they issue recommendations on the future structure of the program under study. The Program Review Groups report to the BSA.

Progress Review Groups establish another new scientific review mechanism to address high-priority, cross-cutting areas of cancer research. Progress Review Groups composed of physicians, scientists, and lay advocates will assess the state of knowledge in broad areas of research, such as breast cancer, and identify overarching scientific opportunities and needs. NCI will use the Groups' advice/recommendations to help set and sharpen scientific directions to move the science forward as rapidly as possible.

In addition, the NCI recently established an *Office of Science Policy* to initiate and support the NCI's planning activities and evaluation activities. This office also advises and assists the institute leadership in the areas of science policy and program direction, assessment, analysis and coordination.

AREAS OF RESEARCH EMPHASIS

Ms. Northup: In your budget certain areas of emphasis are listed including research on the biology of brain disorders, pathogenesis, study of disease origins, preventative strategies, to name a few.

How are these priorities selected?

Dr. Varmus: I began identifying Areas of Research Emphasis several years ago as a way of highlighting those areas that show the most promise for addressing public health needs and yielding medical advances that will lead to improvements in human health. These areas of emphasis represent broad categories of National Institutes of Health (NIH)-sponsored research in which scientific advances and accomplishments are expected to occur over several years. Each year, I also request proposals from the Institute and Center (IC) Directors for areas of research that would benefit from special emphasis. The ICs are encouraged to identify and bring collaborative projects to the table; these can be either basic or clinical research projects, but more generally represent a research area that encompasses both basic and clinical research. I then evaluate the proposals and determine those with the highest priority, based on scientific opportunity and public health needs. A new Area of Research Emphasis, New Avenues for the Development of Therapeutics emerged this year, based on the proposals submitted by the Institutes. The remaining five were also identified as Areas of Research Emphasis in fiscal year 1997.

I use a variety of mechanisms to obtain advice and other information to establish the overall, broad priorities for NIH, including encouraging and expanding intra-Institute collaborations. Some of the ways in which I glean information about each institute's specific priorities and accomplishments include regular senior staff meetings, discussions with NIH scientific interest groups, and briefing sessions with Institute Directors.

Ms. Northup: Is there coordination between research project grants and clinical research in these areas?

Dr. Varmus: Medical research is a continuum in which basic science discoveries are translated into clinical applications that advance human health. Scientific advances within the Areas of Research Emphasis may eventually lead to effective treatment and prevention strategies for a number of diseases. The recent achievements in the treatment of infection by the human immunodeficiency virus (HIV) provide a good illustration of the progression from basic science to clinical application. NIH-supported basic research allowed researchers to elucidate the viral life cycle and identify three specific enzymes critical to HIV replication, one of which is HIV protease. NIH-sponsored researchers and industry scientists subsequently determined the crystalline structure of protease, which has been vital to designing effective protease inhibitors. Identification of one of several HIV protease inhibitors by industry scientists led to a preclinical evaluation of that agent

and a Phase I clinical trial of the agent in HIV-infected adults. Four of these inhibitors have subsequently been approved by the Food and Drug Administration for the treatment of HIV infection. NIH continues to be involved in basic, preclinical, and clinical development of new antiretroviral drugs, and priority has been given to NIH-sponsored clinical studies of individual and multi-protease inhibitors in combination with nucleoside antiretroviral agents.

CLINICAL RESEARCH PROGRAM

Ms. Northup: What proportion of the clinical research program is completed at NIH Clinical Center and what proportion is being completed off the NIH campus?

Dr. Varmus: NIH does not have an accurate estimate of the proportion of clinical research conducted at the NIH Clinical Center, compared with what is conducted in extramural programs. The NIH Computer Retrieval of Information on Scientific Projects (CRISP) system captures both intramural and extramural research projects. Using CRISP, projects for FY 1996 are being analyzed according to the definition of clinical research established by the NIH Clinical Research Panel, including patient-oriented research, epidemiological and behavioral studies, as well as outcomes and health services research. Once this analysis is completed, we would be pleased to provide it to the Committee.

FUNDING FOR CLINICAL RESEARCH

Ms. Northup: It seems to me that a larger percentage of the National Institutes of Health (NIH) budget should focus on clinical research, to determine how findings from the research grants actually work in patients. Why is the NIH budget for clinical research limited?

Dr. Varmus: There is no limit placed on the amount of the National Institutes of Health (NIH) budget that may be devoted to clinical research. A balance between basic and clinical research is, however, difficult to achieve. This involves priority-setting by scientific leaders based on the projected benefits associated with a laboratory finding. There are vastly more basic findings that are the product of inspired, creative thinking in laboratories than there are culminations of those findings resulting in translation to practical clinical applications. The NIH remains, however, steadfastly committed to clinical as well as basic research.

Further, using the definition for clinical research developed in FY 1996 and adopted by the Clinical Research Panel, NIH has determined that in FY 1996, with regard to competing extramural awards, 27% of its awards and 38% of associated dollars supported clinical research projects:

	Number of Projects	Percent Competing	Total Dollars	Percent Competing
Clinical Research	2,795	27%	$905,852,246	38%
Clinical Trials[1]	518		$313,435,513	
New & Competing Awards[2]	10,493		$2,361,434,220	
Human Subjects[2]	3,665		$1,139,061,717	

1 Includes: clinical trial, clinical trial phase I, clinical trial phase II/III/IV
2 From NIH Information for Management Planning, Analysis and Coordination database

INSTITUTE OF MEDICINE RECOMMENDATIONS

Ms. Northup: While it is my first year on the Subcommittee, I am aware of the Institute of Medicine recommendations to accelerate the work of NIH in clinical research. Why has there been a delay in addressing these recommendations?

Dr. Varmus: The Institute of Medicine (IOM) recommendations were published late in 1994, and the NIH Director's Clinical Research Panel was established shortly thereafter in the spring of 1995. The Panel began its work by carefully reviewing the recommendations of the IOM report and built its conclusions from that starting point. At the first meeting of the Panel in May 1995, its members heard a presentation from a member of the IOM committee. Thus, as NIH implements the Panel's recommendations, it is responding to the concerns expressed in the IOM recommendations as well.

The NIH Director's Panel on Clinical Research presented its interim report to the Advisory Committee to the NIH Director on December 12, 1996. The panel's interim report contains 11 recommendations that overlap with the recommendations of the IOM Committee. These recommendations range from broad ones, e.g., that NIH foster partnerships with other entities for the support of clinical research, to highly specific recommendations, e.g., that NIH create a clinical research training program for medical students. These recommendations are being implemented in a stepwise fashion, beginning with the medical student training program that will begin in the summer of 1997. Further, the Institute and Center Directors have been asked to review their support of young investigator and mid-career awards for clinical researchers in order to consider mechanisms to fund such investigators. The NIH continues to meet with its partners in clinical research, including specifically representatives of the managed care industry and pharmaceutical companies in efforts to sustain clinical research. The Guidelines for the General Clinical Research Centers have been rewritten in response to suggestions made

by the Clinical Research Panel, and a system has been devised by NIH to collect accurate data on its support of clinical research. At least one recommendation would require Congressional action, i.e., a limited debt reduction program for clinical investigators.

COORDINATION WITH OTHER AGENCIES

Ms. Northup: I noticed in your budget that you are providing funding for research on drug abuse and drug treatment and prevention as part of a coordinated approach to combating drug abuse, and also extending NCI's effort with the ASSIST program as part of a more coordinated effort to stop youth smoking. I agree that our agencies must work together in an effort to address any disease. What other coordinated programs have you initiated and which agencies will you be working with on these programs?

Dr. Varmus: The results of NIH research are used to develop national policy, to inform public education efforts, and improve the access to and the delivery and effectiveness of health care services. Our research and its translation into clinical practice represents a continuum from "bench to bedside." This link between research and practice is strengthened by collaboration and coordination between NIH and other agencies. Examples of coordinated programs and the agencies NIH is working with include:

Expanding Access to Cancer Clinical Trials. NIH (NCI) is continuing to pursue coverage for all phases of cancer clinical trials with health care payor organizations. NIH and the Department of Veterans Affairs (VA) have signed an agreement in which eligible veterans gain access to the full range of studies, including phase I, for cancer treatment, prevention and diagnosis. NIH (NCI) and the Department of Defense have also established an agreement which allows DOD employees with CHAMPUS managed health insurance to enroll in NCI clinical trials. These agreements with the VA and DOD provide veterans and DOD military personnel and their dependents access to research studies of promising therapies while ensuring an adequate number of patients for NCI's clinical research.

Improving Adolescent Health. NIH (NICHD, NIAAA, NCI, NIDA, NIDCD, NIGMS, NIMH, NINR, OAR, OD, OBSSR, and ORWH), other components of HHS, the Centers for Disease Control and Prevention, and the National Science Foundation are collaborating on The National Longitudinal Study of Adolescent Health (Add HEALTH). This study examines the health habits and behaviors of young people, and the contexts in which they occur, to better understand normal and at-risk behavior of teens and to help design better interventions to prevent these behaviors.

Reducing Infant Mortality. NIH (NICHD, ORMH) is supporting a program of community-based clinical trials of interventions to reduce infant mortality, in the District of Columbia. This effort involves 11 collaborating organizations, including universities, the D.C. Government, and local hospitals.

Understanding Developmental Effects of Prenatal Drug Exposure. NIH (NICHD, NIDA) also supports the Maternal Lifestyle Study, a longitudinal, observational study of the sequelae of intrauterine exposure to drugs of abuse, in collaboration with the Substance Abuse and Mental Health Services Administration and the Administration on Children and Families.

Educating the Public About Asthma and its Prevention. NHLBI's National Asthma Education and Prevention Program, a partnership of more than 32 professional, medical, and voluntary health organizations as well as other Government agencies is translating and disseminating the results of NIH-supported asthma research.

Informing the Public About Potentially Toxic Chemicals. NIH (NIEHS) collaborates with the Centers for Disease Control, the Food and Drug Administration, the Occupational Safety and Health Administration, the Environmental Protection Agency, and the Consumer Product Safety Commission in the National Toxicology Program. This purpose of this Program is to provide information to health, regulatory, and research agencies, and the general public about potentially toxic chemicals, as well as strengthen the science base of toxicology.

Improved Technology for Individuals with Hearing Impairments. NIH (NIDCD) and the Department of Veterans Affairs are continuing an innovative collaboration designed to support the development of better hearing aids. NIH (NIDCD) is also collaborating with the National Aeronautics and Space Administration (NASA) and the VA to identify new technologies that may also be applicable to improving hearing aids.

Identifying Risk Factors For and Improving Clinical Management Of HIV/AIDS. NIH (NICHD, NIAID, NIDA) and Health Resources Services Administration (HRSA) are supporting a nationwide study of the natural history of HIV infection and disease in adolescents with and at-risk of acquiring HIV infection, as well as evaluating how to optimize clinical management for affected adolescents.

Improving the Detection of Breast Cancer. NIH (NCI) is collaborating with National Aeronautics and Space Administration (NASA) to facilitate technology transfer of military advances to breast imaging applications and, ultimately, the commercial development of digital imaging systems.

AIDS RESEARCH

Ms. Northup: There is concern in the research community that the focus on AIDS funding is limiting funding elsewhere. Since you can never tell where a cure for a disease may come from (noting discoveries from research on other diseases) why is it your intent to focus so much time and energy on AIDS programs rather than other programs?

Dr. Varmus: HIV/AIDS is still the number one killer of young people between 25 and 44 years of age, and among children age 1-4 years, AIDS is one of the eight leading causes of death. It is true that in past years, a significant portion of NIH budget increases were provided for research into HIV/AIDS. For instance, between 1987 and 1996, NIH's budget increased 77.7 percent. A significant portion of that increase (21.5 percent) was provided for research into HIV. During this period, the immensity of the public health threat and social burdens associated with HIV/AIDS were recognized and substantial funds were necessary to create a new research program on this newly identified disease. As the field has matured, however, and we have developed a knowledge base and cadre of researchers on HIV/AIDS, increases in AIDS funding have been comparable to those for the overall NIH budget. Last year, for example, the NIH budget increased by 6.8% and the increase in funds devoted to AIDS research was 6.4%. For Fiscal Year 1998, the President's budget request for NIH also includes an equal increase of 2.6% for both AIDS and non-AIDS related research.

This investment in AIDS research is producing valuable dividends. New pediatric cases are beginning to decline, due largely to NIH-supported research that discovered and demonstrated the efficacy of AZT in reducing mother-to-child transmission of HIV. Recently, the Centers for Disease Control and Prevention (CDC) reported that AIDS deaths have dropped significantly in the first half of 1996 compared to same period a year earlier. While it is premature to attribute the drop to specific factors, it seems likely that it is due primarily to new prevention regimens and more effective treatments for opportunistic infections. Due to research, Bactrim and other antibiotics have been used to prevent *Pneumocystis carinii* pneumonia and toxoplasmosis in many HIV-infected individuals, rifabutin or clarithromycin has been show to prevent *Mycobacterium avium* complex disease, and 23-valent vaccine has been used to prevent pneumococcal pneumonia. We are also better able to treat opportunistic infections that commonly affect people with AIDS. For example, fluconazole has been shown effective in treating cryptococcal meningitis, foscarnet has proved effective against cytomegalovirus (CMV) retinitis, a combination of pyrimethamine and clindamycin has been show effective in treating toxoplasmic encephalitis, and itraconazole has proved useful in treating disseminated histoplasmosis.

In addition, the combined use of anti-HIV therapies has slowed HIV disease progression and improved the quality of life for many patients, and promising new treatments for HIV-infected patients are also on the horizon. By bolstering the immune system, a protein called Interleukin-2 (IL-2) has demonstrated the potential to improve the health and prolong the life of HIV-infected patients. There is also new evidence that an individual's risk of disease progression can be predicted from the level of HIV genetic material (RNA) detected in the bloodstream. Improved methods of predicting disease progression in HIV-infected individuals will enable health care providers to determine the most appropriate treatment strategies for HIV infected people. Our increased understanding about the relationship between treatment history and the effectiveness of specific anti-HIV drug regimens will also be useful to health care provided in designing individualized treatment strategies for their patients.

While budget limitations will always force difficult and complex choices in medical research funding, research targeted at specific diseases such as AIDS will yield information relevant not only to AIDS, but also to many other seemingly unrelated diseases. There are many examples of this type of "crossover." For instance, research targeted at AIDS has advanced our understanding not only of AIDS, but also of cancer, autoimmune diseases, Alzheimer's disease, various neuropsychiatric disorders, encephalitis, and meningitis.

CONGRESSIONAL EARMARKS

Ms. Northup: Similar to my previous question, I would like you to comment on the earmarking of funding for disease oriented science which occurs at NIH. I know sometimes Congress is responsible for these earmarks and I would like to know if you have any comments regarding the prevalence and consequences of these earmarks?

Dr. Varmus: Although the use of earmarks has been decreasing in the last few years, any approach that emphasizes disease-specific earmarking disrupts the process of allocating medical research dollars based on scientific opportunity and public health need. The NIH relies heavily on non-directed, investigator-initiated research to generate the most creative ideas for advancing scientific knowledge about human health and disease. The funding of meritorious research on a competitive basis has provided the foundation upon which the NIH has improved the Nation's health across many disease categories.

Earmarks may have serious consequences on the rate at which human health discoveries are made. Disease-specific earmarking fails to take into account all the factors that are considered in selecting the most meritorious research projects, but tends to focus on only one or two factors. For example, earmarking based on the number of individuals affected by a disease would result in funding of research focused on common diseases, but might have limited impact on overall health and survival. In this case, much research would be done on the common cold and allergies but little on childhood cancers. Earmarking based on number of deaths would neglect chronic diseases that strike at an early age and produce long-term disability and high costs to society. So, a great deal of research would be done on heart disease and cancer but little on mental illness and arthritis. Earmarking based solely on immediate dangers to public health may divert funds from areas of research of much broader long-term impact. This choice would mean, for example, that a great deal of research would be done on AIDS and tuberculosis and little on Parkinson's disease and asthma. Funding according to disability or economic cost raises questions about how precisely disability or economic costs can be quantified, and whether only the direct costs of medical care or the indirect costs such as lost productivity in the work force should be included. Making this choice would underfund diseases that result in a short illness and rapid death. For instance, this would provide a great deal of funding for Alzheimer's Disease and muscular dystrophy, but little

for stroke or certain types of cancer. All of these criteria for weighing health needs would underfund research on rare diseases, research which has taught us so much not only about the rare diseases themselves, but also about normal human biology and about other diseases and new approaches to treatment.

Disease-specific earmarking also fails to take into consideration the role of basic research in solving health problems. Tangible results of scientific inquiry cannot always be defined, predicted, or assigned to a disease. Research in one area has often led to dramatic improvements in treatment in a seemingly unrelated area. Isolation of the colon cancer gene, for example, depended on over 30 years of developing techniques to localize genes on human chromosomes and to amplify them in bacteria. The function of the colon cancer gene was rapidly understood because the gene is closely related to bacterial and yeast genes that protect the integrity of DNA by repairing mutations in these other, much simpler organisms. In this way, over 20 years of support for basic studies of DNA damage and repair unexpectedly revealed a new and important mechanism for causing cancer, a mechanism that is likely to have a role in cancers arising in many other organs.

The process of planning and allocating funds is complex and must take into account all of the factors summarized above. Earmarks impose obligations that have not been considered in the overall, carefully thought out funding priorities by the Institutes and the NIH as a whole.

RESEARCH TRAINING

Ms. Northup: Please provide more details about the research training activities in NIH. Can you comment on the current state of training programs for future scientific researchers?

Dr. Varmus: The NIH supports a number of different extramural and intramural training and career development activities for graduate students and postdoctorates in biomedical and behavioral sciences. Some of the larger programs are listed below. We believe these programs continue to support high quality training experiences. In order to ensure that trainees and fellows are being adequately prepared for productive research careers, the NIH has launched a comprehensive career outcome study. Results from this study should become available over the next two years. As required by Section 489 of the Public Health Service Act, the NIH also asks the National Academy of Sciences (NAS) to examine the size and nature of these programs every four years. The next report in this series is expected early in fiscal year 1999.

EXTRAMURAL PROGRAMS

National Research Service Award: This program supports research training experiences for approximately 8,000 predoctoral students and about 7,000 postdoctorates at academic medical centers and other research institutions around the nation. This support is provided either through awards to an institution in the case of training grants or

through direct awards to the individual in the case of fellowships. The National Research Service Award program has been identified by the National Academy of Sciences in its 1995 report *Reshaping Graduate Education* as a model to be adopted by all Federal graduate training programs.

Career Development Awards: The NIH uses career development awards to support research experiences for approximately 1600 physicians and dentists who typically have already completed a clinical residency. These awards support a period of intensive didactic and mentored research experience necessary to launch an independent research career.

INTRAMURAL PROGRAMS

Clinical Associates: The NIH Intramural Programs support approximately 161 physicians and dentists who participate in clinical and laboratory research training that includes primary patient care responsibilities. These programs are accredited by the American Council of Graduate Medical Education or by boards in their respective disciplines.

Intramural Clinical Research Training Initiative: The NIH offers a core curriculum in clinical research composed of four modules that cover scientific, ethical, legal, and social issues relevant to clinical research for approximately 250 students.

Intramural Research Training Award (IRTA): The IRTA was established to enhance the research capabilities of promising postdoctoral scientists in the early stages of their postdoctoral careers. Fellowships may be awarded to candidates with the Ph.D., M.D., D.D.S., D.M.D., D.V.M. or equivalent degrees. Candidates must not have had more than five years of relevant postdoctoral research experience at the time of appointment. Currently, 1,411 individuals are supported by IRTAs.

NIH Intramural Clinical Research Loan Repayment Program for Disadvantaged Investigators: The NIH has established a program of educational loan repayment to attract clinical researchers from disadvantaged backgrounds. The program may pay up to $20,000 per year towards a participant's outstanding eligible educational debts. Concurrent with the loan repayment, participants agree to conduct clinical research as NIH employees for a minimum of two years. It is anticipated that an additional 15 physicians will be recruited in FY 97.

Research Associates: These training appointments are used by physicians, dentists, and research doctorates who are interested in a research career that does not include clinical responsibilities. At the current time, there are approximately 35 clinicians and 90 Ph.D.'s enrolled in this program.

Senior Staff Fellows: This position is used by research doctorates who are seeking biomedical laboratory research training in the intramural programs. Individuals who enter this program have completed three or more years of intensive postdoctoral research training. Approximately, 320 individuals with the Ph.D. occupy these positions at the current time.

Visiting Associate/Visiting Fellowships: These fellowships offer foreign scientists the opportunity to receive further research training or to conduct research in their specialties at the NIH. There are approximately 295 Visiting Associates and 997 Visiting Fellows at the present time.

ADMINISTRATIVE BURDENS ON GRANTEES

Ms. Northup: I know the Subcommittee in the past has focused on the administrative burdens which accompany NIH grants. It is my understanding that the extramural community has pointed out ways in which duplicative rules and regulations divert time and resources away from productive laboratory work.

Are you taking these comments into consideration as you focus on streamlining your activities?

Dr. Varmus: NIH shares the concerns of the extramural community regarding the burden of rules and regulations on research institutions and investigators. Under the auspices of the National Performance Review, NIH has undertaken numerous activities to reduce unnecessary administrative burden related to extramural programs, particularly in areas that have been identified by the extramural community. For example, beginning in fiscal year (FY) 1995, NIH implemented the Streamlined Noncompeting Award Process (SNAP), which greatly streamlined and reduced annual reporting requirements for 64 percent of NIH awards, thus saving time for investigators that can be devoted to research. An NIH effort to reduce duplicate submission of information is the creation of the Institutional and Professional Profiles, components of NIH's Electronic Research Administration system that are currently being developed and tested. These systems will allow standard data elements pertaining to research institutions and investigators to be collected and maintained in an electronic system, thus eliminating the need to provide the information repeatedly in every grant application and report submitted to NIH. In addition to these efforts to streamline administrative requirements, NIH continues to work with grantee institutions to assist them in complying with federal requirements in a cost-effective way. In FY 1996, the DHHS responded to the House Commerce Committee regarding the costs of regulation and other administrative procedures. This included the response from the NIH. It was noted that most HHS rules relate to the proper spending of Federal funds by our grantees and contractors. We require, for example, that our grantees have financial management systems in place to track the spending of the taxpayers' dollars. As another example, we require that some types of health care providers meet key safety standards to protect our clients.

Ms. Northup: For example, do you make any recommendations to researchers on how to reduce compliance costs associated with hazardous waste disposal or cost accounting standards?

Dr. Varmus: We have not made any specific recommendations to grantees regarding costs associated with hazardous waste disposal or the cost accounting standards.

COLLABORATION WITH THE DEPARTMENT OF DEFENSE

Ms. Northup: The last few Congress have provided funding for medical research within the Department of Defense in areas such as prostate cancer and breast cancer. Does NIH recognize DoD projects as valid research?

Dr. Varmus: NIH does indeed recognize DoD projects as valid research. The DoD has developed a high-quality breast cancer research program since funding began in 1993, closely adhering to the recommendations of an Institute of Medicine panel convened expressly to advise the DoD on establishing its Breast Cancer Research Program. A 24-member Integration Panel, which is responsible for advising the DoD on the overall direction of the Program and its investment strategy, provides a second-level of review for grants, much as does NCI's National Cancer Advisory Board. The program, especially most aspects of the scientific review of applications and priority setting with regard to funding decisions, has essentially followed the NIH model. The program identified and engaged scientists to serve on peer-review panels resembling NIH-type "study sections." It has appointed Executive Secretaries for each panel, many of whom are former NIH Executive Secretaries or other NIH extramural program staff members, to oversee the study section meetings and prepare summaries of the reviewers' comments — "pink sheets". The Executive Secretaries also prepare review summaries for the Integration Panel and assign grant applications to the appropriate study section for review.

Ms. Northup: Is NIH coordinating with the research which is coming from DoD projects?

Dr. Varmus: NCI has maintained close contact with the DoD program since its inception. There is an NCI representative on the Integration Panel, and other NCI scientists have served as members of many of the scientific review panels and as ad hoc consultants to the Integration Panel at several programmatic meetings. Using NCI database resources, NCI has performed a portfolio analysis of all its grants and contracts having a breast cancer component. This information includes the number of active grants and contracts and the level of funding in each of the tracking categories used by the DoD's grants administration unit. This information is also provided to members of the

Integration Panel at the yearly meetings when grant funding recommendations are made to the DoD. The purpose of this information sharing is to avoid unnecessary scientific overlap and duplication and to maximize resources for breast cancer research for both NCI and the DoD Breast Cancer Research Program.

The NCI has recently established a Breast Cancer Program Review Group. The Review Group will examine the field of breast cancer research and the current NCI efforts in this field. The results of this analysis will be made available to the DoD Integration Panel.

The NCI and DoD have ongoing collaborations on breast cancer genetics research. One such collaboration effort is the Breast Cancer Genetics Research Initiative. The goal of this initiative is to ensure that research projects funded by NCI and DOD will complement each other and be consistent with the overall breast cancer program objectives of the National Cancer Program. The initial meeting between NCI and DOD resulted in the establishment of four proposed working groups: Genetics and Prevention, Transplantation / Vaccine, Lung Cancer (a predominant site of breast cancer metastasis), and Molecular Pathology / Diagnostics. As part of this last group, Phase I and II clinical trials will focus on the more predominant tumors, breast, prostate, and lung. A follow-up meeting with participants from NCI, NIH, and DOD will take place in June.

Currently, the NCI is also collaborating with the National Naval Medical Center (NNMC) Breast Care Center and the Keesler Air Force Base to initiate activities involving evaluating breast cancer genetics including the identification of susceptibility genes, genetic counseling and education.

Ms. Northup: Why do researchers claim that there is less bureaucracy in dealing with DoD to obtain funding, than there is with NIH?

Dr. Varmus: It is possible that it is not bureaucracy that is the issue but rather the brevity imposed by the DoD program on grant applications: for training/recruitment and Innovative Developmental and Exploratory Award (IDEA) proposals, there is a strict 5-page limit, and for proposals in other categories, it is 10 pages. This compares with the 25-page limit for most NIH grant applications.

The DoD also deals with considerably fewer grants than does the NIH. Each system has pros and cons. Shorter grant applications perhaps take less time to write and review. Larger grants provide more information on which reviewers can base their selections.

Ms. Northup: Do you think this perception is diverting researchers to DoD?

Dr. Varmus: Most researchers obviously believe that their work is worthy of grant support. Given that the NIH funds only about one in four grant applications, researchers look for alternative funding mechanisms for breast cancer research. These

would include the DoD as well as other sources including the Komen Foundation and the American Cancer Society. I would not characterize this as "diversion" but "diversification". It is not uncommon for the same researchers to seek support from multiple funding sources.

FIVE YEAR BUDGET

Ms. Northup: What is the five year projection for your agency?

Dr. Varmus: The five year projection in the President's FY 1998 Budget Request for the National Institutes of Health is as follows (dollars in millions):

Fiscal Year	Amount
FY 1998	$13,078
FY 1999	13,132
FY 2000	13,186
FY 2001	13,240
FY 2002	13,294

Ms. Northup: Do you see any reduction in the 5th year?

Dr. Varmus: No, there is no reduction in the 5th year.

HUMAN EMBRYO RESEARCH

Mr. Obey: Currently, the rider in our appropriations bill bans NIH from conducting any human embryo research. Many people believe this has led to a total lack of any acceptable ethical standards in this country that otherwise would have been developed by NIH and been generally applied in privately funded research as well. The current ban would also apply to cloning humans.

I realize that the President has asked the National Bioethics Advisory Commission to consider whether federal policies relating to human embryo research should be reconsidered in light of the recent sheep cloning experiments. How active should Federal policy be in regulating this type of research, especially the legal and ethical concerns in privately funded research which is now largely unregulated?

Dr. Varmus: Non-human, animal cloning research has the potential to yield knowledge that can contribute to improving human health and the quality of life. For example, the recent advances in sheep cloning could be instrumental in the development of new methods to produce large amounts of human therapeutic proteins in sheep's or cow's milk, and in the development of much needed animal models for studying human diseases, such as cystic fibrosis. The sheep cloning experiments also have the potential to increase our understanding of another important area--the study of how genes are turned on and off. The ability to analyze and ultimately to direct this process could eventually lead to the reprogramming of human cells to replace bone marrow destroyed by chemotherapy, to treat burn victims with transplants of skin derived from their own cells, or to treat other diseases.

There is great public concern that the recent advances in animal cloning could open the door to cloning humans. Most scientists concur that human cloning faces significant scientific barriers. As important, human cloning also raises profound ethical questions. As was stated in the report of the Human Embryo Research Panel, the cloning of human beings would be unacceptable for Federal funding. The President's Executive Order ensures that no human cloning will be attempted using Federal funds until the ethical issues can be fully considered by the National Bioethics Advisory Commission (NBAC). The President also urged the entire scientific community, including the private sector, to adopt a voluntary moratorium on cloning of humans until the NBAC fully discusses the ethical issues involved. Proposed restrictions on human cloning should be considered extremely carefully to ensure that the beneficial biomedical and agricultural research applications of this technology are not also prohibited.

PIPELINE FOR YOUNG INVESTIGATORS

Mr. Obey: In 1994, the National Research Council issued a report raising concerns that we are losing the pipeline of young investigators. They documented a reduction in the total number of grants to young investigators under age 36 from 1,308 in 1985 to 527 in 1993. What are the comparable number of young investigators funded in 1996?

Dr. Varmus: The data reported by the National Research Council (NRC) represented the number of competing individual research grant awards made to principal investigators aged 36 and under in FY 1985 and in 1993. The comparable number for FY 1996 is 475. However, it is important to note that these data represent only the competing awards and exclude the non-competing, or continuation awards. Moreover, individual research grants represent only a part of the research project grants (RPG) portfolio and the data indicated that young investigators received other RPG awards as well. Thus, a more complete picture of support showed that 1,453 RPG awards were made to young investigators in FY 1996. The comparable number of awards was 3,593 in FY 1985 and 1,949 in FY 1993.

The trends observed in the 1994 report from the Commission on Life Sciences of the National Academy of Sciences, *The Funding of Young Investigators in the Biological and Biomedical Sciences* appear to be continuing. The median age of first-time applicants for NIH research support continues to increase and is now about 39 years. This does not mean, however, that the number of applications from new investigators has decreased. On the contrary, it has gone up, on average, so that it is now 15 percent higher per year than in 1980. In addition to serving as principle investigators on NIH awards, young investigators also participate as co-principle investigators and this is an added measure of NIH support to this population.

Mr. Obey: Can you tell us what the NIH is doing to respond to this problem, and tell us if you think it is adequate, or does more need to be done?

Dr. Varmus: Although the age of the NIH applicant pool continues to increase, it is not clear what impact these trends have on the nature or the quality of the research sponsored by the NIH or on the life-time productivity of young biomedical scientists. It is also not clear that changes in NIH funding policies could reverse this trend. Nevertheless, we have asked the Commission on Life Sciences to conduct a follow-up study in order to identify root causes and to propose interventions if necessary. We expect a report to be issued later this year.

CAP ON MANAGEMENT AND SUPPORT COSTS

Mr. Obey: Although the budget was increased by $819 million for FY 1997, the Committee specifically froze the budget for research management and support. Describe any problems this cap has presented for individual institutes, centers or divisions.

Dr. Varmus: The institutes are pursuing several strategies to constrain Research Management and Support (RMS) costs to the FY 1996 level. Some are not filling existing vacancies or terminating non-permanent personnel, such as those in the Stay-in-School program. Use of overtime, promotions, bonuses, and staff training may be restricted. Travel, including site visit travel to monitor and review grantees and contractors may also be reduced. Reinvention efforts, heavily dependent on the increased use of automation, may be delayed by reductions in the purchases of computer hardware and software. New publications for the public and health professionals may be curtailed or eliminated, as will many science-based workshops, conferences, and town meetings.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS WORKING GROUP

Mr. Obey: An outside review of the Human Genome Project's ethical, legal and social implications (ELSI) Working Group has recently issued a report recommending better coordination among institutes on research ethics in genetic studies to avoid possible inconsistent policies. The report recommended that the Director of NIH establish an ongoing process for communication and coordination that would build upon the ELSI efforts at the National Center for Human Genome Research, and provide information, guidance and oversight for all NIH intramural and extramural research. What are your plans for acting on that recommendation?

Dr. Varmus: NIH is forming an internal work group to devise options for implementation of the ELSI Working Group recommendation to have NIH-wide coordination of these issues, including ELSI concerns that have implications for the design, methodology, and conduct of overall NIH research; genetics research which raises a range of ELSI issues such as informed consent, testing of minors, and confidentiality; oversight of research quality in accordance with recognized ELSI principles and concerns; consistency in standards for the conduct of research across NIH; avoiding duplication of effort; and developing consistent policies. It is also important to recognize that the ELSI Working Group recommendations include establishment of an HHS-level Advisory Committee on Genetics and Public Policy which would serve as another level of oversight group for all of these efforts.

RESEARCH RELATED TO MINORITIES

Mr. Stokes: The NIH programs funded by this committee are absolutely essential to improving, prolonging, and protecting the health and well-being of the American people. And, as you are keenly aware, the health of African Americans and other minorities lags dramatically behind that of the general population. Can you update the Subcommittee with respect to the NIH's research agenda as it relates to minorities?

Dr. Varmus: Because the NIH recognizes that minorities at nearly all stages of life suffer poorer health and higher rates of premature death than members of the majority population do, a series of multi-year research studies aimed at improving the health of minority populations and developing protocols for intervention in health behaviors which affect the longevity and quality of life of minorities were initiated in 1992. This effort, as you know, is called the Minority Health Initiative (MHI) and is administered by the Office of Research on Minority Health (ORMH). This project also has a component designed to prepare minority scientists for careers in biomedical sciences. These programs are initiated by the institutes, are peer reviewed, and administrated by the institutes. The MHI provides total or supplemental funding for these programs.

In FY 1997, the MHI will continue to invest in studies of issues related to extending the life-span and address the major health problems experienced by minority Americans. Programs supported include those that will improve prenatal/infant health in cooperative community-based settings and interventions, as well as studies of the fetal alcohol syndrome in minority infants. Investigations of childhood/adolescent health problems encompass the areas of prevention of lead poisoning, health behavior research, research on HIV infection and AIDS in adolescents, and alcohol and drug use in adolescents. Research in adults includes studies of cancer, diabetes and obesity, hypertension, cardiovascular diseases and stroke, asthma, visual impairments, alcohol abuse and alcoholism, and a number of mental disorders.

While most of the Institutes and Centers also fund and manage their own portfolios of research training activities on minority health independent of the MHI, the ORMH coordinates these studies to assure that the health research agenda is on target. The ORMH has underway a major assessment/evaluation. As with all NIH programs, this has been an ongoing process to ensure that, if an initiative is effective and providing important results, it is sustained. On the other hand, if it is found that an effort is not useful, ORMH attempts to use the evaluation process to bring about changes so that these programs work as intended. A successful health research agenda can only be effective with such a rigorous evaluation. The minority research training initiatives also undergo this type of evaluation.

FUNDING FOR NIH

Mr. Stokes: What was the funding level appropriated for the National Institutes of Health (NIH) in FY 1996 and FY 1997, and what was the percentage increase for each of those years? What was the dollar amount of the increase for each of these years?

Dr. Varmus: The following table addresses your questions:

Funding for NIH

Dollars in thousands

	Fiscal Year 1996	Fiscal Year 1997
Appropriation	$11,927,562	$12,740,843
Percent change from previous year	5.17%	6.81%
Dollar change from previous year	$586,721	$813,281

FUNDING FOR THE OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: With regard to the Office of Research on Minority Health (ORMH), in FY 1996 and FY 1997, what was the NIH's Allocation to the ORMH? And what was the percentage increase for each of those years?

Dr. Varmus: The NIH allocation to the ORMH is shown below:

Office of Research on Minority Health
Dollars in thousands

	Fiscal Year 1996	Fiscal Year 1997
Appropriation	$8,920	$9,444
Percent change from previous year	-.25%	5.87%

Mr. Stokes: So, in FY 1997, the budget remained relatively flat for the ORMH. Is that correct? What is the percentage increase in the FY 1998 budget request for ORMH? And how does that compare with the increase requested for the NIH in total?

Dr. Varmus: The ORMH budget increased by 5.9 percent over that for FY 1996. The increase proposed in the FY 1998 budget for the ORMH is 1.1 percent. This compares to a proposed aggregate NIH increase of 2.7 percent in FY 1998.

FUNDING FOR THE OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: What was the budget request for the Office of Research on Minority Health (ORMH) at each stage of the budget formulation process?

Dr. Varmus: The NIH budget was formulated at the aggregate level until the OMB submission. In the OMB submission the ORMH was to be funded at $9.4 million.

Mr. Stokes: Also, what was the NIH professional judgment budget for the office in FY 1997 and FY 1998?

Dr. Varmus: The NIH professional judgment budget is not formulated to the office level.

Mr. Stokes: How do you arrive at the professional judgment figure? And what factors are used to establish the bottom line for the program?

Dr. Varmus: The NIH professional judgment budget is put together understanding that NIH has the responsibility to fund the highest quality research. Therefore, NIH is not only engaged in developing a budget without regard to budget constraints, it is also concerned about the science that can be supported with the projected funds. The FY 1998 professional judgment budget for NIH is $13.9 billion.

Mr. Stokes: Please include in the record a table displaying NIH funding by ICD for research in minority health and in women's health for each of the last five fiscal years and the FY 1998 budget estimate?

Dr. Varmus: The following table reflects women's health funding:

Women's Health Research

Dollars in thousands

	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998
NCI	$366,195	$462,840	$470,400	$487,720	$500,256
NHLBI	204,288	194,750	202,756	214,900	220,100
NIDR	14,056	18,559	18,831	20,143	21,047
NIDDK	199,500	205,000	213,100	224,700	228,900
NINDS	48,934	50,742	50,050	52,483	53,692
NIAID	59,420	71,432	82,701	86,009	87,729
NIGMS	5,943	11,352	15,146	15,930	16,288
NICHD	173,724	182,535	178,760	190,200	195,000
NEI	7,088	7,609	7,890	8,384	8,582
NIEHS	40,043	46,059	51,499	53,816	55,162
NIA	46,567	48,109	52,416	54,500	55,000
NIAMS	88,628	110,156	113,801	120,330	123,420
NIDCD	5,508	5,397	5,801	6,235	6,431
NIMH	57,001	101,402	120,131	128,818	135,108
NIDA	64,509	67,754	70,608	75,340	80,400
NIAAA	28,167	35,851	39,590	41,300	43,500
NINR	13,697	14,200	13,006	13,900	14,250
NHGRI	6,851	14,488	16,051	16,656	16,915
NCRR	33,836	35,883	37,944	40,682	41,528
FIC	1,548	2,010	2,044	2,138	2,153
NLM	n/a	n/a	n/a	n/a	n/a
OD	69,325	69,420	69,224	70,705	68,920
Total, NIH	1,534,828	1,755,548	1,831,749	1,924,889	1,974,381

The next table displays minority research and training programs:

Minority Research and Training Programs
Dollars in thousands

	FY 1994	FY 1995	FY 1996	FY 1997	FY 1998
NCI	$79,694	$80,657	$108,905	$112,629	$116,000
NHLBI	136,884	145,207	149,122	158,100	161,925
NIDR	10,732	14,144	13,894	14,960	15,488
NIDDK	61,700	78,100	78,096	82,200	84,000
NINDS	31,040	32,581	30,854	32,705	32,970
NIAID	138,987	139,707	144,298	150,071	153,071
NIGMS	58,147	63,238	66,625	67,581	68,345
NICHD	120,129	131,850	132,353	140,800	144,300
NEI	24,131	23,084	23,320	24,780	25,364
NIEHS	9,771	13,917	14,756	15,351	15,745
NIA	33,718	35,147	37,954	39,100	39,200
NIAMS	23,057	26,199	27,808	29,519	30,249
NIDCD	6,959	8,639	8,688	9,304	9,620
NIMH	168,091	189,914	210,435	226,070	236,258
NIDA	62,386	64,211	66,328	70,800	75,500
NIAAA	21,677	22,656	29,677	31,951	32,906
NINR	9,937	11,429	11,002	11,775	12,077
NHGRI	562	385	2,715	3,095	3,156
NCRR	58,984	62,523	49,557	50,890	50,693
FIC	575	575	575	575	575
NLM	785	800	832	803	821
OD	64,607	67,133	71,394	72,241	72,970
Total, NIH	1,122,553	1,212,096	1,279,188	1,345,300	1,381,233

ORMH CO-FUNDING

Mr. Stokes: You just recently provided me a package of NIH materials which give an overview of how the Office of Research on Minority Health plans to spend FY 1997 dollars by Institute and the number of projects supported. It appears that the Office of Research on Minority Health is supporting more programs and activities than in previous years. What impact does the relatively flat budget have on ORMH's ability to effectively implement the minority health initiative and to effectively operate the office? Are the Institutes providing a greater share of the funding of these projects so as to allow the ORMH to more efficiently meet its commitments?

Dr. Varmus: In FY 1997 the increase in funds allocated to the Office of Research on Minority Health (ORMH) was 5.9% above the level for FY 1996. This is consistent with the overall increase for the rest of the NIH. In FY 1998, the budget request increases the funds for ORMH by 1.1% which, although lower than the overall increase of 2.6% for NIH as a whole, is higher than that for the Office of the Director, overall. This relatively flat budget will allow the ORMH to continue to support important projects related to the health concerns of minority projects and the effort to prepare minority students for biomedical research careers, albeit at a somewhat slowed pace.

It should be noted that many of the Institutes and Centers (ICs) are collaborating with ORMH as well as providing funds for a number of important initiatives so that the NIH, as a whole can provide considerable funds for health-related projected aimed at minority populations. It is important to understand that NIH intended, from the establishment of ORMH, that it would provide but a portion of support for these activities which the ICs also committed funds. In many cases, there is co-funding and, often, the ORMH starts a project which, once underway, is assumed by an IC.

Mr. Stokes: Please provide for the record, a list of minority programs at NIH, by Institute, that are jointly sponsored by the ORMH and the Institutes, Centers, and Divisions, and include a breakout of ORMH and Institute, dollars for each. Also provide a list of the minority projects conducted by the Institutes, not in partnership with the ORMH, and the dollar amount for each of these projects.

Dr. Varmus: Provided under separate cover are tables that list the minority programs at NIH, by Institute, that are jointly sponsored by the ORMH as well as programs/projects supported independently by the ICDs. A breakout of ORMH and Institute dollars is provided by each. The third and final annual round of project approvals scheduled for FY 1997, will result in additional projects being funded.

(Clerk's Note: Information submitted was too lengthy to be printed. Available in Committee file.)

MINORITY INTERNATIONAL RESEARCH TRAINING PROGRAM

Mr. Stokes: Like the MARC and MBRS programs, the committee takes pride in the Minority International Research Training Program directed by the Fogarty International Center. The Institutions participating in the program have expressed excitement and strong support for the program. So, you can imagine how concerned I was to see, in the material that you provided to my office, that the funding for this effort in FY 1997 is being cut in half.

Is the program no longer viable, what is the rationale for this dramatic cut?

Dr. Varmus: Viability was not the primary determinant in the decision to reduce funding for the MIRT program from the MRI. Since we implemented the MIRT program as a pilot just over four years ago, it has grown substantially. The program started with a budget of $2.5M in FY 1993 and in FY 1996 the budget had expanded to

$7.75M--a three-fold increase and over 10% of the total MRI budget. We believe that we need to intensify research in other high-priority research and training areas affecting minorities such as prostate, colorectal, and breast cancer, genetics and epidemiology of hypertension, chemical dependency, AIDS, diabetes, and infant mortality. After careful consideration, the budget for the MIRT program was reduced by about 50% for FY 1997. In addition, the planned FY 1997 competition for new and competing renewal applications has been postponed to give us an opportunity to take a careful look at the magnitude of our international research training efforts in relation to other competing minority health priorities.

Mr. Stokes: What impact is this going to have on these programs?

Dr. Varmus: The most immediate response will be on program activities that would occur in the summer of FY 1998. In addition to reducing the number of new trainees, the noncompeting programs will also take a modest reduction. The programs in their last year of funding, including those with no-cost extensions and current bridge awards, will be given one-year interim or "bridge" funding.

Mr. Stokes: Have the current recipients been advised, and have they advised you as to what impact this will have on their programs?

Dr. Varmus: The current MIRT grantees have been advised of the postponement of the FY 1997 competition for new and competing renewal applications. They have also been advised that the current level of funding for the MIRT program was limiting the level of support for other high priority areas of minority health. MIRT program directors are also aware that their programs will operate at a reduced level in FY 1998. The extent to which individual MIRT programs will be reduced is unknown until we can receive an accurate accounting of unobligated funds among the current MIRT programs. Noncompeting programs have not had the opportunity to advise us as to how the reduction in budget might impact their programs; they only received formal notification on the status of the MIRT program the week of March 4.

Mr. Stokes: What are you proposing in FY 1998 for the Minority International Research Training Program?

Dr. Varmus: The future of the MIRT program will be determined with guidance from an ad hoc group of extramural scientific experts, and it is anticipated that the next request for applications (RFA) will be published later in the current fiscal year or early in FY 1998. It is anticipated that the RFA will be released in time to allow the most meritorious programs to receive support for activities that would take place largely in the summer of 1998. At this time $2.5M has been allocated for the MIRT program in FY 1998.

MINORITY HEALTH STANDING ADVISORY COMMITTEE

Mr. Stokes: The Office of Research on Minority Health has now been a part of the NIH for almost seven years. Do other offices under the Office of the Director have standing advisory committees?

Dr. Varmus: Yes, several offices in the Office of the Director have standing advisory committees.

Mr. Stokes: What about the Institutes and Centers, do they have standing advisory committees?

Dr. Varmus: Yes, the Institutes, Centers, and Divisions have standing advisory committees. The National Institutes of Health (NIH) manages several types of federal advisory committees that furnish expert advice to the NIH Director and staff to accomplish the mission of the NIH and maintain the public trust. The legislative authority for the creation and operation of the NIH's advisory committees is the Federal Advisory Committee Act. This Act authorizes the use of committees, boards, commissions, councils and similar groups to advise officers and agencies in the Executive Branch of the Federal Government. Authority for managing these committees is also promulgated in the Public Health Service Act and the Government in the Sunshine Act. The types of advisory committees managed by the Institutes, Centers, and the Office of the Director, include initial review groups, special emphasis panels, boards of scientific counselors, program advisory committees, and national advisory councils.

Mr. Stokes: What is the purpose of such committees?

Dr. Varmus: Initial review groups and special emphasis panels provide scientific and technical merit review, which is the first level of peer review, of research grant applications and contract proposals. Boards of scientific counselors review and evaluate the research programs and investigators of the intramural laboratories. Program advisory committees advise on specific research programs, future research needs and opportunities, and identify and evaluate extramural initiatives. National advisory councils perform the second level peer review for research grant applications and offer advice on policy and program development.

Mr. Stokes: Where does authority reside for making appointments to these committees?

Dr. Varmus: The authority for making these appointments resides in the Public Health Service Act. The Director, NIH, appoints members to most of NIH's advisory committees. The President appoints members to two committees: the President's

Cancer Panel and the National Cancer Advisory Board; the Secretary appoints members of the national advisory councils; and, in a few cases, Institute or office directors are authorized to appoint members to a committee.

Mr. Stokes: Last year, this Subcommittee urged the NIH to establish a standing advisory committee to the Office of Research on Minority Health and to report back to the subcommittee on the progress of this action. What is the status of the Office of Research on Minority Health Standing Advisory Committee?

Dr. Varmus: The Director, NIH, has the authority to establish the committee. A charter for the Advisory Committee on Research on Minority Health is being drafted. I have signed the charter establishing the committee and soon the members will be appointed.

INSTITUTE OF MEDICINE STUDY

Mr. Stokes: Last year's Senate report that accompanied the FY 1997 appropriations bill included language calling for the Institute of Medicine to conduct a review of the status of NIH research on cancer among minorities and the medically underserved. What is the status of that study and when is it expected to be completed?

Dr. Varmus: NIH recently received the Institute of Medicine's proposal to conduct the review of research on cancer among minorities and the medically underserved. We expect the study to be completed in the summer of 1998.

THE ROLE OF THE OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: As you know, AIDS is a health concern that touches upon all of the NIH Institutes and Centers, much like minority health. As such, there is an AIDS office that is "trans" NIH. This office oversees AIDS policies across all of the NIH; I understand that it negotiates the entire NIH-wide AIDS budget. These are just a few of the functions this office performs as the "central coordinating arm" of the NIH relative to AIDS.

Does the Office of Research on Minority Health function in this same manner?

Dr. Varmus: The Office of Research on Minority Health (ORMH) does function as a trans-NIH activity. However, in contrast to the Office of AIDS Research, to which the entire appropriation for AIDS research is provided, ORMH serve as more of a focal point for coordinating activities related to minority health and research training. As was intended from the beginning of the establishment of ORMH, just like the role of all the program offices in the OD, its role is to work collaboratively with all the Institutes and Centers (ICs) so as to allow its appropriated funds to be additive to

the funds from those same ICs. In this way, research and research training broadly related to the diseases that particularly afflict minorities can advance as effectively as possible.

Mr. Stokes: When the Directors of the various Institutes tell us about what they are doing in the area of minority health, are all of those programs and the funds associated with them coordinated by the Office of Research on Minority Health?

Dr. Varmus: Much of the research funded by the ICs and which is in areas related to the health of minorities is undertaken independently of ORMH and in response to needs and opportunities recognized by the ICs. However, ORMH has the responsibility to assure that appropriate coordination and collaboration across NIH is undertaken and, in addition, to provide funds to important areas of research which are found to be "gaps" in knowledge which are not being undertaken by any of the ICs.

EPIDEMIC OF PULMONARY HEMORRHAGE AMONG CLEVELAND INFANTS

Mr. Stokes: Approximately 90 cases of pulmonary hemorrhage in infants have been reported to the CDC, about a third of the cases have been in Cleveland, Ohio. All but two of the Cleveland infants were African American; most were male. A CDC investigation has linked the disease to exposure to toxins produced by a mold found in the infants' home. Are there rapid methods available to detect and quantify airborne toxic fungi?

Dr. Varmus: At present there does not appear to be a rapid method to detect and quantify these mold toxins.

Mr. Stokes: Is there research underway or planned in animal models that would delineate the role of different fungal toxins in producing human disease in infants?

Dr. Varmus: Research grant applications to develop an animal model, to study the disease in humans and to develop a detection method are under consideration at the National Institutes of Health. If this work is successful, it may begin to provide some answers to these serious and mysterious cases of pulmonary hemorrhage.

RESEARCH PROJECT GRANTS

Mr. Stokes: According to the budget submission, the FY 1998 budget request would allow the National Institutes of Health (NIH) to provide a 3.9 percent rate of growth in funding for research project grants, the NIH's highest priority. In total, the budget would support well over 26 thousand investigator initiated grants. In dollars and percent, what portion of the NIH budget is invested in research project grants?

Dr. Varmus: Of the total NIH budget request of $13.1 billion for FY 1998, funding for research project grants (RPGs) is $7.4 billion, or 57 percent.

Mr. Stokes: To what extent has this percentage remained fairly constant over the years?

Dr. Varmus: Funding for RPGs as a percent of the total NIH budget has remained constant from FY 1993 to FY 1996, increasing slightly, in the FY 1997 and FY 1998 Estimates. The following table reflects the total NIH budget, total RPG funding and the percent that total RPG funding is to the total NIH budget from FY 1993 to FY 1998.

NATIONAL INSTITUTES OF HEALTH
Research Project Grants as a Percent of Total NIH Funding
(Dollars in Thousands)

	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997 Estimate	FY 1998 Estimate
Total, RPGs	$5,657,630	$5,981,328	$6,194,524	$6,612,358	$7,129,838	$7,408,198
Total, NIH	$10,328,117	$10,910,969	$11,340,841	$11,927,562	$12,740,843	$13,078,203
% to total	55%	55%	55%	55%	56%	57%

NUMBER OF MINORITY AND WOMEN INVESTIGATORS

Mr. Stokes: What was the rate of growth in funding for research project grants in each of the last five fiscal years? How does this compare with the rate of growth in the amount of funding and number of research project grants awarded to women principal investigators, and to African American and Hispanic research investigators for each of the years indicated?

Dr. Varmus: This information is summarized in the tables below; however, to comply with federal mandates, all questions related to race and gender are identified as optional on all NIH research grant applications. Although statistics vary from year to year, and across Institutes and Centers, a significant number of grant applicants choose not to identify their race and/or gender.

Growth in Number of Research Project Grants

	FY 1992	FY 1993	FY 1994	FY 1995	FY 1996
Total RPGs	24,033	23,952	24,964	24,899	25,519
Percent Increase		-0.3%	4.2%	-0.3%	2.5%
RPGs to Women	4,927	5,383	5,824	5,982	6,150
Percent Increase		9.3%	8.2%	2.7%	2.8%
RPGs to African Americans and Hispanics	769	847	1,153	1,256	1,698
Percent Increase		10.1%	36.1%	8.9%	35.2%

Growth in Research Project Grant Awards
(Dollars in thousands)

	FY 1992	FY 1993	FY 1994	FY 1995	FY 1996
Total RPGs	$5,459,375	$5,657,630	$5,981,328	$6,194,524	$6,612,358
Percent Increase		3.6%	5.7%	3.6%	6.7%
RPGs to Women	$ 927,500	$1,089,500	$1,207,000	$1,268,900	$1,384,500
Percent Increase		17.5%	10.8%	5.1%	9.1%
RPGs to African Americans and Hispanics	$ 158,161	$ 192,523	$ 261,467	$ 284,375	$ 421,721
Percent Increase		21.7%	35.8%	8.8%	48.3%

EXTRAMURAL CONSTRUCTION

Mr. Stokes: Last year, the committee included bill language identifying $37 million in extramural biomedical facility renovation and construction. As you are aware, these funds are to be awarded consistent with the requirements of Section 481A of the Public Health Service Act which allocates 25 percent of total funding to Institutions of Emerging Excellence. Can you tell the Committee how the agency complied with the requirement that 25 percent of the funding be provided to Institutions of Emerging Excellence?

Dr. Varmus: Eighty applications, including 9 from the Centers of Excellence, were submitted in FY 1997 to the extramural construction program of the National Center for Research Resources (NCRR). These Centers support programs of excellence in health professions education for minority individuals. The applications will be reviewed later this spring. Of the $20 million appropriated to the NCRR for this purpose, at least 25 percent ($5 million) will be awarded to Centers of Excellence in compliance with the requirement of Section 481A of the Public Health Service Act. To assist the eligible Centers of Excellence in submitting applications that are technically

excellent, a technical assistance workshop was held prior to the submission of these grant applications. In FY 1996, the NCRR made 6 awards to Centers of Excellence, $5.7 million or 29 percent of the funds available, to these institutions. We anticipate similar success in FY 1997.

Mr. Stokes: How much is included in the FY 1998 budget for the extramural biomedical facility renovation and construction account?

Dr. Varmus: The FY 1998 President's Budget Request for extramural construction is $6.6 million. This includes $2.6 million in the request for the National Cancer Institute, and $4.0 million in the request for the National Center for Research Resources.

MAMMOGRAPHY

Mr. Stokes: According to a panel of experts convened by NIH, mammographies may not be the best option for women between the ages of 40 and 49. However, several studies have shown a significant reduction in mortality for women who have mammography screening in their forties. Screening and detection are extremely important, women and their doctors must have the clearest and best information available. What is the NIH's position with respect to the benefit of regular mammograms in women who are 40 to 49 years of age?

Dr. Varmus: The National Institutes of Health (NIH) Consensus Development Conference panel was convened to examine all relevant studies on the subject of mammography in women ages 40-49. Some published studies have shown a statistically significant reduction in mortality for women who have mammography screening beginning at some time in their forties, while others have not. The panel analyzed nearly 150 published research papers and more than 300 abstracted papers over a period of nearly two months, and heard more than 30 oral presentations of data during two days of testimony. The salient conclusions of the panel in its final report, issued on March 20, 1997, were the following: (1) At the present time, the available data do not warrant a universal recommendation for mammography of women ages 40-49. (2) Each woman should decide for herself whether to undergo mammography, after hearing the benefits as well as risks of the screening procedures. (3) If a woman in her forties decides in favor of mammography, there should be no impediments to her decision; and third party payers should pay for the mammogram.

A minority report of the panel was also issued, concluding that routine screening mammography for women in their forties should be actively encouraged, and that information should be provided to women and their health providers to assist women in deciding whether to accept or reject that advice.

The conclusions of the panel at the Consensus Development Conference reflect the deliberations of an independent group of experts; and therefore the panel conclusions are not official NIH policy. As for most NIH Consensus Development Conferences, the conclusions of the panel are the beginning of a deliberate process within the lead Institute in the area of interest to assimilate the panel report and to develop a plan to use the new information. In this case, the lead Institute is the National Cancer Institute (NCI). On February 25, 1997 the draft conclusions of the NIH Consensus Development Conference were discussed, along with plans to address the situation, at a meeting of the National Cancer Advisory Board (NCAB). On March 27, 1997, the NCAB issued its recommendations to the NCI. Recognizing uncertainty surrounding the issue, the NCAB voted that the NCI should recommend regular screening mammograms every one to two years to women ages 40-49 at average risk of breast cancer. Women at higher risk should seek expert medical advice about beginning mammography prior to age 40, and about the screening interval. The NCI has accepted the recommendations of the NCAB as its official policy.

Mr. Stokes: What is being done to ensure that an appropriate number of African American women are included in test trials that seek to determine the effectiveness of mammography screening services?

Dr. Varmus: The NCI has a very good history of racially and ethnically proportional representation in randomized clinical treatment trials. Indeed in certain diseases such as breast and prostate cancer we accrued disproportionately more African American patients to cancer treatment trials. The Institute published its accrual figures in the Journal of the National Cancer Institute in June of 1996. Among women enrolling in breast cancer treatment trials, 10% of participants were African American -- 8.4% of breast cancer patients in the U.S. are African American -- and 3.2% of participants were Hispanic -- 3.3% of breast cancer patients in the U.S. are Hispanic.

The Institute has had difficulty enrolling minority women into many prevention and screening studies. The institutions that provide us with proportional representation for treatment trials are the same institutions that are unable to accrue minorities to prevention trials. The Division of Cancer Prevention and Control and the newly formed NCI Office of Special Populations have published information about, and continue to study, the dynamics of accrual to clinical trials. A key theme among participants in prevention trials is that they tend to be highly educated and of higher than average socioeconomic status.

One major NCI research effort that has been successful in recruiting minority women is the Breast Cancer Screening Consortium. It is evaluating community-based mammography screening. Two sites have significant percentages of black or Hispanic women in their study samples: Los Angeles with 27% black and 37% Hispanic women and North Carolina with 15% black women.

The NCI Office of Special Populations is convening meetings of persons interested in breast cancer in special populations -- advocates, and medical and public health professionals. These experts are being asked to help shape the message we should send to minority women about the importance of participating in these non-therapeutic studies as well as to help determine how to convey that message.

GRANT SUCCESS RATE

Mr. Stokes: To what extent does the grant success rate vary across the institutes? Please include in the record a chart displaying the grant success rate by institute for each of the last five fiscal years, and the FY 1998 budget request projected rate.

Dr. Varmus: In FY 1998, we estimate that success rates for competing research project grants (RPGs) will range from 20 percent to 45 percent by institute. In total, the NIH will fund an estimated 28 percent of competing RPG applications in FY 1998. Several factors produce variations in success rates among institutes. These include the impact of funding an unusually large or small number of competing RPGs in a prior year, size of an institute's RPG portfolio, and size of the grantee community in certain research areas. The following table reflects success rates by institute from FY 1993 to FY 1998.

NATIONAL INSTITUTES OF HEALTH
Research Project Grant
Success Rates
FY 1993 - FY 1998

Institute	FY 1993	FY 1994	FY	FY 1996	FY 1997 Estimate	FY 1998 Estimate
NCI	25%	22%	24%	29%	26%	25%
NHLBI	22	23	27	25	30	27
NIDR	24	37	29	24	25	23
NIDDK	22	25	27	26	29	27
NINDS	25	26	31	29	25	26
NIAID	29	25	25	32	33	34
NIGMS	30	33	39	34	35	35
NICHD	21	21	18	23	22	24
NEI	32	40	36	38	39	37
NIEHS	21	26	16	21	21	20
NIA	23	25	29	32	34	28
NIAMS	21	20	24	26	21	22
NIDCD	29	32	34	33	35	37
NIMH	20	21	19	22	25	24
NIDA	32	33	30	26	24	27
NIAAA	19	29	22	21	19	20
NINR	11	12	32	26	33	26
NHGRI	28	28	26	29	27	31
NCRR	28	18	23	33	48	45
FIC	0	27	65	40	42	40
NIH	25%	25%	27%	28%	28%	28%

AIDS AND MINORITIES

Mr. Stokes: As last year's report language indicated, AIDS is the leading cause of death in people between the ages of 25 and 44, and is spreading most rapidly among African American and other at-risk minorities, adolescents, and women. The Committee therefore urged the NIH to carefully monitor changes and ensure that the research plan includes objectives and strategies to strengthen the response to demographic changes in a timely fashion. The NIH was also strongly encouraged to strengthen and to include the direct participation of African Americans and other minorities in its AIDS/HIV research, research training, and outreach activities. What progress has the NIH made in achieving these objectives?

Dr. Varmus: The NIH has taken a number of steps to improve and/or retain the participation of African Americans and other minorities in its AIDS/HIV research, research training, and outreach activities. The following are a few examples of these efforts:

- The NIH continues to emphasize the enrollment of minority populations in clinical trials; 60 percent of the current enrollment in National Institute of Allergy and Infectious Diseases (NIAID)-supported therapeutic trials are people of minority background.

- A number of NIH Institutes collaborate in supporting the Women's Interagency HIV Study (WIHS). The study is addressing the clinical, immunologic, virologic, and behavioral aspects of HIV disease progression in women. The current participation of the Washington, DC consortium site of Howard University, Whitman-Walker Satellite Clinic and Georgetown University, is 80 percent African American women. This program gives the participants an incentive by providing increased access to gynecological care.

- The National Institute of Mental Health, the NIH Office of Research on Minority Health, and the NIAID, awarded 11 collaborative AIDS research projects to foster communication between the investigators participating in the Centers for AIDS Research and the Research Centers in Minority Institutions (RCMI).

- Several of the institutions selected for National Cancer Institute funding to pursue research activities as part of its AIDS malignancy program were specifically considered for their ability to recruit minorities.

- The National Library of Medicine (NLM) has had a long-standing outreach program with Historically Black Colleges and Universities that has been expanded to include HIV/AIDS. This collaboration enables NLM to place important information in the hands of health professionals working closely with those most heavily affected communities.

- The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is actively encouraging minority participation in a program that will develop alcohol-related HIV preventive interventions. NIAAA is interested in determining the prevalence and interrelationships of various diagnoses, including alcohol abuse/dependence, in African Americans and other minorities who are diagnosed with AIDS/HIV.

- In FY 1996, 11 of the 18 grantees in Research Centers in Minority Institutions funded by the National Center for Research Resources, participated in AIDS relevant research. These projects focused on many different aspects of AIDS research including transmission of the AIDS virus from mother to child.

- The Fogarty International Center established a minority health initiative within the AIDS International Training and Research Program.

RESEARCH PROJECT GRANTS AS PRIORITY

Mr. Stokes: According to the budget submission, research project grants are your highest priority. Briefly explain why this component of the NIH portfolio has to be your highest priority.

Dr. Varmus: The use of research project grants as a mechanism of support covers the entire biomedical continuum, from basic research to clinical studies. Most grant applications are investigator-initiated, whereby individual investigators develop proposals for research in their area of expertise and interest. The NIH awards scientifically meritorious research project grants to support biomedical and behavioral research activities in the areas that represent both the specific interests and competence of the principal investigators and the Institutes' identified program needs. The research project grant is the primary vehicle through which new ideas flow into the Nation's health care system.

MINORITY INVESTIGATORS

Mr. Stokes: How critical is it to furthering advances in diseases and disorders that disproportionately impact women and minorities to have significant members of these populations directly involved as principal investigators in the conduct of investigator initiated research project grants, in the development of protocols, and the design of outreach and public education initiatives? Please elaborate on your response for the record.

Dr. Varmus: Conducting research to further advance knowledge about diseases and disorders that disproportionately affect minorities is collectively termed "minority health research." Outreach, public education and the use of community-based approaches to ward intervention strategies have emerged as necessary components in the conduct of minority health research. Consultation with minority communities is a major function of the Office of Research on Minority Health, the trans-NIH office responsible for promoting biomedical research aimed at improving the health status of minority Americans. Such consultation has revealed that every minority group, without exception, believes that community involvement in addressing particular health problems, proposing real and workable solutions and reacting to the cultural relevance of potential strategies are critical elements to the success of efforts to improve the health of all minority groups.

Consensus building and adequate consultations will ensure trust and allow expression of all points of view and are inherent in the decision-making process. Participation of patients in this process, as well as well-trained minority investigators

who understand the culture and are trusted both by the participants and the scientific community, provides a powerful tool for cultivating the kind of community cooperation that is necessary in the conduct of any clinical research project, but particularly one related to minority health.

RESEARCH INFRASTRUCTURE

Mr. Stokes: As the Director of the nation's preeminent biomedical and behaviors research enterprise, the budget submission indicates that the NIH plays a singular role in nurturing and supporting the nation's medical scientific research infrastructure, especially in biology and medicine, but also in chemistry, computer science, and other disciplines. It is thought that for some of the nation's leading research institutions the NIH has played a tremendous and extremely vital role in growing their infrastructure.

Could you explain what is meant by this?

Dr. Varmus: Indeed, NIH has played a vital role in the growth and maintenance of the research infrastructure of academic institutions. There are many facets to this infrastructure:

Research training programs, supported by NIH, are designed not only to develop new scientists, and to provide them with postdoctoral experiences, but also to set the standards of quality of such training in regard to breadth of courses required, mentoring of students, stimulating the development of new ideas and new technologies, and imbuing students with a sense of the ethics of the scientific enterprise.

Special initiatives are supported by NIH, to provide "high technology" instrumentation such as electron microscopes, spectroscopes, imaging instruments such as nuclear magnetic resonance; important medical and biological databases; the newest in computer technology; library materials and searches; and access to information regarding clinical research studies throughout the country.

Provision of support through specific funds to the academic institution, for central services such as heat, water, light, plumbing, disposal of chemical and microbiological waste, electrical, and gas lines to deliver oxygen and carbon dioxide to laboratories.

Many of these components of the biomedical research infrastructure have a finite span of usefulness as new, better, more sensitive and more specific equipment is developed, which, in turn, speeds up the pace of important studies.

Mr. Stokes: How is this "NIH Singular Role" reflected in your efforts to strengthen the research infrastructure at historically black colleges and universities?

Dr. Varmus: The continued support of the needs of institutions, particularly historically black colleges and universities, to upgrade equipment and other infrastructure provides these institutions with access to the most modern laboratory environment and permits the biomedical researchers at these institutions with the ability to perform competitive research and prepare future scientists for studies yet to be done.

SMALL BUSINESS INNOVATION RESEARCH GRANTS

Mr. Stokes: The NIH recently convened a Small Business Innovation Research Grants (SBIR) conference. The small business innovation research community has expressed concern with regard to the SBIR program. Among their recommendations for improvement to the program are reducing the length of time between Phase-1 and Phase-II awards, and having the grant reviewers to be representative of the SBIR community. It is also thought that the grant cap can prove an impediment to taking significant research and development projects all the way through to successful conclusion. Smaller businesses complain that they just do not have the financial resources to sustain them, and so significant work in the field remains dominated by larger companies. To what extent is there a bias against applied research? Specifically, what is NIH doing to address these concerns?

Dr. Varmus: The NIH SBIR Conference of January 22 was a constructive forum for the discussion of ideas to strengthen and enhance the SBIR program at the NIH. A summary of the conference is available electronically on NIH's "Small Business Funding Opportunities" home page, which can be found on the World Wide Web at http://www.nih.gov/grants/funding/sbir.htm.

In an effort to address legislative encouragement to reduce the time-gap in funding for some applicants between Phase I and Phase II, the NIH initiated a "Fast-Track" process in 1996. Fast-Track is a parallel review option designed to expedite the decision and award process for Phase II funding. Under this option, those small business concerns satisfying the criteria may concurrently submit Phase I and Phase II applications; this option is designed to reduce or eliminate the funding gap between phases. The Fast-Track initiative is in addition to the general NIH policy of allowing Phase I small business grantee organizations to submit Phase II applications during the Phase I budget period, which also serves to decrease funding gaps between phases.

Long-standing NIH policy requires representation from the small business community in the peer review of SBIR applications. At present, the average is three such persons per SBIR scientific review group, which may account for up to one-third of a particular group. This level of representation seems optimal; higher levels would also increase the possibility of competitors serving as reviewers. Review groups will continue to include reviewers from various research environments, including the small business community, who understand the scientific and technical aspects of proposed projects.

The legislative dollar levels provided for SBIR phases are considered to be "guidelines" rather than absolute maximums. The SBIR Program Policy Directive of the Small Business Administration (SBA) provides agencies the authority to exceed those levels on a case-by-case basis. The NIH is fully committed to the SBIR program and welcomes the SBA's flexibility by advising applicant small business concerns to submit applications with budgets that reflect the total estimate of the cost of the proposed research and development project.

THE INVESTMENT IN MINORITY RESEARCH PROGRAMS

Mr. Stokes: Research intensive minority health professions schools have historically been undercapitalized, and have struggled against great odds to conduct quality biomedical research that focuses on improving the health status of minorities. I remain concerned that funding for several key programs such as MARC and MBRS have remained static during the last couple of years while the rest of the NIH has grown. Given the exceptional need, how can we insure that minority research programs grow at a rate that is at least equal to that of the NIH total budget?

Dr. Varmus: The NIH is committed to ensuring that resources provided to minority programs are commensurate with scientific opportunities and overall resources available to the NIH. In fact, the MBRS and MARC programs in the NIGMS have increased by 24% over the past five years (FY 1993-1997), compared to the total NIH appropriation, which has increased by 23% over the last 5 years.

BIOMEDICAL ENGINEERING RESEARCH

Mr. Stokes: I understand that while the NIH has received significant increases in funding, less than six percent of these funds are invested in biomedical engineering research and development, a field which many consider the most applied of the biomedical disciplines. One would find this percentage surprisingly small when you consider the central role that biomedical engineering plays in the development of new technologies that improve health care and reduce medical costs, not to mention how critical biomedical engineering is to the national economy. It appears that biomedical engineering falls in the area between the National Science Foundation, which has responsibility for engineering-related research, and the NIH, which has responsibility for health-related research.

I understand from the biomedical engineering community that there exists several biomedical technological breakthroughs that hold greater promise to revolutionize the field of medicine including tissue engineering and advanced medical imaging. What initiatives are underway or planned at the NIH to exploit opportunities in this promising area?

Dr. Varmus: The NIH supports a broad portfolio of science to improve health. Included in this portfolio are basic research to expand the frontiers of knowledge and targeted research to develop diagnostic and prognostic tools, to promote prevention (including vaccines), and to improve treatment (including drug development.) Each of these areas incorporates bioengineering research, a broad range of interdisciplinary efforts that applies engineering principles to biological and medical research. A study of NIH funding in FY 1993 showed that approximately 4% of the NIH extramural budget (over $300 million) went to 1,781 research project grants with more than three-fourths effort directly related to bioengineering research. Of that amount, approximately $80 million supported basic bioengineering research. NIH was the largest source of support for bioengineering research within the public sector, providing approximately two thirds of all federal funding in FY 1993. Bioengineering projects received $15 million from the National Science Foundation in FY 1993. The largest funder of bioengineering research in the private sector, the non-profit Whitaker Foundation, provided $23 million in that same fiscal year.

Two new initiatives to increase bioengineering research are under way at NIH. A new program on Innovative Approaches to Developing New Technologies was announced by the National Center for Research Resources in December 1996. The purpose of this initiative is to encourage submission of new grant applications to explore new research paradigms in engineering, instrumentation, physics, mathematics or computer science as applied to biomedical research. A second initiative, to be funded jointly by the National Heart Lung and Blood Institute and the National Institute for Dental Research on Tissue Engineering, Biomimetics, and Medical Implant Science, will be announced shortly. The objective of this initiative is to encourage multidisciplinary research in the design and bioengineering of natural and novel approaches for the repair, restoration, and replacement of tissues and whole organs based on a comprehensive understanding of biological structures and their functions, for the purpose of developing a new generation of natural and synthetic implants, including totally biological solutions for instances in which synthetic implants have historically been used. Plans are also underway at the National Heart Lung and Blood Institute for an initiative that would use bioengineering technologies to tap the enormous potential of Cardiac Magnetic Resonance Imaging (CMRI) for assessing ischemic heart disease and heart failure in the clinic and in population trial.

Mr. Stokes: To what extent are there collaborative efforts underway between the NSF and the NIH?

Dr. Varmus: The NIH has collaborative efforts underway with the National Science Foundation (NSF) and with other government agencies to promote bioengineering research. The NSF funds biomedical research on areas such as biomaterials and cardiovascular devices in the Engineering Research Centers (ERC)

Program; the decision to fund these Centers is in part based on key investigators having independent and non-overlapping NIH support. This provides a synergistic environment for discovery, invention and the introduction of novel technologies through the ERC interface with industry.

The Biomaterials and Medical Implant Science Coordinating Committee at the NIH is developing a joint memorandum of understanding (MOU) between the National Institute of Standards and Technology (NIST), the Food and Drug Administration (FDA), and the NIH. This MOU will facilitate the development of Reference Materials (RMs) and Standard Reference Materials (SRMs). These standards will be useful in generating baseline data on the biological performance of synthetic and biologic materials used in medical device and implant applications. These RMs and SRMs will be used in research, regulation, and industry.

Mr. Stokes: Within the NIH, how many study sections are assigned responsibility for bioengineering research and development?

Dr. Varmus: Of the 103 study sections that review R01/R29 grant applications, four (Surgery and Bioengineering, Orthopedics and Musculoskeletal, Diagnostic Imaging and Genome) have a significant workload of bioengineering. Several other study sections review fewer bioengineering applications; these include but are not limited to Cardiovascular, Pharmacology, General Medicine A-1, Metallobiochemistry, Biophysichemistry, Molecular Biophysics (the last three review biochemical instrument development). In addition, all of the SBIR Special Emphasis Panels (approximately 37) review bioengineering applications, some exclusively. Research project grant applications that can not be reviewed in regular study sections are also reviewed by the Division of Research Grants (DRG) in Special Emphasis Panels or in Institute/Center review branches. Many of these review panels also include bioengineering researchers or scientists with bioengineering expertise.

Mr. Stokes: What is the extent of the representation of biomedical engineering academics and medical product and device industry personnel on NIH councils and study sections?

Dr. Varmus: Scientific review groups in the DRG indicate at least one member with bioengineering expertise in 18 of their study sections. Those reviewing more substantial numbers of applications with some bioengineering component have more such reviewers, although precise numbers are not readily available. More than one thousand reviewers serving on DRG Special Emphasis Panels are listed as having bioengineering expertise. With the new computer database being developed under the Electronic Reinvention Administration, such information will become more readily available, not only for DRG review groups but for all review branches across the NIH, and can be even more closely monitored.

Some ICs have specific biotechnology and/or bioengineering programs, and councils reflect this programmatic emphasis. For ICs where there is less bioengineering research, they would be able to invite ad hoc members with that expertise for those occasions when discussions were focused on bioengineering issues. With the new computer database being developed under the Electronic Reinvention Administration, such information will become more readily available, not only review groups but also for councils.

Mr. Stokes: Has the agency considered implementing a more balanced research and development funding system to adequately address the needs of academic biomedical research and development?

Dr. Varmus: I have established a bioengineering consortium to serve as a focus for bioengineering issues. The consortium is chaired by the NIH Deputy Director for Extramural Research and is composed of senior staff from various NIH Institutes and Centers. Consortium meetings will identify major issues and establish small working groups augmented with individuals with appropriate expertise drawn from NIH staff and other federal agencies. Interagency collaboration in bioengineering may be encouraged by inviting representatives of other federal agencies to serve as ex-officio members of the consortium. Among the topics that the consortium will examine initially are postdoctoral training in bioengineering for biological scientists; support of bioengineering research, including an examination of peer review of bioengineering research applications; communication and outreach to the bioengineering community on the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs; and development of databases on topics relevant to bioengineering. The establishment of this consortium demonstrates our agency commitment to addressing the needs of biomedical research and development. As collaboration among purely biological and biomedical engineering researchers increases, this group will serve as a focus for important current and emerging issues.

Mr. Stokes: More specifically, is there a role for the Small Business Innovation Research Program in this field of biomedical engineering research?

Dr. Varmus: There is clearly a role for the Small Business Innovation Research (SBIR) Program in bioengineering. The majority of NIH SBIR projects involve some aspect of bioengineering. In FY 1995 more than 30% were biomedical equipment projects, with many others involving other aspects of bioengineering such as drug design and development or biomedical computer applications. The FY 1997 increase in the SBIR set-aside should ensure sufficient funds for SBIR projects including those in bioengineering.

Mr. Stokes: Is there a focused program at the NIH to foster Biomedical Engineering research and development and to help ensure adequate funding for this promising field?

Dr. Varmus: There are various efforts at the NIH which focus on biomedical engineering, and our current establishment of a Bioengineering Consortium will help ensure that these are coordinated. The various efforts which will be coordinated through the Consortium and which are already underway are a collaborative effort with the National Science Foundation and other government agencies to promote bioengineering research and the development of a joint memorandum of understanding between the NIH's Biomaterials and Medical Implant Science Coordinating Committee and the National Institute of Standards and Technology and the Food and Drug Administration. In addition, the Consortium is examining overall support of biomedical engineering at the NIH, including peer review of bioengineering research applications, postdoctoral training in bioengineering for biological scientists, communication and outreach to the bioengineering community on small business research opportunities, and the development of relevant databases to facilitate tracking and information dissemination. All of these efforts will contribute to our ability to ensure that high quality research projects in this promising field are funded.

EMPLOYMENT RATES FOR AFRICAN AMERICAN MALES

Mr. Stokes: According to material provided by the NIH, the employment separation rates for African American males exceed their percentage representation in the NIH work force. What is causing this increasingly negative trend, and more specifically, what is being done to address the problem?

Dr. Varmus: The NIH has been concerned with turnover of employees, particularly African American men and white women for some time. For the last several years, different strategies have been tried to identify and eliminate barriers that may have adverse impact on retention. These strategies, which included a pilot NIH Employee Separation Survey, the NIH Task Force on Fair Employment Practices and an NIH-wide Mentoring Program, have met with minimal success.

The NIH started actively monitoring the separation rates for African American males after a 1993 audit by the Equal Employment Opportunity Commission (EEOC). The EEOC reviewed NIH separation rates by race/ethnicity and gender for fiscal years (FY) 1991 -1993, and reported that African American men were separated at rates higher than their representation in the work force. Our review of EEOC data, as well as additional NIH data over the past six years, reveals that African American men have separated at an average rate of 10% each year while continuing to represent 8% of the NIH work force over the same six year period. This is clearly a negative and disturbing trend, but the good news is that the separation rate of African American men has shown no increase for most of the past six years. The summary table shows that the separation rate for African American men peaked in FY 1992 at 11.4% and has dropped in subsequent years. White men maintained the same rate of separation over the past two years, which was slightly lower than their representation in the work force and white women maintained a rate slightly higher than their representation.

The NIH continues to look for opportunities to capture useful information that will identify the reasons for this turnover. Results from the voluntary separation questionnaire initiated by the NIH in FY 1994 were inconclusive due to the lack of response from separating employees. Another means that the NIH is considering for capturing this information is through face-to-face separation interviews. This would allow NIH institutes, centers and divisions to collect employee separation information and to document what factors employees say affect their decisions to leave the NIH. This information would be analyzed to identify systemic barriers and corresponding practices could then be implemented to reduce turnover. Additionally, the NIH is currently undertaking the Workplace Diversity Initiative (WDI), a long-term strategy for improving the work environment for all employees. The object is to create a work environment that allows everyone to reach their full potential, increase overall productivity, use multiple perspectives for problem solving and reduce the number of complaints and grievances filed. Effective management of diversity will have added benefits for African American employees and ultimately impact on their retention and separation rates.

NIH PERMANENT SEPARATIONS PROFILE
FY 1991 - FY 1996

Fiscal Year	Whites		Blacks		Hispanics		Asians		Native Americans		Total
	M	W	M	W	M	W	M	W	M	W	
1991 #	486	807	206	285	30	23	65	71	1	6	1,980
%	(25.0)	(41.0)	(10.0)	(14.0)	(2.0)	(1.0)	(3.0)	(4.0)	(.05)	(0.3)	(100.0)
1992 #	439	686	193	218	25	21	57	51	1	4	1,695
%	(26.0)	(40.5)	(11.4)	(12.8)	(1.5)	(1.2)	(3.4)	(3.0)	(0.06)	(0.24)	(100.0)
1993 #	362	583	135	206	14	21	34	46	4	2	1,407
%	(26.0)	(41.0)	(10.0)	(15.0)	(1.0)	(1.5)	(2.4)	(3.3)	(0.28)	(0.14)	(100.0)
1994 #	239	373	80	123	6	14	13	15	0	3	866
%	(27.6)	(43.1)	(9.2)	(14.2)	(0.7)	(1.6)	(1.5)	(1.7)	(0.0)	(0.3)	(100.0)
1995 #	275	536	109	179	6	8	19	17	3	1	1,153
%	(23.9)	(46.5)	(9.5)	(15.5)	(0.5)	(0.7)	(1.6)	(1.5)	(0.3)	(0.1)	(100.0)
1996 #	185	348	82	119	3	8	9	16	0	3	773
%	(23.9)	(45.0)	(10.6)	(15.4)	(0.4)	(1.0)	(1.2)	(2.1)	(0.0)	(0.4)	(100.0)

INCLUSION OF MINORITIES IN CLINICAL RESEARCH

Mr. Stokes: In general, what is the NIH doing to ensure the inclusion of African American and other minority patients, professionals, research organizations, and disproportionate share institutes in clinical research?

Dr. Varmus: With the implementation of the 1994 NIH Guidelines on the Inclusion of Women and Minorities in Clinical Research, the NIH requires applicants to address the appropriate inclusion of women and minorities in clinical research. Applications that fail to meet these requirements, as evaluated by peer review, are barred from funding. In such cases, the NIH staff work with the applicants to resolve problems, e.g., by changing the composition of the study populations or identifying projects in the Institutes' portfolios that address similar research objectives and that include women and minorities with which data can be compared. Initial analysis of the first year of implementation of the Guidelines indicates that over 92 percent of the applications involving human subjects were found to meet the inclusion requirements as submitted, and that greater than 23 percent of the enrollment in clinical research protocols represents African Americans.

The NIH continues to conduct and sponsor a variety of outreach activities to educate the community about the Guidelines, including professional meetings, workshops, and meetings with the Institutional Review Board (IRB) chairs and administrators. The Office of Protection from Research Risks conducts several regional meetings each year to address inclusion strategies, and these are generally co-sponsored with local minority organizations and academic institutions. Moreover, the Office of Research on Women's Health has established the Recruitment and Retention Task Force and an NIH-wide Tracking Committee to monitor enrollment data.

Mr. Stokes: What is being done to ensure that health professionals from these populations are included in the conduct of research and research training?

Dr. Varmus: The NIH recognizes the value of the contributions made by African American health professionals to the conduct of research and research training. A number of NIH programs and policies are specifically designed to recruit individuals from underrepresented racial and ethnic groups into research careers. These programs provide training and research opportunities across the continuum from high school students to independent investigators, with the goal of increasing the diversity of the labor pool in all segments of health related research. Below are some examples.

For individuals at the high school, college, graduate, postdoctoral, and investigator levels, the NIH offers Research Supplements for Underrepresented Minorities. Using this program; the principal investigator on a currently funded research project can request an administrative supplement to support the salary of an individual from an underrepresented group who wishes to participate in the ongoing research.

At the undergraduate level, the NIH supports training and research opportunities at institutions with a substantial minority enrollment through the Minority Access to Research Careers (MARC), the Career Opportunities in Research (COR), the Minority Biomedical Research Support (MBRS), and the Minority-Research Infrastructure Support Program (M-RISP) programs.

All National Research Service Award (NRSA) institutional research training grants are required to actively recruit graduate and postdoctoral trainees from underrepresented groups. All competing and non-competing applications are specifically examined to ensure that recruitment plans are appropriate and that every effort is being made to identify, recruit, and retain minority trainees.

The National Center for Research Resources (NCRR) operates the Minority Clinical Associates Program (MCAP) which provides supplements to existing General Clinical Research Centers (GCRC) awards specifically for the training and career development of minority physicians interested in clinical research.

Several of the NIH institutes offer travel awards that allow students and postdoctorates from underrepresented groups to travel to scientific meetings. Many institutes also offer specific career development programs for minority postdoctorates or faculty at minority institutions who wish to complete their training in a health related field.

The Office of Research on Minority Health, in collaboration with the National Institute of General Medical Sciences, offers two "Bridges" programs that support minority students during the transition from community colleges to baccalaureate granting institutions and from masters level programs to doctoral programs.

Mr. Stokes: Is the representation of African Americans in research protocols proportionate to their membership and/or relative morbidity in the general population?

Dr. Varmus: The aggregate enrollment data collected one year after the implementation of the NIH Guidelines showed that African Americans are adequately represented in clinical research protocols (>23% of total enrollment). This figure is higher than the proportion of African Americans within the US population; however, there are many health problems where African Americans bear a disproportionate burden.

Mr. Stokes: How do co-morbidities among African Americans and those among other minorities affect research protocols?

Dr. Varmus: Comorbidities generally have little or no major influence on research protocols or on recruitment of minorities. Comorbidity is the simultaneous occurrence of one or more disease conditions in an individual other than the condition of principal interest in the study. The planning of research protocols, whether

observational or interventional, involves estimation of the number of clinical events likely to occur in the population to be studied. This estimate is important in assuring that statistically confident findings will result. The likelihood of such events may vary by age, gender and race/ethnicity; therefore, in planning, these rates are taken into account in determining the number of individuals to be recruited and the duration of the study. Studies of hypertension treatment require determination of the number of clinical events anticipated and the differences in risk among minorities is accounted for in planning. Comorbid conditions are considered in recruitment for several reasons. A comorbid condition such as obesity or diabetes or both may increase the risk of a clinical event. The investigators may want to be able to study the effect of the intervention on both the principal condition (hypertension and heart attack) and whether the comorbid condition (diabetes) is altered by or changes the effects of treatment. If this is intended, one might want to increase enrollment to have adequate numbers to study these interactions. To the degree that the comorbid conditions occur more frequently in minorities, this would favor recruitment of more minority participants. There is another aspect to the comorbidity. If an accompanying comorbidity predisposes to an adverse effect from the treatment under study, then individuals with that comorbidity should be excluded for their protection. Similarly, one would not include persons in a trial if they have a condition (e.g., cancer) that requires a treatment likely to adversely affect the treatment under study and thereby deny them appropriate treatment. For example, persons with advanced cancer would not be expected to benefit from treatments to lower blood pressure and thus should not join a trial of blood pressure lowering agents. However, the exclusions for comorbid conditions are generally uncommon for most clinical trials and rare for observational studies. With appropriate planning there should be little or no effect on minority representation.

Mr. Stokes: What factors affect recruitment and retention of African Americans in clinical research?

Dr. Varmus: The recruitment and retention of African Americans in clinical research is a crucial ingredient for the success of clinical research studies, especially for diseases or conditions that disproportionately affect this population. The low enrollment of African Americans historically has been due to many factors: limited access to research-oriented hospitals, lack of information, poor communication by researchers about studies, poverty, etc. We must also continue to address the mistrust still felt by some African Americans toward the medical establishment. However, the enactment of the legislation mandating the NIH Guidelines on the Inclusion of Women and Minorities in Clinical Research (Federal Register, March 28, 1994) is a clear signal that there is a shift in attitudes, from viewing participation in research experimentation as a burden to viewing it as a potential benefit.

Through ongoing NIH-supported studies, recent workshops and numerous discussions, the NIH has determined that the following factors should be considered in its outreach efforts to recruit and retain African Americans in clinical research (published in *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as subjects in clinical Research)*:

Understand the study population. Identify the potential research participants, the medical settings and the community where they reside. This may require an assessment of community structure, cultural norms, points of access to medical care, and needs and values of the potential research participants, including reasons for seeking health care.

Achieve agreement on the research plan. Confirm that the investigators, medical and health care staff, and community all agree to the design, methodologies, implementation, and completion of the study.

Establish and maintain communication. Establish mechanisms for keeping all of those involved in the study apprised of progress and study findings. This will not only increase understanding and awareness of the projects, but will also acknowledge the fact that the participants and their community are valuable partners in the scientific process.

While the underlying factors of understanding and communicating are common to all recruitment efforts, the operational details in recruiting and retaining African Americans may differ when they are recruited in hospitals, clinics, or other health care centers, rather than from the general community (work sites, schools, places of worship).

Mr. Stokes: What factors affect the ability of African American health professionals to participate in clinical trials?

Dr. Varmus: Achieving adequate representation of African Americans within the ranks of the clinical research community requires developing an understanding of the barriers these individuals encounter if they choose to pursue a clinical research career. Factors that affect their participation include barriers to academic achievement such as access, equity, excellence in educational curriculum, academic services (inappropriately large load of service activities rendered for the institution), financial assistance, and a scarcity of mentors. The high level of debt with which physicians leave medical schools affects participation in clinical research, and it is especially serious for African American health professionals. Data from the American Association of Medical Colleges (AAMC) for 1995 showed that at the end of medical school, many physicians had debts of nearly $65,000. Moreover, the length of time required for clinical training, including specialty and subspecialty, adds to the cost of medical training. Institutions must be committed to supporting their minority professionals by providing adequate salary and resources such as adequate support staff, study leaves or teaching release time.

The NIH has implemented a number of programs to enhance participation of minority clinical investigators, e.g., the loan repayment program for disadvantaged individuals, the Howard Hughes Medical Institute (HHMI) training program for early recruitment into clinical research careers, and the Minority Clinical Associate Physician (MCAP) Program at the National Center for Research Resources.

NEUROSCIENCE

Mr. Stokes: According to the budget submission, the NIH has identified six medical research "Areas of Emphasis" in which opportunities abound in emerging technologies, approaches and treatments. I understand that "Research on the Biology of Brain Disorders" is among the areas that offer great promise for furthering the Nation's health. Over the past year, newspapers and television have brought to the public's attention news of advanced treatment and discoveries made by neuroscientists. How much is the NIH currently investing in medical research on diseases of the brain, and how does this compare with the FY 1998 budget request?

Dr. Varmus: The NIH investment in research on brain disorders in total was $2.3 billion in FY 1996, and estimated at $2.5 billion for FY 1997 and $2.5 billion for FY 1998. Under the FY 1998 President's Budget, funding for NIH increased 2.6 percent compared to FY 1997; for total brain disorders research, the increase was 3.4 percent.

Mr. Stokes: Why is this field of research so ripe for investment at this particular time, and what major improvements in the health of the American people are expected to be achieved?

Dr. Varmus: Brain disorders are among the most common and debilitating in our society. Any person at any age may be at risk, for example, from developmental disorders of the brain; from a genetic disease, injury, tumor, or infection that compromises brain function; from drug and alcohol abuse; from vision and hearing disorders; from mental illness; and from the degenerative disorders of the brain such as Alzheimer's disease and Parkinson's disease. In recent years, the process of medical research discovery and application to health has been especially productive in the field of neurosciences. For example, we have new methods to prevent and treat stroke, new treatments for multiple sclerosis, a new treatment for spinal cord injury, and new discoveries of the genetic basis for many diseases of the brain and the nervous system. Further progress can be expected as scientists discover and explore the events that lead to the development of a healthy nervous system, the ways by which nerve cell growth can be regulated and the nervous system can be repaired, the means by which nerve cells communicate with each other and neural connections are strengthened, and the cascade of cellular and metabolic events that cause the death of brain cells.

As more is learned, the American people will benefit from improved diagnoses; new treatments to preserve nervous system function and limit the amount of disability, such as following head and spinal cord injury or stroke; treatments to delay the progression of degenerative brain disorders, thus enabling individuals to continue to pursue daily activities; improved therapy for mental and addictive disorders; and interventions to improve memory, learning, or muscle control in children with developmental disorders of the nervous system so they might approach their full potential.

PIPELINE

Mr. Stokes: Specifically, what is NIH doing to address the pipeline issues with regard to the underrepresentation of minorities in biomedical research?

Dr. Varmus: As part of the Minority Health Initiative (MHI), the NIH through the Office of Research on Minority Health (ORMH) focuses on the recruitment and retention of minorities in a wide array of biomedical research and health professions. In recognition of the underrepresentation of minorities in biomedical research, a systematic approach has been taken ranging from support of students at the precollege and undergraduate levels, through graduate/post doctoral and faculty training. ORMH collaborates with the National Science Foundation to support science and mathematics educational programs at the kindergarten level through grade 12, including classroom and laboratory research experiences for student participants, teacher training and standards-based curricula. Community-based outreach activities to encourage minority students to pursue biomedical careers are also conducted in collaboration with the HHS Office of Minority Health. At the same time, NIH continues to support the Minority Access to Research Careers (MARC) and the Minority Biomedical Research Support (MBRS) programs -- two primary undergraduate research training programs. The Minority High School Research Apprenticeship Program is continuing. ORMH funds a relatively new program called "Bridges to the Future" which encourages students at key transitional points in their education to continue for their bachelor's degree -- if they started a two year college -- at partner colleges and to continue to work toward the Ph.D. degree -- if they attend terminal master's degree institutions -- at a partner university. Also, the ORMH supports pre-existing NIH minority training and educational programs, international research training programs through the Fogarty International Center, as well as research supplements, for undergraduate students. A new program co-sponsored by the ORMH and the National Institute of Neurological Diseases and Stroke (NINDS) has established a graduate/post doctoral neuroscience program at Morehouse Medical School. Further, the NIH continues to fund clinical associates programs and career development opportunities for minority faculty development. In the intramural program of NIH, a loan repayment program for young clinical researchers is aimed primarily at disadvantaged students. As with the health research agenda, the assessment/evaluation underway by the ORMH will review these training initiatives to ensure that they are operating as they are intended.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. Stokes: How many institutions are now supported by the Research Centers in Minority Institutions (RCMI) clinical initiative?

Dr. Varmus: There are currently six RCMI schools of medicine that are participating in the clinical research infrastructure initiative.

Mr. Stokes: What is the annual cost and what impact has this had on the RCMI program since no additional funds have been requested for this special initiative?

Dr. Varmus: The cost of the RCMI Clinical Initiative program was $4.5 million in 1996, and $4.6 million is estimated for FY 1997. Six five-year awards have been made to expand the capacity for clinical research at RCMI institutions with affiliated medical schools. This initiative is providing the critical infrastructure so that these institutions can participate in multi-center clinical trials and other clinical research studies, supported by other NIH institutes and centers.

CLINICAL RESEARCH PANEL

Mr. Hoyer: I am pleased to hear of your increased emphasis on clinical research, particularly with regard to patient oriented research.

What were some of the findings of the NIH Directors Panel for Clinical Research?

Dr. Varmus: The Clinical Research Panel addressed the critical importance of clinical research in the nation's biomedical research portfolio and made the following series of important recommendations that the National Institutes of Health (NIH):

- Assess in detail its own contributions in clinical research;
- Provide NIH resources in clinical trials design and analysis to extramural investigators and ensure fair and effective reviews of their grants;
- Broaden the roles of the General Clinical Research Centers and continue to improve the quality of its own intramural clinical research;
- Improve training and monitoring of clinical researchers, and provide new support mechanisms for young and mid-term clinical investigators, including training of medical students and creation of a program of limited debt reduction for clinical investigators;
- Work with its partners, the academic health centers, the foundations, and the pharmaceutical and managed care industries to sustain clinical research; and
- Expand public education about the importance of clinical research.

CLINICAL RESEARCH PANEL

Mr. Hoyer: What plans do you have for implementation?

Dr. Varmus: The NIH is presently in the process of implementing the recommendations from the Clinical Research Panel. Some have already been implemented, such as creating a system that allows NIH to measure its support of clinical research, both now and prospectively. In addition, changes have been proposed in the General Clinical Research Center Guidelines that address their enhanced leadership role in clinical research and research training. Also, a medical student training program in clinical research is being initiated this summer on the NIH campus and will serve as a model for programs in extramural centers. An implementation plan is being prepared to address other recommendations and will include additional specific extramural initiatives.

RESEARCH ON LEARNING

Mr. Hoyer: The Child Health and Human Development Research Project endeavors to discover just how children learn. Also, the resulting implications for teaching children how to read.

What mechanism does NIH use to transfer this information from scientists to educators?

Dr. Varmus: The NIH uses many different mechanisms to disseminate its research findings to educators, as well as parents and the public. In the case of the learning disabilities research being supported by the NICHD, a wide variety of transfer mechanisms have been utilized. These include: annually publishing a book aimed at investigators and educators that summarizes the advances in the research; regularly publishing articles in education journals; making large numbers of presentations to educators and professional education organizations; working directly with state departments of education--special efforts have been undertaken in Connecticut, Vermont, Texas, and California; distributing large quantities of packets of information describing the research and its findings; and jointly developing with the U.S. Department of Education a set of materials entitled, "Learning to Read: Reading To Learn," which summarizes the research and findings and is widely distributed to teachers and parents.

COOPERATION WITH THE DEPARTMENT OF EDUCATION

Mr. Hoyer: Is there an established procedure for informing the Department of Education?

Dr. Varmus: In the case of the NICHD learning disabilities research that particularly focuses on reading disabilities, the Institute has an established communication process in place with the Department of Education's Office of Special Education Programs. NICHD staff regularly provide information to, and periodically meet with the director of this office and his staff.

INCREASE IN DIABETES INCIDENCE

Mrs. Lowey: Diabetes research advocates continue to be very concerned about the fact that, to the extent to which we can adequately track the numbers, diabetes research across NIH has lagged quite substantially in recent years. Yet, the number of people with diabetes continues to rise and the disease remains a leading cause of disability. Can you comment on this concern?

Dr. Varmus: Within our available resources, we believe we are supporting the very best research efforts in diabetes. These include a very large portfolio of fundamental research projects studying aspects of the cause and course of diabetes and the complications resulting from it, research on the genetics of diabetes, two major clinical trials investigating whether diabetes can be prevented, possible new treatments for diabetes, and a national diabetes education program. Later this year, the NIH will sponsor a conference to identify opportunities for expanded research efforts in diabetes. This conference will underscore the importance of diabetes research as a trans-NIH endeavor and will involve all the relevant institutes. We will make every effort to pursue these opportunities. In this context, I am continually evaluating the NIH research agenda, in consultation with the biomedical community, to see that NIH funds are put to the best scientific use, including the most promising diabetes research.

INITIATIVES FOR DIABETES RESEARCH

Mrs. Lowey: Is NIH planning any special areas of emphasis initiatives which would address scientific issues directly related to diabetes?

Dr. Varmus: NIH is planning a number of new or expanded initiatives in Areas of Research Emphasis related to the understanding, diagnosis, treatment, and prevention of diabetes. For example, within "New Approaches to Pathogenesis," we anticipate expanded efforts directed to the study of pediatric antecedents of adult disease, particularly Type 2 diabetes. This has traditionally been regarded as a chronic disease of adulthood. Evidence is accumulating, however, to suggest that adult onset diabetes (like other chronic conditions) originate through genetic-environmental interactions in childhood and may be related to insulin resistance. A great deal of research remains to be done to identify candidate genes and their variants that predict the onset and severity of insulin resistance, of diabetes, and of other conditions later in life. In addition to genetic markers, there is a need to develop biochemical or physiologic markers. If we can predict susceptibility to these conditions at an early age, we may be able to delay or prevent their onset through appropriate dietary and lifestyle interventions.

Another initiative will focus on elucidating the mechanisms of how hyperglycemia causes diabetic retinopathy, an all too common complication of diabetes that can result in blindness. There is mounting evidence suggesting that a particular isoenzyme of protein kinase C may be involved in this disease process.

We also plan to extend research on genetic susceptibility to diseases that disproportionately affect African-Americans. One means of accomplishing this will be to enhance our interaction with Historically Black Colleges and Universities. A project that would benefit from additional funding is at Howard University and is to study the West African origins of genetic susceptibility to Type 2 diabetes in African Americans.

Within "New Preventive Strategies Against Disease," diabetes is one of the disorders that will receive increased attention. Additional support will be provided for a major prevention-oriented clinical trial assessing the novel prophylactic use of parenteral/oral insulin as an immunomodulator of Type 1 diabetes mellitus. Animal studies and preliminary human studies suggest that low-dose insulin therapy may prevent or delay the onset of the clinical manifestations of Type 1 diabetes. Other research has led to the ability to identify individuals at high risk for the development of Type 1 diabetes. Both of these findings are being applied through a major multi-center clinical trial on the prevention or delay of the onset of Type 1 diabetes. This clinical trial will test whether intervention during the time prior to the onset of Type 1 diabetes can delay the clinical appearance of the disease in intermediate and high-risk first-degree relatives of individuals with established Type 1 diabetes. Because Type 1 diabetes is considered an autoimmune disease, attempts will be made to "immunize" at-risk individuals against self destruction of their insulin-secreting cells, which otherwise could result in Type 1 diabetes.

Additional support will also be provided for a recently begun trial examining whether any one or more of the following: different insulin-sensitizing drugs, dietary/exercise interventions, or adoption of a healthful lifestyle, can prevent or delay the onset of Type 2 diabetes in individuals at risk for developing this disease. Because Type 2 diabetes disproportionately affects minority populations, approximately half of the 4000 patients to be enrolled across the U.S. will be from minority populations. All of these interventions are aimed at preventing progression from the pre-diabetic, impaired glucose tolerance state to diabetes or delaying it over a period of about four and one half years.

Within "New Avenues for Development of Therapeutics," we will expand efforts to discover and develop additional drugs to combat diabetes. New understanding of the pathogenesis of and risk factors for diabetes is leading to new opportunities to develop drugs for the treatment of diabetes. For example, the sulfonylurea drugs which are used to stimulate insulin secretion in patients with Type 2 diabetes have been found to exert their effect through changing the function of "potassium channels" in the islet cells. This system is being studied in hopes of producing improved drugs to stimulate insulin secretion.

Within the "Genetic Medicine," area of emphasis, a number of initiatives will include a diabetes component. For example, we will begin to fund the Human Genome Diversity Project. Its goal is to survey human DNA from distinct populations throughout the world to provide a comprehensive description of human genetic variation. This Project is a natural outgrowth of the substantial progress that has been made in mapping

and sequencing the human genome and in identifying genes associated with many simple genetic traits. Geneticists predict that the information gained from the Diversity Project will facilitate the identification of genes associated with complex disorders, such as diabetes, hypertension, arthritis, and various cancers.

The NIH also anticipates expanding the new Center for Inherited Disease Research. The primary goal of this Center is the identification of the genes that play important roles in abnormal development, physiology, and behavior. Its focus is on mapping genes responsible for the genetic contribution to common human disorders, including diabetes, cardiovascular and pulmonary disease, cancer, psychiatric disorders, and autoimmune diseases.

Finally, within "The Biology of Brain Disorders," the NIH anticipates expanded activity in the area of neuroendocrine regulation of metabolism, body weight, and appetite control. As you know, obesity is a major risk factor for diabetes, and more than one third of all adults are now considered obese. In addition, childhood obesity also is on the rise. This expanded initiative will include new research on molecules that have been identified as playing an important role in obesity, such as melanocortin, urocortin, leptin, peptide T, and other brain/gut peptides and receptors. Research funded by NIH suggests that obesity is a complex condition based partly on genetic factors affecting metabolism in obese individuals. Growing evidence indicates that the regulation of food intake and the level of energy expended is controlled by an intricate network of neuropeptide factors that carry signals between the brain and fat, muscle, and liver cells. Research in this area was energized by the discovery of the obesity gene in mice, and the subsequent finding that leptin, the hormone produced from the obese gene, could have dramatic effects on weight and energy expenditure. Mutations in the gene for the leptin receptor cause obesity and diabetes in rats and mice. In Mexican-Americans, chemical variations in the obese gene region have been shown to be associated with both insulin precursors and obesity-related traits. Other studies suggest that leptin in obese individuals may act directly on liver cells to modulate glucose metabolism, reinforcing the idea that it is a contributing factor in the onset of Type 2 diabetes mellitus.

The leptin receptor is present in the brain, among other tissues, and presumably serves as a means for leptin to interact with other neuropeptide signals. Defective leptin signaling in mice has been demonstrated to lead to overexpression of neuropeptide Y in the hypothalamus, which in turn is related to overeating. In another strain of genetically obese mice, being fat appears related to blocking of melanocortin-4 receptors in the hypothalamus. Likewise, the newly discovered hormone, urocortin, appears to act through receptors in the hypothalamus to dramatically reduce food intake. All of these peptides and receptors present potential candidates for design of drugs to block or enhance their actions, with potential for improved interventions in obesity, which in turn could help prevent the development of Type 2 diabetes.

CHILD ABUSE AND NEGLECT

Mrs. Lowey: Both the FY 97 House and Senate Appropriations Subcommittee Reports, in recognition and magnitude and significance of the problem of child abuse and neglect, called upon the National Institutes of Health (NIH) to better coordinate its research in this area. In its report language, this Subcommittee encouraged NIH to convene a working group of its component organizations currently supporting research on child abuse and neglect. We requested that at the FY 98 hearings this working group be prepared to report on current NIH research efforts in this area, the accomplishments of that research, and future plans for improved coordination of child abuse and neglect research. The Senate language went a step further than the House and encouraged the working group to hold a conference on child abuse and neglect and to assess the science and make recommendations for a research agenda. They added that outside organizations and experts should be invited to this conference.

What is the current status of the working group and what Institutes and offices have been invited to participate?

Dr. Varmus: The Child Abuse and Neglect Working Group (CANWG) has begun regular meetings to review NIH research efforts in child abuse and neglect, identify accomplishments and future research needs, coordinate child abuse-related research across NIH, and plan future activities. The members of the NIH CANWG are drawn from the major research institutes and offices conducting child maltreatment research, principally the National Institute of Mental Health, the National Institute on Child Health and Human Development, the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute on Nursing Research, as well as the Office on Behavioral and Social Science Research within the Office of the Director, NIH.

Mrs. Lowey: What specific plans are there to improve coordination and perhaps expand research in this important area?

Dr. Varmus: A report on the working group's activities, research efforts in this area, the accomplishments of that research, and plans for future coordination efforts is being prepared for submission to the Congress as requested. Included in that report are specific plans to improve coordination and expand research and plans to hold a series of conferences and/or workshops.

Given the array of obstacles that have hampered research efforts in the child maltreatment area to date, isolated efforts addressing any single problem area are not likely to be successful. Instead, a coordinated, concerted effort to address the range of infrastructural, content-related, and translational problems will be needed to generate and maintain the necessary research progress to address this important health problem in children and families. The CANWG plans to work closely with other federal agencies to

explore ways to increase knowledge transfer and research application to practice. In order to establish relationships and coordinate its activities with other sectors of government, the CANWG has already met with representatives of other federal agencies including the Administration for Children and Families, the National Institute of Justice, the Office of Juvenile Justice and Delinquency Prevention, the Department of Education, and the Department of Defense.

Mrs. Lowey: Does the NIH have any plans to hold a conference on research on child abuse and neglect?

Dr. Varmus: Working with its NIH representatives, the CANWG identified a range of potential program-building activities that might be undertaken to increase efforts in child maltreatment research across the NIH institutes and with other federal partners. To build the research capacity of this fledgling field, the CANWG is planning a series of conferences and workshops to train and attract new investigators. We expect that these meetings will include training potential investigators in issues of child abuse assessment, identifying areas of research opportunity, and enabling young investigators to engage in the necessary interdisciplinary research strategies needed to find answers to important child abuse questions.

Other proposed meetings will focus on the continued enhancement of the methodological and conceptual sophistication of the field of child abuse, and will be aimed at fostering improvements in sampling procedures, definitions, measurement and assessment, research designs in longitudinal and treatment research studies, and data analytic methods. Several meetings addressing these definitional and assessment issues have already been initiated, sponsored in partnership with other federal agencies through the Federal Interagency Research Committee on Child Abuse and Neglect.

RESEARCH IN OBSTETRICS AND GYNECOLOGY

Mrs. Lowey: Research in three critical fields are vital to maternal and child health --obstetrics, gynecology and pediatrics. The 1993 NIH Revitalization Act directed a program in obstetrics and gynecology to be established in the NIH intramural program. Has such a program been established and in how many Institutes?

Dr. Varmus: The National Institute of Child Health and Human Development (NICHD) has established intramural programs in obstetrical and gynecologic research. The Perinatology Research Branch addresses obstetrics and the Section on Gynecology Research, resides within the NICHD intramural Developmental Endocrinology Branch.

Mrs. Lowey: What areas of research are they pursuing and what continuing measures are being taken to implement that program on the NIH campus?

Dr. Varmus: The Perinatology Research Branch investigates causes of infant mortality including premature labor and delivery, congenital malformations, and hypertension in pregnancy. The clinical research activities of this branch require a location other than the NIH campus. Although in November of 1995, the NICHD terminated a contract with Georgetown University which had hosted this branch, the Institute intends to re-issue a request for proposals (RFP) to host the branch within the next few months. A stipulation of the RFP is that the host institution must be located no more than a one hour drive from the NIH campus.

Recently, the Section on Gynecology Research has been expanded and re-named the Section on Women's Health. This section studies the physiology and pathophysiology of female growth and development, reproduction, and aging; examines the biological roles and mechanisms of action of estrogen and progesterone; and conducts both clinical and basic research on the causes and treatment of obesity, menstrual cycle disorders, endometriosis, premature ovarian failure, and polycystic ovarian disease. This section is physically located at NIH Clinical Center on the NIH campus.

CONTRACEPTIVE AND REPRODUCTIVE HEALTH TRAINING PROGRAMS

Mrs. Lowey: There were very few boarded obstetrics/gynecologists employed within the intramural program in 1993. At present, how many boarded obstetrician/gynecologists hold permanent full-time (FTE) positions as intramural scientists?

Dr. Varmus: There are eight permanent full-time (FTE) positions occupied by board-certified obstetricians/gynecologists at NIH, who are credentialed in their specialty by the NIH Medical Executive Committee.

Mrs. Lowey: The NIH Revitalization Act also directed NIH to establish centers in contraceptive and reproductive health with training programs designed to recruit students by establishing a loan repayment program. Where are these centers located?

Dr. Varmus: NICHD funds three specialized centers in contraception development research and two in infertility research that have authorization for loan repayment programs. Information on these centers follow:

Contraception Development Research Centers

University of Virginia, Charlottesville, Virginia
University of California, Davis, California
Population Council, New York, New York

Infertility Research Centers

Massachusetts General Hospital, Boston, Massachusetts
University of Michigan at Ann Arbor, Ann Arbor, Michigan

Mrs. Lowey: How many students has the loan repayment program been able to recruit as trainees?

Dr. Varmus: The loan repayment program is in the final stages of implementation. It is expected that 10 to 20 students will be recruited into this program by the end of this year.

PEDIATRIC RESEARCH

Mrs. Lowey: Pediatric research is also of major importance to the health of the Nation. How many programs in pediatric research are there at NIH and in how many Institutes?

Dr. Varmus: Virtually all of the NIH Institutes are engaged in some aspect of pediatric research. The extent and focus of each Institute's efforts in pediatric research vary considerably, however, with seven Institutes accounting for approximately 75 percent of the overall effort. The collective NIH pediatric research portfolio spans a broad range of children's diseases and health problems and includes basic biological and behavioral studies, clinical trials, health services research, and public education activities. While most of the Institutes focus their pediatric research efforts on those children's health problems that relate to their own programmatic goals, there are also many instances of multi-disciplinary, integrative approaches to pediatric research. Because research on the causes, consequences, prevention and treatment of any single disease requires diverse areas of expertise, multiple Institutes often play an important role in exploring the nature of a complex disorder. One example of this is research on childhood asthma. Three Institutes are engaged in pediatric asthma research, targeting distinct, but equally important, facets of this increasingly serious health problem—the National Institute on Environmental Health Sciences focuses on the effects of air pollutants on respiratory health; the National Heart, Lung, and Blood Institute supports studies relevant to the development of new pediatric asthma therapies and coordinates the National Asthma Education and Prevention Program; and the National Institute of Allergy and Infectious Diseases seeks to understand the immunological aspects of asthma, identify risk factors and risk reduction strategies for inner-city children, and develop ways to lessen asthma morbidity by reducing allergens in the home. Given the increasing severity of the asthma problem among minority populations, all three Institutes are also exploring measures to address the special problems of minority and/or economically disadvantaged children.

In 1996, the NIH prepared a *Report on NIH Pediatric Research* in response to a request from the House Committee on Appropriations. The Report includes a comprehensive overview of the NIH pediatric research portfolio, and illustrates the broad scope and diversity of children's research issues being addressed and the importance placed on studies that speed the translation of knowledge from the laboratory to the clinic. The Report also describes efforts being made across NIH to strengthen pediatric research activities, to measure progress in achieving a stronger portfolio of pediatric research, and to increase the participation of children in research.

NUMBER OF INTRAMURAL PEDIATRICIANS

Mrs. Lowey: What number of board certified pediatricians are working in permanent (FTE) positions as intramural scientists?

Dr. Varmus: There are 88 permanent full-time equivalent (FTE) positions occupied by board-certified pediatricians at the National Institutes of Health (NIH), who are credentialed in their specialty by the NIH Medical Executive Committee.

RESEARCH IN OBSTETRICS, GYNECOLOGY, AND PEDIATRICS

Mrs. Lowey: Considering the need for research in the areas of obstetrics, gynecology, and pediatrics, how does the National Institutes of Health (NIH) plan to promote these fields?

Dr. Varmus: The NICHD has in place a number of career development and other programs aimed at encouraging young obstetrician-gynecologists and pediatricians to pursue careers in research related to their clinical interests.

In FY 1993 the NICHD announced the availability of the Clinical Investigator Development Award (CIDA). These awards provide support for research career development clinically trained individuals, who have a range of research experience, and who are committed to developing careers as independent investigators. This award allows candidates to undertake three to five years of advanced study and supervised research with the goal of developing into independent investigators. In FY 1996, NICHD supported 39 of these awards to clinical investigators with interests in obstetrics, gynecology or pediatrics.

The NICHD also supports Physician-Scientist Awards. The Physician-Scientist Award is a postdoctoral career development award which is intended to encourage newly trained clinicians to develop independent research skills and experience. In FY 1996, NICHD supported 18 of these investigators through individual awards and 20 through institutional awards in pediatrics, obstetrics and gynecology.

In the area of obstetrics-gynecology, NICHD is the lead co-sponsor of a multidisciplinary, multi-institution Physician Scientist Program, jointly funded by the private sector and NICHD, called the Reproductive Scientist Development Program. This program is specifically designed to provide clinically trained obstetrician-gynecologists with basic science research skills and experience leading to careers in academic medicine. Its aims are to increase the awareness and attractiveness of a career in academic obstetrics and gynecology, directly facilitate the development of research career efforts in the biomedical sciences, and stimulate the retention and maximal productivity of young clinically trained obstetrician-gynecologists engaging in academic careers as physician scientists. The NICHD currently supports 8 career development positions under this program.

The Pediatric Scientist Development Program was initiated approximately 10 years ago under the sponsorship of the Association of Pediatric Department Chairmen. This program has proven extremely successful and has support not only from NICHD but also from private foundations. The NICHD currently supports 12 career development positions under this program. Of the graduates from this program, more than 85 percent have remained in academia, doing research, clinical work, and teaching.

In addition to these career development awards, the NICHD supports research centers and cooperative clinical research programs that provide unique training and development opportunities for clinical investigators in the areas of obstetrics, gynecology and pediatrics. Examples of these programs include the contraception research and infertility centers and the maternal-fetal medicine and neonatal intensive care networks.

The NIH is currently engaged in a number of other activities to strengthen pediatric research. For example, we are working to develop a policy that will ensure the appropriate inclusion of children in clinical research. In June 1996, the NIH and the American Academy of Pediatrics convened a workshop to address the inclusion of children in clinical research in order to assess the current situation, identify barriers, and develop options for policy changes. Following the workshop, the NIH established a committee on inclusion of children in clinical research, which is charged with developing NIH's policy in this area. Most recently, we published a notice in the *NIH Guide for Grants and Contracts* (Vol. 26, Number 3, January 31, 1997) apprising the field of our intent to develop a policy on the inclusion of children as subjects in clinical research and encouraging investigators to consider including children in clinical research projects. The NIH will continue to involve the scientific and professional community as it moves forward with its efforts to develop and implement policy in this area, and will keep the Committee apprised of progress on this critical issue.

As you know, the FY 1997 NIH appropriation included $5 million within the Office of the Director to fund a Pediatric Research Initiative. I have identified three areas which will be emphasized under this initiative--pediatric therapeutics, developmental abnormalities, and pediatric asthma--and I am working with the Institute Directors to develop a plan for the allocation and use of these funds.

NIH staff are currently preparing a report for the Appropriations Committees on NIH activities to strengthen pediatric research. This report is an update to the 1996 Report on NIH Pediatric Research. It should be completed soon and will focus on NIH's continued efforts to strengthen its research portfolio, and will highlight recent research accomplishments, expanded and new pediatric research activities, efforts to increase the participation of children in research, public education activities, and planned pediatric research activities. It provides a brief overview of the continuing and expanded pediatric research activities of NIH's Institutes, describes some recent advances from children's health research, highlights new pediatric research activities that were initiated and/or planned since preparation of the 1996 report on pediatric research, and includes examples of NIH efforts to inform the public of recent findings in pediatric research.

WOMEN IN CLINICAL TRIALS

Ms. DeLauro: What kinds of strides has the NIH made to include women in clinical trials?

Dr. Varmus: Much progress has been made in the implementation of the National Institutes of Health (NIH) Revitalization Act of 1993 for the inclusion of women and minorities in clinical research supported by the NIH. As a result of collaborative efforts between the Office of Research on Women's Health (ORWH), the Office of Minority Health, the Office of Extramural Research, the Office of Intramural Research, and the ICDs, revised policies and procedures based on scientific considerations, have been developed and implemented. A computerized tracking system is now in place to assist in the trans-NIH monitoring of inclusion. For the first time, aggregate NIH and individual institute data are available to document the numbers of women and minorities included in clinical research. Preliminary analysis has been completed for Phase III trials active on or after October 1, 1994. Data for 1995 are currently being compiled and will be evaluated for trends in future studies. The ongoing collection of data will allow for longitudinal examination of trends of inclusion and continued monitoring of compliance.

Grant review procedures now reflect that inclusion is considered an issue of scientific merit, to be reflected in priority score; applications that do not meet the requirements can not be funded. Extensive training on the new inclusion requirements has been conducted for over 1,000 NIH staff members with review, program, or grants management responsibilities. Numerous outreach activities have been conducted to communicate policy with members of the scientific community and the public. NIH has distributed thousands of copies of its publications addressing issues of inclusion: *The Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research; Questions and Answers Concerning the 1994 NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research; Recruitment and Retention of Women in Clinical Studies.* A national workshop of Institutional Review Board Chairs (IRBs) was re-convened in 1996 with representation from the ORWH Task Force on the Recruitment and Retention of Women in Clinical Research, to discuss issues related to implementation of the NIH inclusion policy. Participants reported that many of the concerns expressed two years ago were addressed because NIH focused on scientific questions, fostered partnerships and scientific initiatives to implement inclusion guidelines.

Ms. DeLauro: How is the inclusion of women in clinical trials addressed in your FY 98 budget request?

Dr. Varmus: The FY 1998 budget request includes provisions for ORWH to support the ongoing activities of the NIH-wide tracking/inclusion effort and to provide support for ICD data collection and monitoring where needed. ORWH will facilitate the analysis of data from the ICDs on the inclusion of women and minorities in research studies to examine trends and apparent gaps in enrollment. Special studies can then be designed to target health problems of particular communities, specifically those that continue to be underrepresented in research studies. Outreach activities will be designed to address continuing or new concerns of the scientific and volunteer communities which may affect the success of NIH inclusion policies. Furthermore, ORWH staff will continue to discuss the importance of inclusion to many scientific and advocacy groups to help investigators facilitate recruitment of women and to encourage women to volunteer in clinical studies. In addition, ORWH will reconvene the representatives of IRBs to maintain prominence of inclusion as a significant consideration, to determine continuing issues, and provide an opportunity for participants to develop and share successful solutions to inclusion challenges, including those of special populations of women, e.g. women of childbearing age. Finally, recommendations from the regional and national meetings of the Advisory Committee for Research on Women's Health will help to focus on special subpopulations and suggest how best to facilitate the inclusion of these women in clinical studies. ORWH will support these additional outreach activities to ensure inclusion in collaboration with NIH ICDs.

NEW AND COMPETING RESEARCH PROJECT GRANTS

Ms. DeLauro: I noticed that the amount of new and competing research project grants (RPGs) is decreasing by 168 grants in your budget. Could you please explain this decrease?

Dr. Varmus: Research project grants (RPGs) are one of the National Institutes of Health's (NIH) highest priorities. Although the number of new and competing RPGs declines in FY 1998, the total number of RPGs increases by 693 over the FY 1997 Estimate. The decline in number of new and competing RPGs is the result of a large number of competing grants from FY 1997 cycling into the noncompeting RPG pool in FY 1998. As RPGs cycle between the competing and noncompeting pool, the number of new and competing grants will fluctuate from year to year.

INSTITUTE OF MEDICINE RECOMMENDATIONS

Ms. DeLauro: Two years ago, the Committee urged the NIH to implement recommendations of the 1994 Institute of Medicine (IOM) report on clinical research. Subsequently, an advisory committee on clinical research was appointed, and last year the Committee instructed NIH to "accelerate the work of that panel so that NIH can proceed expeditiously to respond to the IOM recommendations, as well as those the panel may have". Why, two years later, does NIH continue to delay much-needed initiatives to support clinical research in the extramural community?

Dr. Varmus: The NIH is now in the process of implementing the December 1996 recommendations of the Clinical Research Panel that are consonant with the recommendations of the Institute of Medicine (IOM) report. These recommendations are designed to support the full spectrum of clinical research, and the greatest effect of the recommendations will be felt in the extramural community. The NIH commitment to clinical research has been recently clarified to be 38% of the total dollar amount of all competing (new and renewal grants) awards to extramural researchers in FY 1996.

CLINICAL RESEARCH AT ACADEMIC MEDICAL CENTERS

Ms. DeLauro: This Subcommittee has supported construction of a new clinical research center on the NIH campus, but we cannot turn a deaf ear to the major obstacles to clinical research at academic medical centers across the country.

Why are NIH initiatives to address challenges confronting clinical research focused primarily on the intramural program?

Dr. Varmus: The NIH initiatives are designed to address the challenges confronting clinical research in extramural programs in a major way. Only two of the eleven recommendations drafted by the Clinical Research Panel focused primarily on the intramural program, and these are intended to act as a focus or pilot for related extramural clinical research activities. These are:

•Continue to improve the quality of clinical research and strengthen research management in the Warren Grant Magnuson Clinical Center and the availability of its resources to extramural investigators.

•Initiate a medical student training program in clinical research on the NIH campus and in academic health centers in collaboration with the private sector.

The scope of these two recommendations will not be limited to the intramural program. For example, as the quality of clinical research is improved in the NIH Clinical Center and its research management strengthened, the Panel recommended that the "availability of its resources [be extended] to extramural investigators." Further, the medical student training program in clinical research, as recommended by the Panel, is intended to serve as a model for extramural centers and to train medical students from around the country.

Ms. DeLauro: What is the point of a medical student training program in clinical research on the NIH campus if NIH does not proceed to offer new mechanisms of support to enable those to pursue clinical research careers in the future?

Dr. Varmus: NIH has been concerned with the issue of supporting young and mid-career investigators for some time. In this vein, the Panel made the following recommendation:

- Initiate new support mechanisms for young and mid-term clinical investigators, if possible in collaboration with the private sector.

Such awards are necessary to relieve clinical investigators from patient care responsibilities required to generate income and to protect their time for clinical research. Innovative approaches to implement this recommendation are presently under discussion by the NIH Office of the Director with the Institutes and Centers.

It is important that NIH support of clinical research in extramural institutions is indeed already very substantial. Using the definition for clinical research adopted by the Clinical Research Panel, NIH has determined that in FY 1996, with regard to competing extramural awards, 27% of its awards and 38% of associated dollars supported clinical research projects.

Ms. DeLauro: When is NIH going to propose much-needed new initiatives for extramural clinical investigation?

Dr. Varmus: The NIH is in the process of implementing the full complement of the recommendations of the Clinical Research Panel. As noted above, these recommendations mainly enhance extramural clinical investigation.

CLINICAL RESEARCH PANEL

Ms. DeLauro: I have reviewed the Panel's latest draft report and find it insufficient in terms of substance. There is little in the way of specific proposals with programmatic details or budget requirements. I note that many of the comments submitted to the Panel as summarized in an appendix are quite negative or recommend much more aggressive action. Why are the Panel's recommendations so vague?

Dr. Varmus: The members of the Clinical Research Panel are committed to clinical research and created a series of far-reaching recommendations to enhance and reinvigorate the field of clinical research nationwide. The Panel has done an admirable job of crafting constructive and feasible recommendations, and it is the National Institutes of Health's (NIH) task to translate the Panel's recommendations into specific programs, while at the same time preserving the delicate balance between basic and clinical research.

Further, NIH depends on proposals developed by prospective investigators to bring creative, new ideas into various fields of biomedical research. This energizes areas of investigation, while, in contrast, excessive specification of programs encourages mediocrity. Excellence in research at the NIH is driven by such investigator-initiated proposals, which must be cultivated and fostered. The Panel's recommendations, while broad, are intended to reinvigorate clinical research and should provide the necessary framework to move forward in a fashion consistent with the above philosophy.

INSTITUTE OF MEDICINE RECOMMENDATIONS

Ms. DeLauro: As you know, I have introduced legislation with three colleagues on this Subcommittee and other prominent House members designed to implement the IOM Report recommendations. I noted that several organizations in comments to the Panel urged support for aspects of this legislation, recommending that NIH should proceed with these new initiatives regardless of whether legislation is passed. Why isn't NIH proceeding on its own to implement new programs such as the career enhancement award and the innovative science award proposed in our legislation? As the Panel stated in its analysis of our bill, NIH already has the authority to proceed with these initiatives.

Dr. Varmus: The NIH has the authority to proceed with initiatives to enhance clinical research, with the exception of the authority to institute a loan repayment program for clinical research in extramural institutions. Many such initiatives are under active consideration as NIH implements the Clinical Research Panel's recommendations. Some of these overlap with provisions in the legislation you introduced last year. However, these initiatives must be carefully planned for maximum effectiveness in conjunction with the NIH Institutes and Centers.

PEER REVIEW OF CLINICAL RESEARCH

Ms. DeLauro: What is the status of implementation of the changes in the peer review of clinical research recommended by the Division of Research Grants (DRG) outside advisory group over two years ago?

Dr. Varmus: The new Director of the Division of Research Grants (DRG), Dr. Ellie Ehrenfeld, has met with members of the Clinical Research Panel and is prepared to develop pilot mechanisms in DRG's study section review process for clinical projects, especially translational projects with both clinical and basic research components. Furthermore a committee of the Peer Review Oversight Group (PROG) is reviewing mechanisms for identifying and recruiting qualified clinical researchers to review clinical research applications.

INITIATIVES FOR CLINICAL RESEARCH

Ms. DeLauro: I think that this Subcommittee has given the NIH ample time to take action on the challenges confronting clinical research, but our patience is not endless. I would like to ask Dr. Varmus to provide to this Subcommittee by the end of March a two-page, summary of specific, extramural initiatives that NIH will undertake in the next six months to reinvigorate clinical research in this country

Dr. Varmus: In FY 97, the NIH has developed several major clinical research and clinical research training initiatives. The following are provided as examples:

The National Cancer Institute (NCI) and the Department of Defense (DoD) signed an agreement to allow DoD medical beneficiaries to participate in various NCI sponsored clinical trials of new cancer treatments. Participants may receive treatments either through the medical treatment facilities that have been approved to conduct NCI trials or through medical care arrangements reimbursed through TRICARE/CHAMPUS, the DoD's health program. This partnership allows DoD beneficiaries throughout the country to receive state-of-the-art care through NCI sponsored clinical activities by participating in emerging new approaches that have significant promise for the successful treatment of cancers.

NCI will continue to provide a user-friendly, active information system through an expansion of the Physician Data Query. This allows physicians quick access to information about open available protocols at the nearest or most appropriate institution or to physician participating in the suitable protocols.

In the training area, the NCI has developed a new program, the Career Transition Award, to provide support to outstanding newly trained basic or clinical investigators to develop their independent research skills through a two phase program; an initial period involving an intramural appointment at the NIH and a final period of support at an extramural institution. The award is intended to facilitate the establishment of a record of independent research by the clinical investigator in order to sustain or promote a successful research career. It is anticipated that this new program will be announced in the NIH GUIDE in the next few months.

In addition, the NCI has recently implemented an Accelerated Executive Review (AER) that targets new competing research grant applications that are within 4 percentile points of the payline for basic research or 10 percentile points for "patient oriented research". This AER is designed to encourage clinical projects by allowing a broader range of eligible applications, 10 percentile beyond the payline for funding. In FY 96, the NCI Executive Committee reviewed 51 applications under the AER (31 basic research and 20 patient oriented research). The committee recommended 26 of these for awards, for a total cost of $6.7 million. Nine of these were for "patient oriented research".

The National Heart, Lung and Blood Institute, in collaboration with the Health Care Financing Administration, is sponsoring a randomized trial, Lung Volume Reduction Clinical Trial, to determine the benefits and risks of this operation to patients with end-stage emphysema. Currently, hundreds of patients are being subjected to this operation despite the fact that its effectiveness had never been established. Furthermore, there are no data on long-term outcome, and no evidence is available to indicate which patients might benefit from the operation. This trial will provide patients with the information they need to make informed, intelligent decisions about their health care.

Within the next six months, the National Institute of Allergy and Infectious Diseases (NIAID) will fund ten new clinical research initiatives in FY 1997 and announce an intent to fund 12 additional ones that will be funded in FY 98. These initiatives span the range of clinical research activities from small pilot studies to large clinical studies and phase II and III clinical trials. New career development activities for clinical investigators are included in the goals of the initiatives on emerging and re-emerging diseases. The clinical research needs and opportunities addressed by these 22 new clinical research initiatives include AIDS, vaccine development and testing, chronic fatigue syndrome, immunological effects of aging, women's health issues, sexually transmitted diseases in adolescents, transplantation, and emerging and re-emerging infectious diseases, including malaria. A list of the titles of these initiatives is attached. The NIAID is also conducting a review of its infectious diseases research training programs to ensure that these programs are producing investigators with the capacity to carry out independent research in clinical investigation.

Beyond its specific initiatives and activities, the NIAID is also applying newly developed, streamlined grants management procedures to expedite the evaluation and funding of clinical research grant applications. These streamlined procedures consist of selective payment of applications that are identified as having important clinical research goals; electronic peer review and early Council review to expedite the award of grants to clinical investigators.

In FY 97, The National Center for Research Resources (NCRR) will support the network of GCRC and other related activities with a total of $157 million. The NCRR funded one new GCRC in FY 96 and depending on available funds, may consider funding an additional new center in FY 97. The FY 96 award was made to Howard University which is particularly significant in that it related to research on diseases that affect African Americans and for Historically Black Colleges and Universities. In addition, NCRR funded a new satellite site at Children's Hospital, Seattle, WA.

The NIH loan repayment program is currently limited to scientists in the intramural program and is being implemented. The NIH may seek a legislative change to broaden the eligibility for the loan repayment program to include clinical researchers at academic health centers throughout the country, a situation under legislative restrictions now.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Overview

FY 1998 Budget	Page No.
Justification narrative	3
Increases for Areas of Research Emphasis	26
Funding Including AIDS	27
Appropriations summary	28
Budget mechanism table	29
Full-time equivalents	30
Appropriation history	31
Budget authority by object	33
Administrative Costs	35
Medical and Health-Related R&D	36
Statistical data - Direct/Indirect costs	38
Research grants & Success Rates	39
Ten-year history of obligations	41
Management Fund	43
Service and Supply Fund	48

THE NATIONAL INSTITUTES OF HEALTH

IMPROVING HEALTH THROUGH MEDICAL RESEARCH

The National Institutes of Health (NIH) is the world's largest and most distinguished organization devoted to maintaining and improving health through medical research. The NIH is actually a federation of 22 research Institutes and Centers (ICs), each created by Congress and charged with a unique mission. A mission may focus on a given disease, such as cancer, mental illness, or infectious diseases; on a particular organ such as heart, kidney, or eye; or on a stage of development, such as childhood or old age. In other instances, a mission might encompass cross-cutting needs and opportunities, such as the development of research resources or the sequencing of the human genome. The assignment of targeted missions to individual ICs accounts for many of NIH's greatest successes.

Given its size and diversity, "NIH" means different things to different people. Many Americans recognize it as a government agency that supports health research. They associate research advances headlined in the news, as well as new treatments they receive from their own doctors, as products of NIH's work. The more than 20,000 patients who come each year to the NIH's Clinical Center view NIH as an extraordinary hospital where they volunteer to be partners in clinical research and receive experimental treatments for rare diseases. Thousands of students and post-doctoral graduates value NIH and its grantee academic institutions for providing outstanding research training opportunities. And, of course, some 50,000 scientists across the Nation and throughout the world view the agency as an indispensable source of support for critical medical research; eight out of every 10 dollars appropriated to NIH are awarded—through a process of rigorous competition—to investigators in many disciplines who have dedicated themselves to the struggle to improve health and conquer disease. To many of these individuals, NIH connotes the individual IC most closely related to a patient or family member's illness, or a student's interest, or a scientist's area of expertise. Yet, NIH's success is based on its ability to bring to bear the full weight of all of its ICs to solve fundamental scientific questions and address the urgent challenges of disease.

The capability for a truly unified scientific effort can be achieved only through design and perseverance. It requires close interaction among NIH's ICs. These collaborations may be informal, such as scientists discussing their research with one another and lending suggestions, reagents, and equipment to fellow scientists. Or, they may be guided by inter-Institute committees or by NIH-wide coordinating offices such as the Office for Research on Women's Health or the Office of Behavioral and Social Sciences Research. As a "laboratory without walls," the NIH affords unparalleled opportunities to simultaneously address different aspects of a given problem from multiple vantage points. Alzheimer's Disease research, for example, takes place in Institutes devoted to aging, neurology, and mental health, among many others. Advances in cardiovascular disease research are based on insights gleaned from research supported and conducted by many Institutes, including those dedicated to heart disease, stroke, arthritis,.

diabetes, and cancer. Similarly, the newly established Center for Inherited Disease Research (CIDR) is co-sponsored by nine participating NIH ICs. The Center is devoted to the genetic analysis of complex, multigenic diseases such as cancers, cardiovascular and pulmonary diseases, hearing and language disorders, neurological diseases, psychiatric disorders, autoimmune diseases, and addictive disorders. These and other complex diseases have been challenging to analyze, since they are often caused by a number of environmental and genetic factors acting in concert. They require very large scale, labor intensive genetic searches.

By maximizing flexibility and encouraging open and collegial dialogue among ICs, as well as between NIH and its sister Public Health Service agencies, research driven by both fundamental scientific questions and pressing public health need can thrive. For example, research supported by the NIH is an essential part of the Administration's comprehensive response to drug abuse and addiction. These problems touch the lives, directly or indirectly, of virtually all Americans. Of special concern is teenage drug use and emerging drug problems, such as methamphetamine use. This research spans the continuum from molecular genetics to drug development and health services research. It continues to provide new insights into the development of medications for the treatment of addiction, to develop new behavioral therapies to meet the unique needs of adolescents, to identify the risk and protective factors for drug use—all in an effort to develop more effective treatment and preventive strategies against this national public health crisis.

The ultimate goal of all NIH research is to improve human health. This research, whether conducted in academic institutions in all 50 States or on the NIH campus, is made possible by a system which fosters both independent thought and collaborative efforts. The success of this approach can be judged from the pages that follow.

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The announcement of an important medical finding on a morning news program appears, at first glance, to be the result of a scientific "eureka!" In most cases, it is not. Medical breakthroughs are usually the result of years of painstaking research that includes episodic disappointments and triumphs, finally culminating in the apparent "breakthrough." The following tells the story of how a major public health problem was virtually eliminated following a 30-year research effort.

Story of Discovery: The Hib Conjugate Vaccine

In September, 1996 four NIH-supported investigators shared the prestigious Albert Lasker Clinical Medical Research Award for their work in developing vaccines against Haemophilus influenzae type b (Hib). The award called attention to a spectacular accomplishment: that Hib infection, once a major cause of death, deafness and acquired mental retardation in children, is now nearly nonexistent in the U.S.

Almost three decades ago, as many as 20,000 children in the U.S. developed *Haemophilus influenzae* type b (Hib) disease each year. The most common and serious complication of Hib

infection was meningitis, a fatal infection of the membranes covering the brain. Even with effective antibiotic treatment, 5 percent of infants and children with Hib disease died and about 30 percent sustained permanent damage to their central nervous system, in the form of mental retardation, deafness, and seizures. The widespread incidence of Hib infections in the U.S. and world-wide, as well as the serious health consequences of the disease vividly highlighted the need for an effective vaccine, especially in infants and children. This was reinforced by two alarming observations—that children in crowded day-care centers were experiencing a 10-fold higher incidence of Hib meningitis than the general population, and that Hib developed resistance to commonly used antibiotics.

Two teams of researchers began working on parallel, but separate, paths to develop a vaccine, choosing to use the Hib bacteria's outer coat of polysaccharide (sugar) as the immunity-stimulating component of the vaccine. Many of their colleagues believed it would be nearly impossible to develop a vaccine for infants using a polysaccharide. Nevertheless, by the early 1970's the scientists had prepared Hib polysaccharide that was suitable for clinical trials. The polysaccharide vaccine proved safe and effective in children older than 18 months of age. Many more years of work supported by NIH and pharmaceutical companies would lead to the eventual licensing and marketing of three Hib polysaccharide vaccines for children older than 18 months.

Although Hib infections occurred mostly in children up to age 5, infants six to twelve months old were especially vulnerable. Unfortunately, Hib polysaccharide vaccine failed to stimulate immunity in these infants, the age group with the highest incidence of serious disease. The scientists set out to make a vaccine that would also be effective in infants, drawing from research carried out in the 1920's and 30's which showed that polysaccharides elicit a stronger immune response if they are chemically attached to a protein. Between 1980 and 1983, both groups succeeded in attaching the Hib polysaccharide to a protein, although they used different proteins and different methods for attaching the polysaccharide to the protein. These were the first "conjugate" vaccines to ever be developed. Both Hib conjugate vaccines elicited higher levels of immunity in adults and children than did the polysaccharide alone. Most importantly, however, these conjugates also elicited an immune response in infants. Extensive clinical trials confirmed that Hib conjugates prevented meningitis in infants, and the Hib conjugate vaccines were licensed by the FDA in the mid-to-late 1980's.

Today, Hib conjugate vaccines are part of the routine pediatric immunization series given to babies starting at the age of 2 months. As a result, Hib meningitis and the other systemic infections caused by Hib—such as epiglottitis, osteomyelitis, and septic arthritis—have virtually disappeared in the U.S., Canada, Iceland, Finland, Sweden, Norway, Germany, Switzerland, and Holland. These studies have pointed out that it is theoretically possible to eradicate both Hib organisms and disease, similar as the case with smallpox and what appears to be occurring with poliovirus and poliomyelitis.

Impressive as this story of discovery is to date, its legacy promises to be even greater. The conjugate concept developed by these researchers is making possible the development of vaccines -

against other bacteria with polysaccharide coats. Scientists are already working, for example, on conjugate vaccines to prevent pertussis, typhoid fever, dysentery, pneumonia, otitis media, and illness from *E. coli* 0157 contamination of beef. The Hib story exemplifies the power of scientific partnerships, for although the teams of researchers worked independently, they routinely and consistently shared their knowledge and insights with one another, ensuring an effective solution to a serious public health problem.

Researchers in non-medical industries also often make innovative use of the findings from NIH's medical research. This can lead to the development of commercially important products, such as the ones described below.

Story of Discovery: Beyond the Boundaries of Medicine

An examination of the "scientific pedigrees" of many non-medical biotechnology products now in the marketplace reveals a vital dependence on the knowledge of basic life processes and the laboratory tools that have emerged from decades of NIH investment in fundamental research. Furthermore, it is apparent that the private sector is closely monitoring advances in medical science and is acting quickly to incorporate new knowledge and methods into valuable commercial applications. The scientific history of several commercially important non-medical biotechnology products illustrates this point.

Genetically engineered crop plants are currently a prime area of innovation and new product development in the biotechnology industry. Nearly 20 such "transgenic" plants are commercially available, and several dozen more are poised to hit the marketplace in the next several years. The first plant to be genetically engineered for quality improvement was developed by Calgene, a U.S. biotechnology company that, in 1994, introduced the *Flavr-Savr™ tomato* to the fresh produce market. The Flavr-Savr™ has been genetically engineered to delay the substantial softening of tomato flesh that normally accompanies ripening. This modification was achieved by inserting an "antisense" gene into tomato DNA that prevents the production of a protein needed for softening the tomato flesh. The NIH was a principal supporter of much of the research underlying antisense technology, including basic recombinant DNA research in the 1960s and 1970s and research in the first half of the 1980s, in which scientists demonstrated that antisense methods could be used for gene regulation in a wide variety of cell types. Agricultural scientists successfully adapted the technique to the Flavr-Savr™ tomato just a few years later.

In 1996, two U.S. agricultural companies, Ciba Seeds and Mycogen Seeds, began to market *hybrid corn plants that are resistant to the European Corn Borer*, a notably destructive insect which has long plagued U.S. farmers. The pest resistance feature of the seeds was the result of genetic engineering. Corn DNA was modified to include a "foreign" gene—from a common soil bacterium—for the production of insecticidal crystal proteins that kill the European Corn Borer. Although corn capable of producing these crystals emerged from agricultural research in the early 1990s, the knowledge necessary for its development emerged out of earlier medical research. NIH-funded researchers, for example, were the first to isolate a crystal protein gene in 1981. This

accomplishment opened the door to an expanded research effort to identify the genes and molecular pathways involved in crystal protein production. The development of genetically engineered corn also depended on novel methods for transferring foreign genes into corn plants—technology which emerged from NIH-funded medical research in the late 1980s.

A third illustrative case is the growing commercial application of laboratory *DNA typing* as a basis for distinguishing differences between organisms, including humans, animals and plants. DNA typing relies heavily upon a technique known as RFLP analysis. RFLP analysis has subsequently been applied successfully to crime scene analysis, paternity determination, farm animal husbandry, quality control of microorganisms used in industry, and ecological and environmental studies. The development of the RFLP analysis technique was predicated on a number of pivotal medical science advances, many of which were supported by NIH in the 1970s, including understanding the role of restriction enzymes, DNA hybridization methods, and laboratory tools for separating DNA fragments.

Areas of Research Emphasis

These stories of discovery illustrate the difficulty of predicting all the applications of medical research. It is still important, however, to establish research priorities. Each year, the NIH Director identifies Areas of Emphasis which show the most promise for addressing public health needs and yielding medical advances that will lead to improvements in human health. Accordingly, six Areas of Research Emphasis have been identified for FY 1998. Five of these were also used in the development of the FY 1997 budget—The Biology of Brain Disorders, New Approaches to Pathogenesis, New Preventive Strategies Against Disease, Genetic Medicine, and Instrumentation and Computers. A new area of emphasis, "New Avenues for Development of Therapeutics" emerged from consideration of Institutes' and Centers' (ICs) proposals for new initiatives. For FY 1998, a number of enticing opportunities have emerged in each of the Areas of Emphasis. These include: new efforts in developmental neuroscience to explore how different types of nerve cells form and organize themselves in the developing brain; the design of diagnostic tests and strategies to respond to emerging food- and water-borne infections as well as the looming threat of cross-species infections; additional efforts to decipher the genome using gene "knockout" techniques; innovative technologies for visualizing and analyzing complex interactions among the molecular building blocks of life—DNA, RNA, proteins, and other substances; and new efforts to assess a broad range of medications for pediatric diseases and conditions.

This approach of providing incentive funding for a focused initiative has successfully stimulated research and fostered collaborations among ICs. For example, within the Biology of Brain Disorders area, an initiative, spurred by the President's strong commitment to spinal cord research, was begun last year to encourage research on spinal cord injury. Spinal cord injury is experienced by approximately 10,000 Americans—more than two-thirds of them under age 30—with often devastating impact. The initiative was kicked off with a major workshop that convened experts on spinal cord injury along with leaders from other scientific areas to foster new ideas and collaborations. As a result of the workshop, a program announcement was issued

highlighting important relevant research topics, including the mechanisms of secondary injury that damage spinal cord cells in the hours immediately after trauma; immune responses that may help or hinder recovery; the identification and study of survival and growth factors; systems that guide growing axons to find appropriate destinations and make functional connections; the development of improved animal models for research on therapeutic interventions; and systematic studies of rehabilitation. NIH expects to continue this strong commitment to spinal cord injury research.

Major medical breakthroughs are usually the result of years of research involving many investigators and laboratories. In the space of a single year, however, NIH-supported research yields many "incremental" advances, seemingly smaller but equally significant findings that represent chapters in an ongoing story of discovery. Each advance has a rich history of science behind it, and it is hoped, a future of clinical application ahead of it.

Advances in the Biology of Brain Disorders

A Window into the Neurobiology of Drug Craving. The imaging technology known as Positron Emission Tomography (PET) has allowed researchers their first glimpse of the brain changes triggered by drug craving. PET scans were taken while human volunteers who abuse cocaine were exposed to environmental "cues" associated with drug use, such as drug paraphernalia. The visual images that were obtained revealed that brain regions involved in several forms of memory (working, episodic and emotional) were specifically activated when the addicts reported craving. In contrast, the same cocaine-related cues did not elicit craving in normal volunteers, and neutral cues (e.g., arts and crafts items) failed to elicit craving in either group of volunteers. This study provides the first evidence that drug craving may be mediated by brain systems involved in memory. It also suggests the relevance of memory processing to future studies of craving in drug addiction and to the development of therapeutic interventions. Such findings likely will contribute to understanding other appetitive disorders that involve powerful urges.

Understanding Nerve Cell Connections. Nerve cells communicate with one another and with other body cells via specialized points of contact known as synapses. Investigators are studying the synapse, between a nerve cell and muscle cell, to find clues to how synapses form and operate. Scientists knew from previous studies that the proteins agrin and MuSK (muscle specific protein kinase) play a role in synapse formation at the synapse between the nerve and the. muscle, the so-called neuromuscular junction. To better define the function of these two proteins, researchers created mice in whom the gene for either agrin or MuSK was "knocked out" (inactivated). The mice missing either protein had severely defective neuromuscular synapses, which left them unable to move or breathe. This suggests that agrin and MuSK are both required for motor nerves to form synapses with muscle. These and other studies are beginning to reveal how a two-way chemical conversation between the nerve and muscle cell guides the formation of the neuromuscular synapse. This knowledge is also an important step toward understanding nerve cell communication and synapse formation in the brain and could also lead to a better understanding of neuromuscular disorders such as the muscular dystrophies.

Learning About Learning. Investigators have begun to identify specific changes that take place in the brain when adults learn a new skill. Researchers used the imaging technique known as functional magnetic resonance imaging (fMRI) to examine changes in brain blood flow that occurred as volunteers were learning a simple motor skill—a particular sequence of finger-to-thumb tapping. As the volunteers became more adept at the finger tapping exercise through practice, the fMRI imaging revealed increased activity in the primary motor cortex region of the brain. This study provides an elegant view of the neural mechanisms involved in learning and memory and suggests that learning and remembering a motor skill occurs through a slowly evolving reorganization and enlargement of the brain "circuits" that are involved in a particular task.

New Approaches to Pathogenesis

Understanding How Cigarette Smoking Causes Lung Cancer. Although it has long been known that smoking is the single most important risk factor for lung cancer, it was unclear just how cigarette smoking causes cancer. Scientists recently discovered how a chemical in cigarette smoke, benzo[a]pyrene, damages a gene, *p53*, that normally suppresses the uncontrolled growth of tumor cells. In the body, benzo[a]pyrene is converted into a potent cancer-causing agent known as BPDE. BPDE in turn preferentially attaches to, or binds at three particular spots on the *p53* gene—sites which are documented "hotspots" for the genetic alterations commonly found in many patients with lung cancer. If the body is unable to repair the damage to the *p53* gene caused by BPDE, the resulting inability to suppress uncontrolled cell growth may lead to cancer. In revealing BPDE's role in the transformation of normal human lung cells into cancerous cells, this study shows, at the molecular level, how exposure to the carcinogen in cigarette smoke leads to lung cancer.

The Ongoing Story of Obesity. Obesity has become epidemic in our Nation—one third of all U.S. adults are considered obese, and obesity is on the rise in children as well. Obese individuals are at increased risk for numerous debilitating and costly chronic diseases, such as diabetes mellitus, cardiovascular disease, hypertension, gallbladder disease, and certain cancers. Recently, scientists have been making rapid strides in understanding obesity at the molecular level—witnessed by important new discoveries regarding the *obese (ob)* gene, its protein product (leptin), and the cellular receptors for leptin.

Investigators have also found important clues to how obesity is a risk factor for diabetes. In one study, scientists demonstrated that two genetic mutations which cause diabetes in animals—the *diabetes (db)* mutation in the mouse and the *fatty (fa)* mutation in the rat—are actually mutations of the gene for the leptin receptor. In another study, researchers added high levels of leptin, comparable to those present in many obese individuals, to cultured liver cells that contained the leptin receptor on their cell surface. The high leptin levels caused marked changes in a number of complex insulin-induced activities in the liver cells. This result implies that, in obese individuals, leptin may act directly on liver cells to modulate glucose metabolism and that leptin may play a role in the onset of non-insulin dependent diabetes mellitus.

Researchers studying metabolism have developed a strain of apparently healthy mice that, although they eat more food—including more high-fat food—than do normal mice, stay about 10 percent leaner. The secret? The researchers had "knocked out" a gene called RII-beta. This gene enables normal mice to produce a component of the PKA (for cyclic AMP-dependent protein kinase A) protein, which plays an important role in regulating cellular metabolism. In the absence of the RII-beta gene, the animals' brown fat was stimulated to burn off the extra calories consumed, instead of turning them into the more familiar white fat. "Brown" fat is fatty tissue the body can burn to produce heat. Because brown fat is found almost exclusively in infants, it is unclear how directly applicable this finding will be to obesity in children and adults. These knockout mice, however, will provide an important model system for studying the molecular basis of obesity and, ultimately, may lead to effective treatments for this major public health problem.

Understanding How HIV Infects Cells. Scientists have known for some time that immune system cells with a surface protein receptor known as CD4 were the preferred targets of HIV. They also realized that CD4 alone was not sufficient to allow HIV to fuse with immune cells and infect them. At least one, and possibly more, surface molecules had to be involved, but their identity eluded researchers for a decade.

Now, NIH-supported scientists and others have discovered two proteins on the surface of target cells that act as "cofactors" or coreceptors with CD4, allowing HIV to fuse with the immune cell and infect it. The first cofactor protein to be identified is called CXCR4. In conjunction with CD4, it allows infection by the strains of HIV that are found in patients in the later stages of HIV disease, when their immune system is compromised. The second protein, named CKR5, acts as a fusion cofactor for the strains of HIV most commonly found in individuals during the early, symptom-free stage of infection. These two proteins are potential targets for the development of anti-HIV drugs that block or interfere with the binding of HIV to the receptors. These findings could also provide clues for developing a vaccine that might work, for example, by triggering the body to produce antibodies against the receptors, thus conferring resistance to HIV.

This work also sheds light on a previously puzzling observation that a small subset of the population is seemingly immune to HIV, despite repeated exposure. Scientists recently determined that just over one percent of Caucasians inherit two mutated, nonfunctional copies of the gene for the CKR5 protein. These individuals are, for all practical purposes, genetically resistant to HIV infection, even when heavily exposed. In this case, inheriting a genetic "defect" is a life saver—HIV is consequently unable to gain entry into the immune system cells because the cell surface lacks the fusion cofactor. About 20 percent of Caucasians have inherited one mutated, nonfunctional version of the CKR5 gene and one normal copy. Although these individuals are susceptible to infection with HIV, they progress to AIDS more slowly than do infected individuals with two normal CKR5 genes. These mutations are not observed outside the Caucasian population.

Although its role as a fusion cofactor for HIV is a recent discovery, CKR5 was previously known to be a cell surface protein, called a chemokine receptor, that functions in cell-to-cell communication in inflamed joints. At first glance, these two roles of CKR5 are seemingly unrelated. The nature of that connection is beginning to unfold, however, from studies of immune system cells and the molecules they secrete. Immune cells known as CD8+ T cells secrete a type of signaling molecule known as beta chemokines, which normally function by recruiting inflammatory cells to the site of an infection. Scientists have discovered that beta chemokines are multi-talented—they also suppress HIV replication in both the blood and the lymph nodes taken from HIV-infected people. Researchers also recently discovered that three specific beta chemokines suppress HIV replication by occupying (blocking) CKR5, thereby preventing HIV from entering its target cells.

Researchers are also gaining new insights into how the body controls HIV replication. It has been known that some immune cells involved in inflammatory responses secrete chemical messengers called cytokines, and that some naturally occurring cytokines boost HIV replication in cultured cells, while others are suppressive. These studies suggest that HIV replication may be regulated by a delicate balance among the body's own cytokines. By altering this balance, HIV replication can be dramatically influenced in the test tube, and potentially even in the body. A complete understanding of the interactions between immune system molecules and HIV could potentially lead to the development of therapeutic strategies capable of regulating this balance in favor of immunosuppression.

New Preventive Strategies Against Disease

New Findings About Optimal Time and Conditions for Conception. Investigators have discovered that, in healthy women, the highest probability of pregnancy each month occurs during the six day window ending on the day of ovulation. This finding challenges the long-accepted medical belief that women are most fertile a few days before and after ovulation. Other researchers determined that the simple practice of douching can significantly reduce a woman's monthly chance of conception. Compared to women who did not douche, women 18-24 years old who douched were 50 percent less likely to conceive. Older women who douched experienced reduced fertility as well, but to a lesser degree (30 percent reduction for women 25-29 years old and 6 percent reduction for women 30-39 years old). These studies provide critical information for couples trying to achieve or avoid pregnancy.

New Hepatitis Virus Discovered. A collaboration between government and industry scientists has resulted in the identification of a new infectious agent, the hepatitis G virus (HGV). The virus is very common—it was detected in up to 2 percent of the volunteer blood donor population and its presence in the general population is likely to be 2-4 fold higher. Although it has not been firmly established whether HGV infection results in disease, the virus frequently persists in the body for many years and is transmissible through blood transfusions and other blood-borne routes. Determining the disease-causing ability of HGV is critical. If the virus proves to have serious disease implications, it will be urgent to develop a screening assay to ensure the safety of the

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Nation's donor blood supply. A preliminary study of HGV infection among prospectively followed transfusion recipients and their donors suggests, however, that HGV may account for only a small proportion, if any, of the transfusion-transmitted cases of hepatitis not caused by the known types of hepatitis viruses. While this finding is welcome news for those infected with HGV, it also suggests that another, as yet unidentified, agent—conceivably more prevalent and more clinically significant than HGV—contributes to transfusion-associated hepatitis. This possibility highlights the vital importance of accelerating viral discovery programs.

Advances in Genetic Medicine

International Team Completes DNA Sequence of Yeast. A worldwide collaboration involving nearly 100 laboratories and some 600 researchers, many supported by the NIH, has culminated in the complete sequencing of the genome of *Saccharomyces cerevisiae*, or brewer's yeast. Containing 6,000 genes, the yeast sequence is the largest genome to be completely deciphered to date. The yeast genome is of particular interest to medical scientists because about one-third of yeast genes are related to those in the human. These similarities suggest that the shared genes play a critical role in cell function in both species, including the essential processes of DNA replication, repair of damaged DNA, protein synthesis and transport, and control of metabolic processes. In cancer research, yeast has emerged as an important model for studying the control of cell division. Despite the great deal already known about yeast, researchers know the function of only about half of its 6,000 genes. The additional research required to understand the role of the remaining genes eventually will provide the first look at how a living cell functions as a unit.

On-Line Maps of the Human and Mouse Genomes. A team of over 100 scientists from government, university, and commercial laboratories around the world have developed a map that, so far, pinpoints the locations of 16,354 genes in human DNA—approximately one-fifth of the entire complement of human genes. NIH recently posted the map on the World Wide Web (http://www.ncbi.nlm.nih.gov/science96/). The map contains extensive links to supporting data about the DNA and protein sequences associated with the mapped genes and offers links, as well, to references in the medical and research literature. Painstaking effort has been taken to present the latest research information about genes and their function in both health and disease in a well organized and easily understandable manner. Thus, the Web site provides scientists and medical personnel, as well as students and the public with a user friendly and continuously updated window of progress on one of the most extraordinary scientific undertakings of the 20th century—the mapping of the human genome. Although it is only partially complete, the mapping project already has advanced our understanding of the genetic basis of many diseases by significantly accelerating a number of disease gene hunts. The map was instrumental, for example, in locating and isolating genes responsible for Alzheimer's disease, inherited colon cancer, achondroplasia (a bone growth disorder resulting in short stature), a type of endocrine tumor, and a congenital digestive disorder known as Hirshsprung's disease.

Another team of researchers recently completed a five year project of mapping the mouse genome. Available on-line as well, the mouse map can also be accessed, by electronic link, from

the human gene map. Because the mouse and human genomes share many similar genes, and capabilities to genetically manipulate the mouse genome (e.g., by adding or deleting specific genes associated with identified traits) are evolving so rapidly, the mouse genome map affords intriguing and informative insights into the function of many human genes.

Advances in Instrumentation and Computers

"Visible Humans" Change the Teaching and Practice of Medicine. The world's first "computerized cadavers," known as the Visible Human Male and Female, are revolutionizing the teaching of anatomy and the practice of medicine throughout the world. The implementation phase of the project began three years ago when a 59-year old female heart-attack victim and a 39-year old male executed for murder donated their bodies to science. They became the world's first digitized humans when NIH scientists obtained detailed CT (computed tomography) and MR (magnetic resonance) images of their bodies, and then cut the bodies into extremely thin crosswise slices that were photographed at high resolution. The images were compiled into a computer database, providing complete, anatomically detailed, three-dimensional representations of the human body. More than 500 licensed users have developed remarkable applications for the data, as well as technologies to create Visible Human-like representations of live patients. Examples of these innovations include non-invasive colon cancer screening; simplified plastic surgery; patient-specific rehearsal of prostate cancer surgery; surgical and spinal tap simulations; the Recyclable Cadaver, which allows for repeated, "reversible" dissection; radiation absorption modeling; and crash testing.

New Avenues for Development of Therapeutics

A Step Closer to Replacing Daily Injections with Pills. NIH-supported researchers, collaborating with industry partners, recently achieved a breakthrough that could make it possible to replace the costly and painful injections currently used for treating conditions such as anemia, diabetes, and human growth hormone deficiencies with an easily swallowed pill. Erythropoietin (EPO) is a naturally occurring substance, produced by the kidney, that stimulates the body to produce red blood cells. Genetically engineered EPO is presently used to treat anemia caused by kidney failure, cancer chemotherapy, and AZT treatment for HIV infection. Currently, EPO must be injected because large, natural proteins such as EPO are destroyed in the stomach if taken orally. Recently, scientists developed a very small molecule that mimics the action of the much larger EPO protein. The new molecule may serve as a model for designing a nonprotein drug capable of stimulating red blood cell production and yet small enough to be administered in pill form. In addition to its potential for improving quality of life, the development of a new generation of oral drugs has significant economic implications. For example, EPO is today the single largest revenue producer of the biotechnology industry.

Mounting an Effective Immune Response Against Tumor Cells. Although tumor cells produce a variety of molecules that are recognized by the body's immune system, the tumor molecules elicit only a mild immune response, one that is not vigorous enough to completely destroy the tumor.

This immunological timidity has challenged researchers to devise methods for "presenting" tumor molecules to a patient's immune system in a way that will evoke a strong immune response. Researchers recently made a promising breakthrough using a mouse model to study the immune response to tumors. It was known that the antitumor response involves a complex balance between signals that stimulate or inhibit the immune system, and that an immune cell protein known as CTLA-4 is one of the inhibitors. Building upon these findings, the researchers used antibodies to block the production of CTLA-4 in mouse immune cells. Most of the mice treated with these antibodies rejected their tumors; in sharp contrast, every one of the untreated tumor-bearing mice died. The work establishes important principles of immunology and suggests an innovative strategy for cancer immunotherapy.

Clinical Advances in Treating and Assessing HIV Disease. A NIH-supported clinical trial involving HIV-infected patients has demonstrated that infusions of a protein called interleukin-2 (IL-2) lead to substantial and sustained increases in the number of CD4+ T cells in the patients. These cells, which play a critical role in the human immune system, are the preferred target of HIV. In the trial, patients who received a genetically engineered version of IL-2 every two months in five day cycles, along with anti-HIV drug therapy, experienced an average two-fold increase in CD4+ T cell counts compared to patients who received anti-HIV drug therapy alone. IL-2 is the first experimental therapy to bring about significant long-term increases in CD4+ T cells without unmanageable side effects. A follow-up trial is planned to determine whether CD4+ T cell increases will also translate into improved health and prolonged life for HIV-infected patients.

A recent study showed conclusively that anti-HIV drugs can prevent AIDS-defining illnesses and reduce the risk of death in asymptomatic people with intermediate-stage HIV disease. The study compared the clinical benefits of four different anti-HIV treatment regimens: AZT alone, AZT plus ddI, AZT plus ddC, and ddI alone. These anti-HIV drugs work by inhibiting the activity of an enzyme necessary for HIV replication. The trial results demonstrated that the two combination regimens and the ddI alone regimen were superior to AZT alone in preventing at least one of the following serious consequences of HIV-infection: a significant decrease in the number of CD4+ T cells, the appearance of an AIDS defining condition, or death. Variations in the clinical benefit of a particular regimen were shown to be a function of previous AZT use; patients who had never taken AZT benefited most from the combination of ddC plus AZT, while those previously on AZT benefited most from either ddI alone or ddI plus AZT. This information about the relationship between treatment history and the effectiveness of specific anti-HIV drug regimens will be useful to health care providers in designing individualized treatment strategies for their patients.

There is new evidence that an individual's risk of disease progression can be predicted from the level of HIV genetic material (RNA) detected in the bloodstream. Researchers measured the HIV RNA levels of 180 HIV-infected patients twice yearly for ten years, while also monitoring their health status. Higher levels of HIV RNA were associated with faster progression to AIDS or death. The study also showed that a patient's prognosis—as predicted by HIV RNA

measures—was independent of their level of CD4+ T cells. These results suggest that HIV RNA level is a more consistent and accurate predictor of disease progression than is CD4+ T cell count. Improved methods of predicting disease progression in HIV-infected individuals will enable health care providers to determine the most appropriate treatment strategies for HIV infected people, and will provide an important tool for assessing the effectiveness of new and potential anti-HIV therapies.

These advances are only a few examples of the many exciting discoveries coming from NIH research. It is, however, impossible in the space of a few pages to fully convey all of the research steps necessary for the development of new treatments, diagnostic methods, and prevention strategies. One of the intermediate steps in the process—gene discovery—has received considerable attention in the media. The announcement of the discovery of a new gene often generates tremendous expectations that a new treatment or cure is just around the corner. It is important to understand, however, that there are many critical intermediary steps between identification of a disease gene and new medical treatments.

Discovery of Human Disease Genes

The isolation of a gene is an important milestone on the path to understanding the role that genetic material plays in who we are, how we function, and what causes some disorders. This past year has witnessed the isolation of genes responsible for or associated with many important human diseases and conditions, including:

- Progressive Myoclonus Epilepsy 1, a rare inherited form of epilepsy
- Retinitis Pigmentosa, a progressive loss of vision
- Inherited basal cell carcinoma, a form of skin cancer
- Werner's Syndrome, which causes premature aging
- Over 50 syndromes involving head and face abnormalities associated with birth defects
- Hereditary hemochromatosis, an iron metabolism disorder causing multiple organ failure
- Hereditary pancreatitis, which often leads to cancer of the pancreas
- Polycystic kidney disease
- Myelodysplastic syndrome, a bone marrow disease
- Susceptibility to nerve gases and pesticides
- An inherited form of Long QT syndrome, an irregular heartbeat which can lead to sudden death
- Severity of Attention Deficit Hyperactivity Disorder
- Alport's syndrome, which involves deafness and kidney disease

In 1996, NIH-supported researchers made important progress towards identifying additional disease genes. They were able to determine the chromosomal locations of genes involved in many important human diseases, including:

- An inherited form of Parkinson's Disease

- A hereditary predisposition to prostate cancer
- Cystinuria, a metabolic defect which causes kidney stones
- Nephrotic syndrome, a congenital kidney disease
- Many forms of hearing loss, as well as genes responsible for normal hearing development and/or function

Identifying the chromosomal location of a gene is an important accomplishment because knowing the location of a gene narrows the "haystack" (chromosomes) that must be searched in the quest of the "needle" (gene).

Another important step in medical research is the development of a model system for studying the origins and consequences of human disease and disability. Animal models of human disease have proven to be essential tools for progress in understanding many diseases.

Animal Models of Human Disease

Human beings are very complex biological organisms, but our cells contain the same fundamental components as those of all living things. Researchers can, therefore, learn much about the way human cells and genes work by studying simpler organisms. Mice are particularly valuable research animals for many reasons. They share many physiological and genetic similarities with humans, they are easily maintained in the laboratory, they reproduce rapidly, and their genetics have been thoroughly studied. Because of this, the role of genes can be determined relatively quickly in mice and other animals and these findings can often be applied to understanding human genetics.

Researchers who want to use an animal model to study a human disease first look for animals that are particularly prone to developing certain tumors, metabolic disorders, or the disease of interest. Many mutant strains of mice have been specially bred for such research. These mouse models can then be used for studying the physiological course of a disease, determining the identity and function of the genes and proteins involved in a disease, testing new treatments, and developing and testing methods for preventing disease.

In many instances, there is no comparable animal model of a disease; however, researchers are able to develop them by modifying the genetic make-up of test animals. This strategy has yielded valuable, and sometimes unexpected, information about the role of a specific gene in healthy and disease states, as well as knowledge about the complex cellular mechanisms that regulate the gene. There are different methods for creating an animal model of a human disease. One technique, the production of so-called "transgenic" animals, involves the insertion of a "foreign" gene (normal or altered) into an animal embryo. Researchers can observe the effect(s) of the new gene in the animal, gaining insights into its role in development or in a physiological process. In another approach, known as "knockout" experiments, scientists inactivate a particular gene, and then observe what effects, if any, this has on the mouse. In this way, it is sometimes possible to infer the function of a gene by noting the problems that arise in its absence. Adding a "foreign" gene to a mouse or "knocking out" a normal mouse gene may recreate a condition in the mouse

similar to a human disease. Researchers may then learn something about the role of that gene and also have an animal model for testing new treatments.

This year, researchers have succeeded in developing a number of new animal models that will provide new knowledge about human disease and facilitate assessments of new treatments and preventive regimens. Examples include:

- A mouse model of Alzheimer's disease that, for the first time, exhibits both the behavioral and neuropathological symptoms of Alzheimer's disease
- A rat model of autism
- Strains of mice that are predisposed to drug-mediated euphoria, which have already allowed researchers to localize two genes that influence alcohol consumption
- Animal models for 5 different rare inherited metabolic conditions: tyrosinemia type I (mouse), adenine phosphoribosyltransferase-deficiency (mouse), Fabry Disease (mouse), Krabbe disease (dog) and glycogen storage disease, type VII

In the past year, NIH-supported researchers have also used animal models and knockout experiments to gain critical insights into how genes function in human health and disease. Below are just a few examples of the gene discoveries made in animal models that are providing tantalizing clues to understanding human disease:

- AML1, a gene linked to acute myeloid leukemia, which appears to be a master regulator of blood cell development
- A cell-growth control gene, p27, which is necessary for a normal pituitary gland and normal body size
- The E2F-1 gene may be a new "tumor suppressor" gene, whose absence leads to tumors in many tissues
- A regulatory gene, Brn3.1, may play a role in inner ear defects and deafness
- A gene for a component of protein kinase A, which plays a role in metabolism and energy processing
- A gene for a surfactant protein, which functions in protecting the lungs against infection
- The genes for the agrin and muscle specific protein kinase (MuSK) proteins, which have an essential role in forming nerve connections to muscles during development
- The ATM gene, which is important for repairing damaged DNA; its absence results in a severe syndrome of neurological impairment and cancer predisposition called ataxia telangiectasia
- One of the serotonin receptor genes, which appear to increase alcohol consumption
- Multiple genes that appear to be involved in drug craving and addiction

With the progress in developing animal models and in discovering and isolating genes come new challenges to ensure that this information is used appropriately. The potential for inappropriate uses of new knowledge about the genetic basis of disease poses additional challenges such as ensuring responsible medical practices with respect to genetic testing and protecting the confidentiality of medical and research information.

Future Challenges: Advances in Genetics—Responsible Medical Practices and Privacy Issues

Information based on molecular genetics is becoming increasingly more important in medical practice and in

the setting of public health policy. In recent years, researchers have identified genes and proteins that play a key role in many diseases, including cancer, as well as in complex human disorders such as hypertension. In addition, rapid progress in the mapping and sequencing of the human genome is facilitating the identification and isolation of additional human disease genes. As knowledge increases regarding the genetic basis of disease, so too does the potential for inappropriate uses of genetic information, such as discrimination and stigmatization. Genetic testing can move rapidly from the research setting into clinical practice, but not necessarily with appropriate technical oversight or requirements for evidence of health benefits. For example, misunderstandings concerning the predictive ability of such tests, and any shortcomings they may have, can have serious implications regarding the very personal decisions that must be made once the results of the tests are known. Society must also find rigorous means of ensuring the confidentiality of all medical and research information and materials. The widespread use of such genetic information can have far-reaching consequences related to the ability to obtain life and health insurance as well as considerations of hiring practices for employees. Efforts are needed to stimulate an informed, broad-based national dialogue about how to monitor data access without hampering treatment or research and, at the same time, to ensure individual privacy while enhancing the quality of health care.

Ensuring steady progress in improving health and quality of life will necessitate a strong infrastructure in which to conduct research. Widespread changes in the financing and delivery of health care are threatening the stability of academic health centers. Investigators at these centers, which are located in every state, conduct much of the medical research funded by NIH. One of the many challenges facing NIH and the nation is maintaining that research infrastructure, including the academic health centers as well as the NIH Clinical Center.

Future Challenges: Updating the Clinical Research Center

Basic science and clinical medicine converge, each amplifying the other, within the walls of the NIH Clinical Center. Currently, an average of 20,000 children and adults are referred annually to the Clinical Center for experimental treatment and study. These patients account for approximately 65,000 inpatient days and 70,000 outpatient visits for frequently occurring, as well as rare or "orphan," diseases.

The Clinical Center is, on several counts, an indispensable national resource. First, from the perspective of medical science, the Center benefits from an unparalleled breadth and depth of expertise; researchers and NIH administrators bring the resources of the surrounding NIH campus to bear on the medical challenges encountered within the Center's walls. Second, the Clinical Center remains one of the premier research training sites in the world. Building on its distinguished record in research "mentoring," the Clinical Center recently launched a formal clinical research training initiative.

The FY97 budget requested $310 million to fully fund the cost of constructing a new state-of-the-art Clinical Research Center. Congress approved the new Clinical Research Center project with

an initial appropriation of $90 million. An international competition yielded a design concept that melds both the form and the function of the existing Clinical Center. Detailed design work now is underway to relocate the existing Clinical Center entrance and modify the site to facilitate construction of the new Clinical Research Center. The project development team, consisting of a development manager, architects, engineers, construction manager, and specialty consultants, is in place. Development of detailed program requirements is substantially complete, and NIH expects that the total cost of the facility will equal $310 million, which is why the Budget requests a total of $220 million in appropriations and advanced appropriations, in addition to the $90 million Congress appropriated in FY97. Construction completion and occupancy of the NIH Clinical Research Center are scheduled for 2002.

Finally, as the Nation looks toward the future, the aging of the baby boomers portends a significant burden to the national healthcare system. The effectiveness of this system and the quality of treatment delivered is dependent, in part, upon continuing medical innovation, which is the result of NIH-supported research.

Future Challenges: The Aging Population—Healthcare, Economics and Medical Research

The next three decades will witness a revolution in America's demographic profile. The most profound change will be a doubling in the number of Americans age 65-and-over, from 33 million today to more than 69 million. A substantial portion of this increase will come from a tripling in the number of persons age 85-and-older, from 3 million to 9 million. Nearly half of those in the latter group will suffer from Alzheimer's disease or other dementias. As a group, they also will be more economically disadvantaged, more fragile physically and emotionally, more likely to live alone, and use health services far more than individuals age 65-84.

Maintaining the health of our elderly citizens and ensuring the quality of and access to health care services under these circumstances presents the Nation with an unprecedented challenge. Remarkable scientific strides in recent years have been paralleled by public health efforts, which, based on research information, are encouraging greater responsibility for healthy behaviors across the lifespan. Preventive strategies and effective treatments for chronic debilitating diseases have improved overall health and quality of life for the elderly, extending the duration of productive adult life and pushing back both the boundaries and the meaning of old age. In general, the future aged are expected to be healthier and more active than their counterparts today, in part because of HHS-supported studies of aging and its common diseases.

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The NIH plays a vital role in the Nation's medical research enterprise. NIH-supported research generates knowledge that leads to improvements in the health and quality of life of the American public. It also provides a continually expanding knowledge base for the development of commercial products by the pharmaceutical and biotechnology industries and other key

components of the national medical research infrastructure. Through its support of research training in intramural and extramural settings, moreover, the NIH continues to produce highly trained scientists who rise to leadership positions in publicly funded research and in the biotechnology and related industries.

As life expectancy increases, the number of people suffering from chronic diseases will sky-rocket, placing ever greater demands on entitlement programs. Noncommunicable chronic diseases and other age-related conditions, such as heart disease, cancer, neurological and emotional disorders, stroke, and injuries, will become the leading causes of death and disability and will strain the Nation's capacity to provide social support and healthcare. NIH research will continue to be a vital source of knowledge and medical innovation which will sustain the health and quality of life of all Americans.

FY 1998 BUDGET POLICY

The Fiscal Year (FY) 1998 President's Budget Request of $13,078 million provides a total increase of $337 million or 2.6 percent over the FY 1997 Estimate.

Basic Goals and Budget Strategy

In developing the FY 1998 President's Budget, NIH has identified goals and a budget strategy to maximize support for basic biomedical research, to promote health and to better understand the biological and behavioral basis for disease to improve prevention and treatment of human disorders. Of particular note is an increase of $30 million for the National Institute on Drug Abuse (NIDA) which is part of the Administration's cross-cutting commitment to combat drug abuse. The increased funding will further the development of a medication for the treatment of cocaine addiction.

To take advantage of the most promising areas of research, NIH has identified the following areas of scientific emphasis for increase in the Fiscal Year 1998 Budget:

The Biology of Brain Disorders (+ $36.7 million) The neurosciences continue to grow at an extraordinary pace, with strong support from the fields of molecular genetics, imaging, and cell biology and signaling. In the coming year, the NIH anticipates expanded activity in the areas of neural development; neurodegeneration, especially in Alzheimer's Disease, Parkinson's Disease, and eye disorders; the biological basis of autism; physiology of pain in adults and newborns; brain imaging during drug and alcohol abuse and behavioral change; traumatic injury to the brain and spinal cord; the use of mouse models to study disease, addiction, behavior, and the regulation of weight and appetite; and the genetic basis of neurological diseases, including hearing impairment.

New Approaches to Pathogenesis (+ $34.6 million) A more precise understanding of genes, proteins, and cells is transforming traditional descriptions of disease processes. In FY 1998, we anticipate expanded efforts directed to the following goals: developing improved animal models to

study carcinogenesis; understanding the mechanisms that cause the heart to fail as a pump; developing new methods for integrating information about complex biological processes; and applying new and diverse methods to the study of osteoarthritis, birth defects and growth disorders, and infections of the liver, lung, and gastrointestinal tract.

New Preventive Strategies Against Disease (+ $51.1 million) New insights into pathogenesis are stimulating tests of novel methods for preventing disease in both animal models and human populations. The disorders that will receive increased attention in FY 1998 include cancers, diabetes mellitus, cerebral palsy, asthma, and alcohol and drug abuse. Infectious agents continue to be a major cause of morbidity; efforts will be made to develop new vaccines against a variety of pathogens, especially HIV, and to expand research on new and resurgent infections. Behavior-based preventive strategies against HIV will also be emphasized. Changes in national and global demographic profiles are occurring rapidly; we will accelerate efforts to understand the significance of these changes with respect to prevention research. Increased emphasis will also be given to training health professionals to guide the use of new genetic information that can promote prevention of disease.

New Avenues for Development of Therapeutics (+$39.8 million) Chemistry, structural biology, genetic information, and advances in cell biology are providing new means to design therapies for a variety of diseases. In this newly-identified NIH Area of Emphasis, we will expand efforts to discover and develop drugs to combat cancer and drug and alcohol addiction; to use methods of bioengineering to repair tissues; to test new methods for treatment of neurological diseases, alcoholism, and drug addiction; to intervene in infectious disease; to treat sensory disorders and mental illnesses in both children and adults; and to improve care at the end of life.

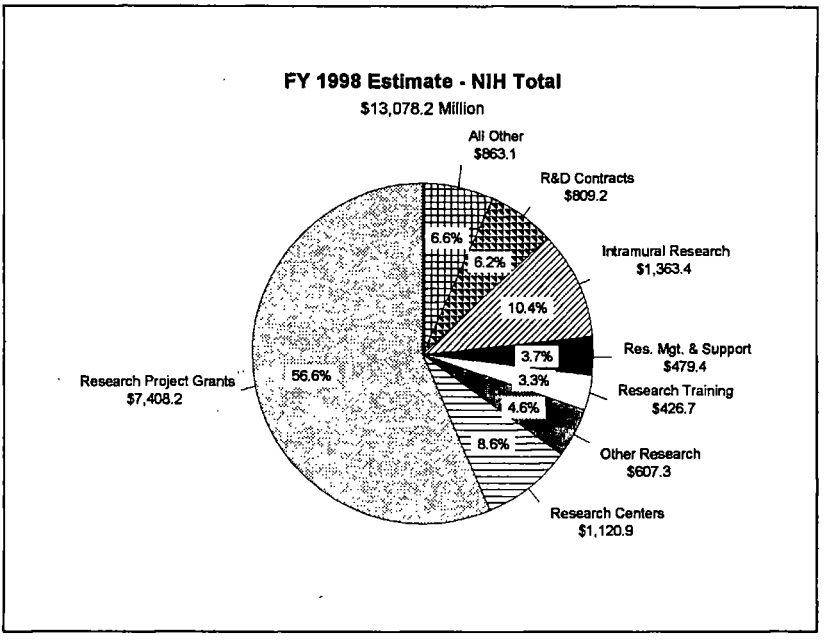
Genetic Medicine (+ $40.9 million) The rapid progress of the Human Genome Project, a growing understanding of the genomes of other species, and new methods for the manipulation of genes are swiftly changing concepts of disease and possibilities for its control. Broadened efforts in FY 1998 to hasten the arrival of gene-based medicine include efforts to: improve the efficiency of genetic analysis and distribution of gene maps and sequences; define the genetic damage in different types of cancer cells (the Cancer Genome Anatomy Project); and identify the inherited mutations that contribute to cancer risk, developmental abnormalities, immunodeficiencies, and mental and neurological diseases (such as epilepsy, stroke, autism, alcoholism, ataxias, psychoses, and sensory and neurodegenerative disorders). In addition, by developing new markers to assess gene-environment interactions, efforts to address the impact of the environment on genetic integrity will be expanded.

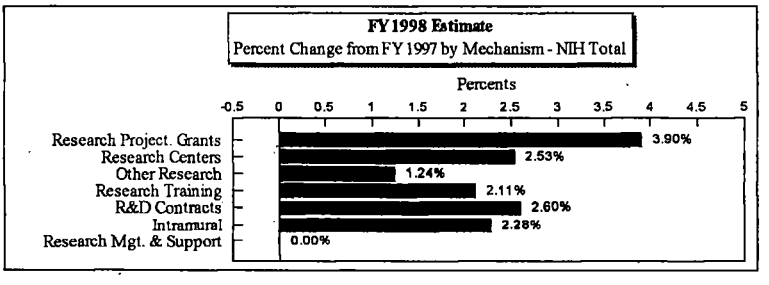
Advanced Instrumentation and Computers in Medicine and Research (+ $20.0 million) Recent advances in basic biology, genetics, diagnosis, and health care have been closely linked to the development of new research instruments and computer hardware and software. In FY 1998 we propose to support new initiatives to improve detection of early cancers; to determine DNA sequence and analyze it more readily; to provide better communication links for research groups

and physicians; and to visualize the central nervous system and the eye with greater accuracy using a variety of sophisticated imaging methods.

The FY 1998 request for NIH once again requests that Congress appropriate all NIH AIDS research funds to the NIH Office of AIDS Research (OAR). A separate appropriation is the most appropriate vehicle for making decisions about allocation of AIDS research funding and helps target NIH research dollars effectively across all the Institutes and enters that carry out HIV/AIDS research. Support for AIDS research will increase by $40 million, or 2.6 percent over the FY 1997 Estimate.

FY 1998 BUDGET OVERVIEW





Mechanism Discussion

NIH's highest priority is the funding of basic biomedical research through research project grants (RPGs). The emphasis on RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. In FY 1998, NIH will support 7,112 competing RPGs. Support for RPGs, including Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) awards will increase by nearly 4 percent over FY 1997.

Replacing the Clinical Center's hospital and associated laboratories with the new Clinical Research Center (CRC) is another top priority. The FY 1997 appropriation provided $90 million for the first phase of construction, and allowed NIH to contract with a project management firm for the entire scope of the project, subject to the availability of funds. This will ensure continuity and professional management of the CRC construction project. The FY 1998 request includes $90 million for the next phase of the project and, consistent with budget scoring rules to fully account for the costs of major construction, NIH is requesting advanced appropriations of $90 million in FY 1999 and $40 million for FY 2000 to complete the project.

NIH continues to be a leader in the training of biomedical and behavioral researchers. Through National Research Service Awards (NRSAs), NIH provides the biomedical research enterprise with a steady flow of highly-trained researchers equipped to conduct the Nation's research mission and to strengthen national science literacy and information dissemination programs in the twenty-first century. In the FY 1998 Request, NIH will support 15,003 pre- and postdoctoral trainees in full-time training positions and provide for the second year of an increase in training stipends of 3.5 percent for postdoctoral fellows with less than two years of experience.

Other Key Issues

In FY 1998, the Laboratory of Diagnostic Radiology Research will transfer from the Office of the Director to the Clinical Center.

NIH continues to utilize reinvention and reengineering laboratories and initiatives in the administration of NIH programs both to achieve greater efficiency and to optimize the Nation's investment in biomedical research.

In order to maximize available funds for research, the Research Management and Support activity is level with the FY 1997 estimate.

The total NIH program level of $13,093.2 million includes third party payments estimated at $15.0 million for the cost of patient care at the NIH Clinical Center.

Cost Management

NIH policy for determining average cost increases for RPGs links the average cost increase to the total program increase for NIH. The FY 1998 President's Budget provides a program increase of 2.6 percent over the FY 1997 estimate. A top priority for NIH in the FY 1998 Request was to increase support to Research Project Grants by nearly 4 percent over the FY 1997 estimate. To achieve this goal and to provide support for new research opportunities, rates identified for increases associated with *A Plan for Managing the Costs of Biomedical Research,* referred to as the NIH Cost Management Plan (CMP) would be modified. Noncompeting RPGs would receive direct cost increases of 2 percent on the average, and the average cost of competing RPGs would increase by no more than 2 percent. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP).

The apparently flat increase in average costs for competing RPGs including AIDS from FY 1997 to FY 1998 is misleading. The cycling of the unusually expensive AIDS Pediatric Clinical Trial Groups from competing to noncompeting status in FY 1998, as well as the NIDA's *Monitoring the Future* grant, at a cost of $4.3 million per year, distorts the average cost calculation for competing RPGs. Adjustments to exclude the impact of these grants results in an average cost increase for competing RPGs of approximately 2 percent in total from FY 1997 to FY 1998.

FULL-TIME EQUIVALENTS

	FY 1996	FY 1997	FY 1998	CHANGE
Total FTEs	**15,153**	**15,153**	**15,153**	**0**

National Institutes of Health

Summary of Increases for
Areas of Research Emphasis
(Dollars in thousands)

	FY 1996	FY 1997 Estimate	FY 1998 ICD/Program Increases	FY 1998 Director's Increases	FY 1998 Estimate
Biology of Brain Disorders	$1,994,464	$2,103,464	$41,331	$36,700	$2,181,495
New Approaches to Pathogenesis	1,563,060	1,624,829	15,448	34,600	1,674,877
Preventive Strategies	1,885,476	1,958,604	21,733	51,100	2,031,437
Therapeutics/Drug Development	646,159	679,525	6,588	39,800	725,913
Genetics of Medicine	936,701	997,104	18,799	40,950	1,056,853
Advanced Instrumentation	297,182	325,883	3,012	20,000	348,895
TOTAL				223,150	

FY 1996 base adjusted to add new area, Therapeutics/Drug Development

NATIONAL INSTITUTES OF HEALTH

Funding Including AIDS

	FY 1996 Budget Authority	FY 1997 Estimate	FY 1998 Estimate
NCI	$2,254,951,000	$2,381,149,000	$2,441,738,000
NHLBI	1,351,440,000	1,432,529,000	1,467,189,000
NIDR	183,478,000	195,825,000	202,831,000
NIDDK	768,530,000	815,607,000	833,802,000
NINDS	683,553,000	726,407,000	747,828,000
NIAID	1,171,168,000	1,256,659,000	1,312,502,000
NIGMS	944,466,000	998,444,000	1,020,192,000
NICHD	593,104,000	631,365,000	647,279,000
NEI	313,109,000	332,597,000	340,431,000
NIEHS	287,614,000	308,487,000	319,907,000
NIA	453,520,000	485,806,000	497,076,000
NIAMS	244,058,000	257,003,000	263,242,000
NIDCD	175,912,000	188,345,000	194,221,000
NIMH	659,959,000	701,050,000	728,249,000
NIDA	458,246,000	489,118,000	521,915,000
NIAAA	198,593,000	211,870,000	219,346,000
NINR	55,676,000	59,721,000	61,052,000
NHGRI	169,311,000	189,529,000	205,187,000
NCRR	389,429,000	415,095,000	410,921,000
FIC	25,249,000	26,557,000	27,168,000
NLM	140,563,000	150,828,000	155,968,000
OD	259,482,000	286,852,000	270,159,000
Subtotal	11,781,411,000	12,540,843,000	12,888,203,000
B&F	146,151,000	200,000,000	190,000,000
(Infrastructure)	(123,151,000)	(110,000,000)	(100,000,000)
(Clinical Res. Ctr.)	(23,000,000)	(90,000,000)	(90,000,000)
Total, Budget Auth.	**11,927,562,000**	**12,740,843,000**	**13,078,203,000**
Third Party Payments	—	6,000,000	15,000,000
Total, Prog. Level	**11,927,562,000**	**12,746,843,000**	**13,093,203,000**

NOTES: Funding for the AIDS portion of the amounts shown above for FY 1998 are contained in the Office of AIDS Research, NIH.

Third party payments are estimated recoveries for patient care costs to the Clinical Center.

NATIONAL INSTITUTES OF HEALTH

Summary of Appropriations

(Dollars in thousands)

	FY 1996 Comparable			FY 1997 Estimate 1/			FY 1998 Estimate 2/			Percent Change 98/97		
	ICD Estimate	AIDS Distribution	Includes AIDS	ICD Estimate	AIDS Distribution	Includes AIDS	ICD Estimate	AIDS Distribution	Includes AIDS	ICD Estimate	AIDS Dist.	Includes AIDS
NCI	$2,029,591	$225,360	$2,254,951	$2,156,416	$224,733	$2,381,149	$2,217,482	$224,256	$2,441,736	2.83	(0.21)	2.54
NHLBI	1,293,563	57,877	1,351,440	1,370,952	61,577	1,432,529	1,404,770	62,419	1,467,189	2.47	1.37	2.42
NIDR	170,525	12,953	183,478	182,893	12,932	195,825	190,081	12,750	202,831	3.93	(1.41)	3.58
NIDDK	756,795	11,735	768,530	802,889	12,718	815,607	821,164	12,638	833,802	2.26	(0.63)	2.23
NINDS	659,779	23,774	683,553	701,582	24,825	726,407	722,712	25,116	747,828	3.01	1.17	2.95
NIAID	571,619	599,549	1,171,168	608,950	647,709	1,256,659	634,272	678,230	1,312,502	4.16	4.71	4.44
NIGMS	918,331	26,135	944,466	970,749	27,695	998,444	992,032	28,160	1,020,192	2.19	1.66	2.18
NICHD	532,391	60,713	593,104	566,998	64,369	631,365	582,032	65,247	647,279	2.65	1.36	2.52
NEI	304,034	9,075	313,109	323,147	9,450	332,597	330,955	9,476	340,431	2.42	0.28	2.38
NIEHS	281,563	6,051	287,614	301,998	6,489	308,487	313,583	6,324	319,907	3.84	(2.54)	3.70
NIA	451,765	1,755	453,520	483,952	1,854	485,806	495,202	1,874	497,076	2.32	1.08	2.32
NIAMS	240,019	4,039	244,058	252,730	4,273	257,003	258,932	4,310	263,242	2.45	0.87	2.43
NIDCD	174,262	1,650	175,912	186,525	1,820	188,345	192,447	1,774	194,221	3.17	(2.53)	3.12
NIMH	566,476	93,483	659,959	604,144	96,906	701,050	629,739	98,510	728,249	4.24	1.66	3.88
NIDA	305,013	153,233	458,246	328,286	160,832	489,118	358,475	163,440	521,915	9.20	1.62	6.71
NIAAA	188,469	10,124	198,593	200,819	11,051	211,870	208,112	11,234	219,346	3.63	1.66	3.53
NINR	50,780	4,896	55,676	54,221	5,500	59,721	55,692	5,360	61,052	2.71	(2.55)	2.23
NHGRI	168,318	993	169,311	186,528	3,001	189,529	202,197	2,990	205,187	8.40	(0.37)	8.26
NCRR	321,059	68,370	389,429	340,994	74,101	415,095	333,868	77,053	410,921	(2.09)	3.98	(1.01)
FIC	15,555	9,694	25,249	16,245	10,312	26,557	16,755	10,413	27,168	3.14	0.98	2.30
NLM	137,647	2,916	140,563	147,463	3,365	150,828	152,689	3,279	155,968	3.54	(2.56)	3.41
OD	232,932	26,550	259,482	251,291	35,561	286,852	234,247	35,912	270,159	(6.78)	0.99	(5.82)
Office of AIDS Res.	1,410,925	(1,410,925)	0	1,501,073	(1,501,073)	0	1,540,765	(1,540,765)	0	2.64	—	0
Subtotal	11,781,411	0	11,781,411	12,540,843	0	12,540,843	12,888,203	0	12,888,203	2.77	0	2.77
B&F	146,151	0	146,151	200,000	0	200,000	190,000	0	190,000	(5.00)	—	(5.00)
(Infrastructure)	(123,151)	(0)	(123,151)	(110,000)	(0)	(110,000)	(100,000)	(0)	(100,000)	(9.09)	—	(9.09)
(Clinical Res. Ctr.)	(23,000)	(0)	(23,000)	(90,000)	(0)	(90,000)	(90,000)	(0)	(90,000)	0.00	—	0.00
Total, Budget Auth.	**11,927,562**	**0**	**11,927,562**	**12,740,843**	**0**	**12,740,843**	**13,078,203**	**0**	**13,078,203**	2.65	0	2.65
Third Party Payments 3/	0	0	0	6,000	0	6,000	15,000	0	15,000			
TOTAL, Prog. Level	**11,927,562**	**0**	**11,927,562**	**12,746,843**	**0**	**12,746,843**	**13,093,203**	**0**	**13,093,203**	2.72	0	2.72

1/ Incorporates the NIH share of the salaries and expenses reduction ($6,140,000) and the public/legislative affairs reduction ($220,000).

2/ The funding for HIV/AIDS research is contained in the Office of AIDS Research, NIH. The distribution of this funding shown by ICD is a proposed distribution.

3/ Estimated recoveries from third party payments for patient care costs to the Clinical Center.

NATIONAL INSTITUTES OF HEALTH
1998 Congressional Justification
Summary by Mechanism

	FY 1996 Budget Authority		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	17,854	$4,726,400,000	18,466	$5,012,228,000	19,567	$5,324,246,000
Administrative supplements	(1,142)	69,646,000	(1,167)	66,329,000	(1,138)	65,869,000
Competing	6,653	1,627,508,000	7,280	1,805,108,000	7,112	1,764,795,000
Subtotal, RPGs	24,507	6,423,554,000	25,746	6,883,665,000	26,679	7,154,910,000
SBIR/STTR	1,012	188,804,000	1,236	246,173,000	1,266	253,288,000
Total, RPGs	25,519	6,612,358,000	26,982	7,129,838,000	27,945	7,408,198,000
Research Centers						
Specialized/comprehensive	653	757,408,000	681	796,244,000	661	818,615,000
Clinical research	78	147,437,000	78	156,656,000	78	157,656,000
Biotechnology	63	49,276,000	63	50,829,000	63	54,693,000
Comparative medicine	40	57,461,000	40	59,897,000	40	60,173,000
Res. centers in minority instit.	17	28,562,000	17	29,606,000	17	29,787,000
Subtotal, Centers	851	1,040,144,000	879	1,093,232,000	859	1,120,924,000
Other Research						
Research careers	2,259	198,442,000	2,326	214,548,000	2,330	218,008,000
Cancer education	75	9,821,000	70	9,992,000	70	10,192,000
Cooperative clinical research	441	185,651,000	486	196,840,000	490	200,827,000
Biomedical research support	186	25,178,000	160	24,604,000	146	24,104,000
Minority biomed. res. support	103	48,954,000	103	50,903,000	103	52,019,000
Other	519	86,417,000	605	103,027,000	605	102,177,000
Subtotal, Other Research	3,583	554,463,000	3,750	599,914,000	3,744	607,327,000
Total, Research Grants	29,953	8,206,965,000	31,611	8,822,984,000	32,548	9,136,449,000
Training	FTTPs		FTTPs		FTTPs	
Individual	2,642	66,585,000	2,655	67,628,000	2,684	69,748,000
Institutional	12,308	328,597,000	12,324	350,245,000	12,319	356,927,000
Total, Training	14,950	395,182,000	14,979	417,873,000	15,003	426,675,000
Research & dev. contracts	1,183	765,068,000	1,308	788,704,000	1,326	809,191,000
(SBIR/STTR)	(52)	(9,949,000)	(87)	(14,283,000)	(89)	(15,074,000)
Intramural research		1,295,980,000		1,333,131,000		1,363,472,000
Res. mgmt. and support		479,870,000		479,368,000		479,368,000
Cancer prevention & control		216,187,000		238,103,000		240,348,000
Construction		22,114,000		23,000,000		6,573,000
Library of Medicine		140,563,000		150,828,000		155,968,000
Office of the Director		259,482,000		286,852,000		270,159,000
Subtotal		11,781,411,000		12,540,843,000		12,888,203,000
Buildings and Facilities		146,151,000		200,000,000		190,000,000
(Infrastructure)		(123,151,000)		(110,000,000)		(100,000,000)
(Clinical Res. Ctr.)		(23,000,000)		(90,000,000)		(90,000,000)
Total, Budget Authority		**11,927,562,000**		**12,740,843,000**		**13,078,203,000**
Third Party Payments		0		6,000,000		15,000,000
Total, Program Level		**11,927,562,000**		**12,746,843,000**		**13,093,203,000**
(Clinical Trials)		(1,166,992,000)		(1,223,148,000)		(1,250,770,000)

NATIONAL INSTITUTES OF HEALTH
Full-Time Equivalents

ICD	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
NCI	2,180	2,180	2,180
NHLBI	834	834	834
NIDR	301	301	301
NIDDK	545	545	545
NINDS	620	620	620
NIAID	1,006	1,006	1,006
NIGMS	169	169	169
NICHD	485	485	485
NEI	233	233	233
NIEHS	640	640	640
NIA	411	411	411
NIAMS	157	157	157
NIDCD	126	126	126
NIMH	828	828	828
NIDA	363	363	363
NIAAA	225	225	225
NINR	40	40	40
NCHGI	187	187	187
NCRR	93	93	93
FIC	72	72	72
Subtotal, ICDs	9,515	9,515	9,515
NLM	575	575	575
OD	690	690	681
Cen. Svcs	4,359	4,359	4,368
Undistributed	14	14	14
Total, NIH	15,153	15,153	15,153

NATIONAL INSTITUTES OF HEALTH

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1988	8,260,277,000 2/	7,036,285,000 3/	6,408,176,000	6,666,693,000
1989	6,535,207,000 4/	6,862,495,000 5/	7,199,298,000	7,152,207,000 6/
1990	6,776,727,000 7/	7,678,625,000 8/	7,713,064,000 8/	7,672,922,000 9/
1990 Sequester				(96,570,000)
1991	7,929,686,000	8,317,654,000 10/	8,347,085,000	8,276,739,000 11/
1991 Sequester				(107,000)
1992	8,774,886,000	8,824,886,000	8,978,133,000	8,921,687,000 12/
1993	10,579,684,000	10,368,551,000	10,387,721,000	10,326,604,000 13/
1994	10,667,984,000	10,936,652,000	10,956,389,000	10,937,653,000 14/
1995	11,473,000,000	11,322,023,000	11,333,181,000	11,299,522,000 15/
1996	11,773,066,000	11,939,001,000	11,639,204,000	11,927,562,000 16/
1997	12,406,300,000 17/	12,747,203,000	12,414,580,000 18/	12,740,843,000 19/
1998	13,078,203,000 20/			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Includes proposed advanced appropriation of $2,726,000 for outyear cost of competing RPGs in 1988.
3/ The House allowance consolidated AIDS funding in OASH.
4/ The 1989 request excludes funds for AIDS, proposed for consolidation in OASH.
5/ Excludes $249,464,000 not considered.
6/ Includes real transfer of $7,443,000 to OASH for AZT.
7/ The 1990 request excludes funds for AIDS, proposed for consolidation in OASH.
8/ Includes $752,670,000 for AIDS research.
9/ Reflects reductions of $10,000,000 for extramural salary cap savings, $4,000,000 for procurement reform and a $10,428,000 reduction in salaries and expenses.
10/ Excludes $304,814,000 not considered.
11/ Reflects enacted administrative reduction of $29,909,000 for salaries and expenses and $205,134,000 associated with the 2.41 percent across-the-board reduction.
12/ Reflects enacted administrative reduction of $69,603,000 for salaries and expenses, a travel reduction of $5,984,000, and a rescission of $13,131,000.
13/ Reflects enacted administrative reductions of an across-the-board .8 percent for $83,571,000, $34,857,000 for salaries and expenses and a consultant services reduction of $1,342,000. All columns adjusted to include transfer from ADAMHA.
14/ Reflects a salaries and expense rescission of $18,120,000. Excludes $1,000,000 supplemental in NCRR for earthquake relief.
15/ Includes $1,299,328,000 for HIV Research appropriated to the NIH Office of AIDS Research. Reflects enacted reductions of $7,446,000 for procurement, $345,000 for rent and $4,401,000 for bonus pay, and rescissions of $10,000,000 in NCRR for construction and $12,384,000 in administrative cost.
16/ Includes $1,410,925,000 appropriated to the ICDs for HIV research. Incorporates the NIH share of the government-wide administrative cost rescission ($5,780,000) and the Labor/HHS/E bonus pay rescission ($5,659,000).
17/ Includes $1,431,908,000 for HIV research in the NIH Office of AIDS Research.
18/ Includes $1,460,312,000 for HIV research in the NIH Office of AIDS Research.
19/ Includes $1,501,073,000 for HIV research in the NIH Office of AIDS Research. Incorporates the NIH share of the salaries and expenses reduction ($6,140,000) and the public/legislative affairs reduction ($220,000).
20/ Includes $1,540,765,000 for HIV research in the NIH Office of AIDS Research.

National Institutes of Health
HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1987 - 1997
(Dollars in thousands)

FISCAL YEAR	NCI	NHLBI	NIDR	NIDDK	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	NIA	NIAMS	NIDCD
1988	$1,469,327	$965,536	$126,297	$534,733	$534,692	$638,800	$632,676	$396,811	$224,947	$215,666	$194,746	$147,679	..
1989	1,570,349	1,045,509	130,709	559,494	472,291	740,257	682,213	425,375	231,170	223,403	222,639	159,891	$94,166
1990	1,634,332	1,072,354	135,749	581,477	490,409	832,977	681,782	442,914	236,533	229,234	239,455	168,930	117,583
1991	1,714,784	1,126,942	148,918	615,272	541,743	906,251	760,010	478,956	253,241	241,028	323,752	193,247	134,935
1992	1,962,587	1,188,593	158,417	658,925	577,938	959,082	816,844	518,251	268,978	248,575	383,382	203,047	148,789
1993	1,981,351	1,214,793	161,301	681,342	600,078	979,471	832,581	527,788	276,188	251,187	399,824	212,456	154,814
1994	2,082,267	1,277,880	169,520	716,054	630,650	1,065,583	875,511	555,195	290,260	264,249	420,303	223,280	162,823
1995	1,913,819	1,257,374	162,430	726,849	627,045	535,199	876,778	512,165	291,095	266,566	431,991	228,176	166,660
1996	2,254,951	1,351,440	183,478	768,530	683,553	1,171,168	944,466	593,104	313,109	287,614	453,520	244,058	175,912
1997	2,381,149	1,432,529	195,825	815,607	726,407	1,256,659	998,444	631,365	332,597	308,487	485,806	257,003	188,345

FISCAL YEAR	NIMH	NIDA	NIAAA	NINR	NHGRI	NCRR	FIC	NLM	OD	B&F	OAR	TOTAL	
1988	..	..	..	$23,380	..	$368,153	$15,651	$67,910	$61,619	$47,870	..	$6,666,693	
1989	..	..	..	29,133	..	358,076	15,790	73,731	72,076	38,492	..	7,144,764	1/
1990	..	..	..	33,513	$59,538	353,734	15,516	81,861	107,419	61,042	..	7,576,352	2/
1991	..	..	..	39,722	87,418	335,255	17,519	91,408	97,651	168,687	..	8,276,739	3/
1992	..	..	..	44,929	104,762	314,213	19,593	99,088	141,854	103,840	..	8,921,687	4/
1993	$583,651	$403,606	$176,619	48,119	106,239	312,468	19,733	113,031	190,325	108,731	..	10,335,996	5/
1994	613,444	425,201	185,617	51,018	128,701	331,915	21,677	119,981	233,605	111,039	..	10,955,773	6/
1995	542,200	290,029	181,150	46,164	151,518	284,693	14,646	125,303	217,882	114,120	$1,333,570	11,299,522	7/
1996	659,959	458,246	198,593	55,676	169,311	389,429	25,249	140,563	259,482	146,151	..	11,927,562	8/
1997	701,050	489,118	211,870	59,721	189,529	415,095	26,557	150,828	286,852	200,000	..	12,740,843	9/

1/ Reflects a 1.2% administrative reduction and procurement reform and transfer to OASH for AZT.

2/ Reflects reductions for Extramural Salary Cap, Procurement Reform, S&E, and Sequestration.

3/ Reflects 2.41% reduction and NIH's share of the $50M reduction for Salaries and Expenses.

4/ Reflects reductions for travel and Salaries and Expenses.

5/ Reflects an across the board .8 percent reduction and reductions for Salaries and Expenses and Consultant Services.

6/ National Center of Nursing Research elevated to Institute status in 1994.

7/ Reflects enacted reductions of $7,446 for procurement, $345 for rent, $4,401 bonus pay and a rescission of $20,533.

8/ Funds for HIV Research in the amount of $1,410,925 appropriated to the ICDs. Incorporates the NIH share of the government-wide administrative cost rescission ($5,780,000) and the Labor/HHS/E bonus pay rescission ($5,659,000).

9/ Funds for HIV Research in the amount of $1,501,073 appropriated to the ICDs. Incorporates the NIH share of the salaries and expenses reduction ($6,140,000) and the public/legislative affairs reduction ($220,000). National Center for Human Genome Research elevated to Institute status in 1997.

NATIONAL INSTITUTES OF HEALTH

1998 CONGRESSIONAL JUSTIFICATION

BUDGET AUTHORITY BY OBJECT

	OBJECT CLASSIFICATION	FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$476,355,000	$496,155,000	$19,800,000
11.3	Other than Full-Time Permanent	100,172,000	103,528,000	3,356,000
11.5	Other Personnel Compensation	22,493,000	23,299,000	806,000
11.8	Special Personnel Services Payments	87,653,000	91,887,000	4,234,000
11.9	**Total Personnel Compensation**	**686,673,000**	**714,869,000**	**28,196,000**
12.0	Civilian Personnel Benefits	143,531,000	150,217,000	6,686,000
13.0	Benefits for Former Personnel	469,000	483,000	14,000
	Subtotal, Pay Costs	**830,673,000**	**865,569,000**	**34,896,000**
21.0	Travel & Transportation of Persons	18,083,000	18,054,000	(29,000)
22.0	Transportation of Things	3,544,000	3,552,000	8,000
23.1	Rental Payments to GSA	5,298,000	5,470,000	172,000
23.2	Rental Payments to Others	6,069,000	6,044,000	(25,000)
23.3	Communications, Utilities & Miscellaneous Charges	44,920,000	44,956,000	36,000
24.0	Printing & Reproduction	11,622,000	11,545,000	(77,000)
25.1	Consulting Services	21,156,000	20,982,000	(174,000)
25.2	Other Services	430,890,000	415,742,000	(15,148,000)
25.3	Purchase of Goods & Services from Government Accounts	761,187,000	761,338,000	151,000
25.4	Operation & Maintenance of Facilities	166,084,000	164,220,000	(1,864,000)
25.5	Research & Development Contracts	687,761,000	704,753,000	16,992,000
25.6	Medical Care	7,997,000	8,024,000	27,000
25.7	Operation & Maintenance of Equipment	32,786,000	32,677,000	(109,000)
25.8	Subsistance & Support of Persons	1,000	0	(1,000)
25.0	**Subtotal, Other Contractual Services**	**2,107,862,000**	**2,107,736,000**	**(126,000)**
26.0	Supplies & Materials	120,924,000	122,116,000	1,192,000
31.0	Equipment	96,771,000	97,556,000	785,000
32.0	Land and Structures	16,000	9,000	(7,000)
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	9,492,309,000	9,792,862,000	300,553,000
42.0	Insurance Claims & Indemnities	2,683,000	2,666,000	(17,000)
43.0	Interest & Dividends	69,000	68,000	(1,000)
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**11,910,170,000**	**12,212,634,000**	**302,464,000**
	Total Budget Authority	**12,740,843,000**	**13,078,203,000**	**337,360,000**

NATIONAL INSTITUTES OF HEALTH

1998 CONGRESSIONAL JUSTIFICATION
BUDGET AUTHORITY BY OBJECT INCLUDING
SERVICE AND SUPPLY
AND MANAGEMENT FUND

	OBJECT CLASSIFICATION	FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$664,599,000	$690,873,000	$26,274,000
11.3	Other than Full-Time Permanent	112,521,000	116,077,000	3,556,000
11.5	Other Personnel Compensation	37,574,000	38,676,000	1,102,000
11.8	Special Personnel Services Payments	88,888,000	93,144,000	4,256,000
11.9	**Total Personnel Compensation**	**903,582,000**	**938,770,000**	**35,188,000**
12.0	Civilian Personnel Benefits	190,204,000	198,590,000	8,386,000
13.0	Benefits for Former Personnel	860,000	883,000	23,000
	Subtotal, Pay Costs	**1,094,646,000**	**1,138,243,000**	**43,597,000**
21.0	Travel & Transportation of Persons	19,652,000	19,663,000	11,000
22.0	Transportation of Things	6,765,000	6,697,000	(68,000)
23.1	Rental Payments to GSA	30,902,000	31,779,000	877,000
23.2	Rental Payments to Others	7,338,000	7,313,000	(25,000)
23.3	Communications, Utilities & Miscellaneous Charges	106,573,000	105,495,000	(1,078,000)
24.0	Printing & Reproduction	17,122,000	17,016,000	(106,000)
25.1	Consulting Services	24,674,000	24,509,000	(165,000)
25.2	Other Services	507,636,000	490,107,000	(17,529,000)
25.3	Purchase of Goods & Services from Government Accounts	101,782,000	99,815,000	(1,967,000)
25.4	Operation & Maintenance of Facilities	166,212,000	164,348,000	(1,864,000)
25.5	Research & Development Contracts	692,281,000	709,028,000	16,747,000
25.6	Medical Care	11,716,000	11,579,000	(137,000)
25.7	Operation & Maintenance of Equipment	63,362,000	61,849,000	(1,513,000)
25.8	Subsistance & Support of Persons	29,517,000	28,187,000	(1,330,000)
25.0	**Subtotal, Other Contractual Services**	**1,597,180,000**	**1,589,422,000**	**(7,758,000)**
26.0	Supplies & Materials	220,008,000	220,833,000	825,000
31.0	Equipment	144,217,000	144,770,000	553,000
32.0	Land and Structures	23,000	16,000	(7,000)
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	9,492,309,000	9,792,862,000	300,553,000
42.0	Insurance Claims & Indemnities	3,993,000	3,980,000	(13,000)
43.0	Interest & Dividends	115,000	114,000	(1,000)
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**11,646,197,000**	**11,939,960,000**	**293,763,000**
	Total Budget Authority	**12,740,843,000**	**13,078,203,000**	**337,360,000**

NATIONAL INSTITUTES OF HEALTH

1998 CONGRESSIONAL JUSTIFICATION

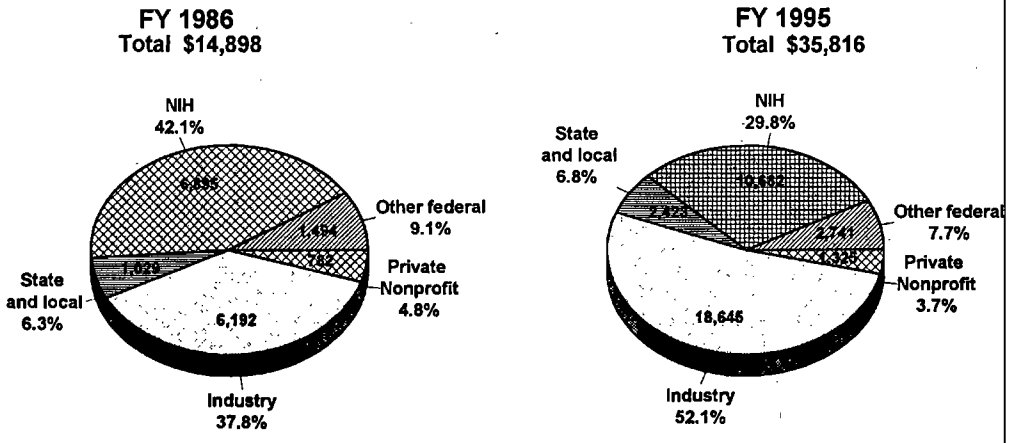
ADMINISTRATIVE COSTS

OBJECT CLASSIFICATION	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$476,355,000	$496,155,000	$19,800,000
Other Than Full-Time Permanent (11.3)	100,172,000	103,528,000	3,356,000
Other Personnel Compensation (11.5)	22,493,000	23,299,000	806,000
Special Personnel Services Payments (11.8)	87,653,000	91,887,000	4,234,000
Total Personnel Compensation (11.9)	**686,673,000**	**714,869,000**	**28,196,000**
Civilian Personnel Benefits (12.0)	143,531,000	150,217,000	6,686,000
Benefits to Former Personnel (13.0)	469,000	483,000	14,000
Subtotal, Pay Costs	**830,673,000**	**865,569,000**	**34,896,000**
Travel (21.0)	18,083,000	18,054,000	(29,000)
Transportation of Things (22.0)	3,544,000	3,552,000	8,000
Rental Payments to Others (23.2)	6,069,000	6,044,000	(25,000)
Communications, Utilities and Miscellaneous Charges (23.3)	44,920,000	44,956,000	36,000
Printing and Reproduction (24.0)	11,622,000	11,545,000	(77,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	21,156,000	20,982,000	(174,000)
Other Services (25.2)	230,890,000	225,742,000	(5,148,000)
Purchases from Govt. Accounts (25.3)	551,337,000	549,567,000	(1,770,000)
Operation & Maintenance of Facilities (25.4)	28,461,000	28,336,000	(125,000)
Operation & Maintenance of Equipment (25.7)	32,786,000	32,677,000	(109,000)
Subsistence & Support of Persons (25.8)	1,000	0	(1,000)
Subtotal Other Contractual Services	**864,631,000**	**857,304,000**	**(7,327,000)**
Supplies and Materials (26.0)	120,291,000	121,355,000	1,064,000
Subtotal, Non-Pay Costs	1,069,160,000	1,062,810,000	(6,350,000)
Total, NIH	**1,899,833,000**	**1,928,379,000**	**28,546,000**

NATIONAL INSTITUTES OF HEALTH

National Support for Health R&D by Source of Funds

(Dollars in millions)



NATIONAL INSTITUTES OF HEALTH

Estimates of National Support for Health R&D by Source of Funds
Fiscal Years 1986-1995
(Dollars in Millions)

Source of Funds	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994	FY 1995
Total	$14,898	$16,933	$19,003	$20,918	$23,095	$25,886	$29,240	$31,088	$33,399	$35,816
Government	7,924	9,028	9,726	10,629	11,416	12,435	13,660	14,162	15,017	15,846
Federal	6,895	7,847	8,431	9,163	9,791	10,602	11,726	12,108	12,821	13,423
NIH /1	(5,401)	(6,328)	(6,847)	(7,474)	(8,028)	(8,780)	(9,566)	(9,765)	(10,338)	(10,682)
State & local	1,029	1,182	1,295	1,466	1,625	1,833	1,933	2,054	2,196	2,423
Industry	6,192	7,105	8,438	9,407	10,719	12,361	14,397	15,711	17,106	18,645
Private nonprofit	782	800	839	882	960	1,090	1,183	1,215	1,276	1,325

1/ Excludes R&D Facilities and Training & Overhead.

Source: NIH Extramural Data and Trends, FY 1986 - FY 1995

NATIONAL INSTITUTES OF HEALTH

Statistical Data - Research Grants, Direct and Indirect Costs Awarded 1/
(Dollars InThousands)

Fiscal Year	Direct Costs Awarded	Indirect Costs Awarded	Total Dollars Awarded	Percent To Total In Dollars		Percent Growth In Dollars	
				Direct	Indirect	Direct	Indirect
1989	$3,315,563	$1,530,547	$4,846,110	68.4%	31.6%		
1990	3,428,392	1,599,286	5,027,678	68.2%	31.8%	3.4%	4.5%
1991	3,748,778	1,744,378	5,493,156	68.2%	31.8%	9.3%	9.1%
1992	4,169,928	1,896,215	6,066,143	68.7%	31.3%	11.2%	8.7%
1993	4,888,871	2,183,265	7,072,136	69.1%	30.9%	17.2%	15.1%
1994	5,098,605	2,279,984	7,378,589	69.1%	30.9%	4.3%	4.4%
1995	5,363,762	2,362,067	7,725,829	69.4%	30.6%	5.2%	3.6%
1996	5,659,180	2,514,439	8,173,619	69.2%	30.8%	5.5%	6.5%
1997 Estimate	6,079,224	2,705,782	8,785,006	69.2%	30.8%	7.4%	7.6%
1998 Estimate	6,294,429	2,801,566	9,095,995	69.2%	30.8%	3.5%	3.5%

Note--1992 and prior years data excludes NIMH, NIAAA, and NIDA. Comparable data is not available.

1/ Actual data from the Indirect Cost Management System (ICMS). Includes research project grants, research centers, research career awards, organ systems, clinical education, cooperative clinical research, minority biomedical research support and cancer control grants

NATIONAL INSTITUTES OF HEALTH

Research Project Grants

Total Number of Awards and Dollars

(Dollars in Thousands)

	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Realigned	FY 1995	FY 1996	FY 1997 Estimate	FY 1998 Estimate
No. of Awards:											
Competing	6,157	5,620	6,462	6,768	6,149	6,822	6,474	6,759	6,653	7,280	7,112
Subtotal (includes Noncomp)	22,725	22,527	23,352	24,033	23,952	24,401	24,050	23,828	24,507	25,746	26,679
SBIR							914	1,071	1,012	1,236	1,266
Total	22,725	22,527	23,352	24,033	23,952	24,401	24,964	24,899	25,519	26,982	27,945
Average Annual Cost:											
Competing	$182.3	$196.7	$208.1	$220.3	$218.3	$223.3	$225.0	$231.2	$244.6	$248.0	$248.1
Total (includes Noncomp)	$193.9	$205.3	$216.1	$227.2	$236.2	$244.1	$243.5	$252.7	$262.1	$267.4	$268.2
Percent Change over prior year Ave. costs:											
Competing	4.0%	7.9%	5.8%	5.9%	-0.9%	2.3%	3.1%	2.8%	5.8%	1.4%	0.1%
Total	5.9%	5.9%	5.2%	5.1%	4.0%	3.4%	3.1%	3.8%	3.7%	2.0%	0.3%
Average Length of Award in Years	4.1	4.1	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9

Note: Two columns for FY 1994 provide comparability. The first column is comparable to FY 1989 - FY 1993. The second column reflects the realignment of RPGs which occurred in FY 1994.

NATIONAL INSTITUTES OF HEALTH
Research Project Grants
Success Rates
FY 1989 - FY 1998

INSTITUTE	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Realigned	FY 1995	FY 1996	FY 1997 Estimate	FY 1998 Estimate
NCI	25%	24%	28%	32%	25%	24%	22%	24%	29%	26%	25%
NHLBI	26%	25%	28%	29%	22%	28%	23%	27%	25%	30%	27%
NIDR	23%	21%	30%	27%	24%	35%	37%	29%	24%	25%	23%
NIDDK	26%	23%	27%	33%	22%	30%	25%	27%	26%	29%	27%
NINDS	32%	24%	30%	27%	25%	27%	26%	31%	29%	25%	26%
NIAID	30%	27%	31%	30%	29%	32%	25%	25%	32%	33%	34%
NIGMS	28%	22%	34%	36%	30%	31%	33%	39%	34%	35%	35%
NICHD	24%	19%	25%	26%	21%	22%	21%	18%	23%	22%	24%
NEI	43%	38%	33%	31%	32%	34%	40%	36%	38%	39%	37%
NIEHS	26%	28%	28%	28%	21%	22%	26%	16%	21%	21%	20%
NIA	23%	21%	30%	29%	23%	26%	25%	29%	32%	34%	28%
NIAMS	26%	20%	31%	18%	21%	20%	20%	24%	26%	21%	22%
NIDCD	38%	37%	31%	30%	29%	32%	32%	34%	33%	35%	37%
NIMH	29%	24%	27%	27%	20%	23%	21%	19%	22%	25%	24%
NIDA	38%	37%	31%	31%	32%	41%	33%	30%	26%	24%	27%
NIAAA	38%	34%	23%	32%	19%	30%	29%	22%	21%	19%	20%
NINR	19%	16%	19%	15%	11%	12%	12%	32%	26%	33%	26%
NHGRI	0%	23%	38%	22%	28%	23%	28%	26%	29%	27%	31%
NCRR	0%	22%	29%	33%	28%	22%	18%	23%	33%	48%	45%
FIC	0%	0%	0%	0%	0%	6%	27%	65%	40%	42%	40%
NIH	28%	25%	29%	30%	25%	27%	25%	27%	28%	28%	28%

NATIONAL INSTITUTES OF HEALTH

History Of Obligations By Total Mechanism

FY 1989 - FY 1998

(Dollars in Thousands)

Mechanism	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Comp.	FY 1994 Realigned	FY 1995	FY 1996	FY 1997 Estimate	FY 1998 Estimate
Res. Project Grants	$4,405,645	$4,625,833	$5,046,134	$5,459,375	$5,657,630	$5,957,244	$5,981,328	$6,184,524	$6,612,358	$7,129,838	$7,408,198
Research Centers	657,767	702,215	796,007	891,772	903,204	973,923	973,923	1,006,009	1,040,144	1,093,232	1,120,924
Other Research	441,349	493,993	546,136	561,400	547,837	542,705	518,621	504,314	554,463	599,914	607,327
Subtotal Res. Grants	5,504,761	5,822,041	6,388,277	6,912,547	7,108,671	7,473,872	7,473,872	7,704,847	8,206,965	8,822,984	9,136,449
Research Training	283,015	318,896	342,260	348,018	350,805	372,688	372,688	380,502	395,182	417,873	426,675
R & D Contracts	583,496	630,487	664,698	705,821	693,508	765,249	765,249	791,415	765,068	788,704	809,191
Intramural Research	882,417	975,871	1,048,834	1,132,166	1,160,950	1,201,091	1,201,091	1,222,646	1,295,880	1,333,131	1,363,472
Res. Mgt. & Support	356,867	405,358	434,706	484,327	493,200	497,886	497,886	506,415	479,870	479,368	479,368
Cancer Control	74,100	75,433	85,390	107,569	105,293	145,600	145,600	192,275	216,187	238,103	240,348
Construction	31,345	16,322	7,349	12,000	7,528	23,421	23,421	17,946	22,114	23,000	6,573
Library of Medicine	78,798	81,683	91,182	102,937	103,496	117,783	117,783	127,723	140,563	150,828	155,968
Office of the Director	74,371	111,729	98,153	143,542	181,935	227,044	227,044	239,390	259,482	288,852	270,159
Subtotal	7,869,170	8,437,820	9,160,849	9,948,927	10,215,386	10,824,634	10,824,634	11,183,159	11,781,411	12,540,843	12,888,203
Buildings & Facilities	24,416	67,436	57,091	61,441	112,731	86,335	86,335	157,682	146,151	200,000	190,000
Total	7,893,586	8,505,256	9,217,940	10,010,368	10,328,117	10,910,969	10,910,969	11,340,841	11,927,562	12,740,843	13,078,203

NATIONAL INSTITUTES OF HEALTH

History of Actual Obligations*
FY 1989 - FY 1998
(Dollars in Thousands)

INSTITUTE	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997 Estimate	FY 1998 Estimate
NCI	$1,570,342	$1,644,330	$1,712,669	$1,947,571	$1,978,340	$2,076,218	$2,129,369	$2,254,951	$2,381,149	$2,441,738
NHLBI	1,045,508	1,070,683	1,125,915	1,190,070	1,214,693	1,277,852	1,314,969	1,351,440	1,432,529	1,467,189
NIDR	130,689	135,432	148,691	158,900	161,116	169,490	174,021	183,478	195,825	202,831
NIDDK	559,274	579,984	615,262	661,446	680,514	715,622	737,043	768,530	815,607	833,802
NINDS	471,632	489,348	542,313	580,790	599,466	630,584	649,121	683,553	726,407	747,828
NIAID	740,239	831,181	906,003	960,082	984,114	1,063,696	1,092,507	1,171,168	1,256,659	1,312,502
NIGMS	682,134	680,305	761,231	814,297	832,191	875,495	904,738	944,466	998,444	1,020,192
NICHD	425,268	441,955	478,947	518,577	527,767	554,836	570,309	593,104	631,365	647,279
NEI	230,999	236,456	253,354	269,766	275,368	289,906	299,383	313,109	332,597	340,431
NIEHS	223,309	228,725	240,606	251,484	251,047	264,111	272,012	287,614	308,487	319,907
NIA	222,545	238,927	323,791	382,882	399,523	420,266	433,288	453,520	485,806	497,076
NIAMS	159,886	168,538	193,449	203,516	212,208	223,160	230,816	244,058	257,003	263,242
NIDCD	94,275	117,263	134,957	148,748	154,655	162,782	168,006	175,912	188,345	194,221
NIMH	384,928	440,222	511,967	560,285	582,851	613,352	631,060	659,959	701,050	728,249
NIDA	228,131	329,560	383,656	399,100	403,065	424,315	436,726	458,246	489,118	521,915
NIAAA	120,051	149,194	158,141	171,481	176,128	185,538	190,548	198,593	211,870	219,346
NINR	29,118	33,508	39,892	44,925	48,477	51,002	52,689	55,676	59,721	61,052
NHGRI	0	59,527	87,389	104,756	106,095	127,017	153,789	169,311	189,529	205,187
NCRR	381,934	353,771	335,776	314,198	312,635	332,903	351,923	389,429	415,095	410,921
FIC	15,739	15,479	17,505	19,574	19,702	21,662	23,729	25,249	26,557	27,168
NLM	78,798	81,683	91,182	102,937	103,496	117,783	127,723	140,563	150,828	155,968
OD	74,371	111,729	98,153	143,542	191,935	227,044	239,390	259,482	286,852	270,159
Subtotal	7,869,170	8,437,820	9,160,849	9,948,927	10,215,386	10,824,634	11,183,159	11,781,411	12,540,843	12,888,203
B&F	24,416	67,436	57,091	61,441	112,731	86,335	157,682	146,151	200,000	190,000
TOTAL	7,893,586	8,505,256	9,217,940	10,010,368	10,328,117	10,910,969	11,340,841	11,927,562	12,740,843	13,078,203

NATIONAL INSTITUTES OF HEALTH

JUSTIFICATION

Management Fund

General Statement

The NIH Management Fund (MF) was established on June 29, 1957, by Public Law 85-67. The MF was created to finance a variety of centralized research support services and administrative activities which are required for the efficient and effective operation of all NIH programs and facilities. The expenses for these activities are paid by the NIH appropriations and other government agencies. The services provided by the MF include utilities and plant maintenance, a 500 bed hospital and outpatient clinic, receipt, review and referral of research and training grant applications, collaborative computer science research and biomedical engineering, and general administrative support services.

To promote the stability of Clinical Center funding and to enable the Clinical Center to operate more efficiently, the following changes are proposed: 1) core Clinical Center costs shall be assessed to the Institutes on the basis of historical usage; 2) NIH is authorized to collect third party payments for the cost of clinical services that are incurred in National Institutes of Health research facilities and that such payments shall be credited to the National Institutes of Health Management Fund; and 3) all funds credited to the NIH Management Fund shall remain available for one fiscal year after the fiscal year in which they are deposited.

The Laboratory of Diagnostic Radiology Research (LDRR) has been transferred from the Office of the Director to the Clinical Center. Although the facility has always been physically connected to the Clinical Center, certain services in support of the program have overlapped administrative lines. This transfer will promote a more efficient service delivery structure in support of both clinical and research activities.

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NATIONAL INSTITUTES OF HEALTH

Management Fund

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Computer Services	137	24,810	121	26,043	121	26,038	0	(5)
Intramural Scientific Services	211	24,539	211	25,581	211	25,581	0	0
Clinical Services	1,838	221,660	1,838	221,380	1,847	223,380	9	2,000
Grant Review and Approval	283	28,936	283	29,123	283	29,123	0	0
Intramural Research and Support Services	826	146,460	826	154,956	826	154,286	0	(670)
Rental Payments	0	26,423	0	27,914	0	26,589	0	(1,325)
Total obligations	3,295	472,828	3,279	484,997	3,288	484,997	9	0
Total, Budget Authority	3,295	472,828	3,279	484,997	3,288	484,997	9	0

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.
Includes transfer of the Laboratory for Diagnostic Radiology Research.

NATIONAL INSTITUTES OF HEALTH

Management Fund

Source of Income

	1996 Actual	1997 Estimate	1998 Estimate
NCI	$140,984,000	$142,102,000	$142,102,000
NHLBI	48,864,000	49,701,000	49,701,000
NIDR	9,030,000	9,429,000	9,429,000
NIDDK	28,108,000	28,607,000	28,607,000
NINDS	34,632,000	34,954,000	34,954,000
NIAID	34,991,000	36,377,000	36,377,000
NIGMS	7,959,000	8,112,000	8,112,000
NICHD	25,022,000	26,523,000	26,523,000
NEI	10,522,000	11,946,000	11,946,000
NIEHS	3,169,000	3,178,000	3,178,000
NIA	7,707,000	7,832,000	7,832,000
NIAMS	8,767,000	8,758,000	8,758,000
NIDCD	3,452,000	3,756,000	3,756,000
NIMH	32,046,000	33,461,000	33,461,000
NIDA	864,000	943,000	943,000
NIAAA	6,386,000	6,632,000	6,632,000
NINR	1,145,000	1,130,000	1,130,000
NCRR	4,145,000	4,158,000	4,158,000
NCHGR	4,078,000	6,592,000	6,592,000
FIC	1,369,000	1,299,000	1,299,000
NLM	9,376,000	9,660,000	9,660,000
FDA	7,297,000	8,172,000	8,172,000
SSF	10,534,000	9,316,000	9,316,000
SUBTOTAL	440,447,000	452,638,000	452,638,000
INTRAFUND BILLING	27,300,000	26,428,000	26,428,000
DIRECT REIMBURSEMENTS	5,931,000	5,931,000	5,931,000
TOTAL, NIH	473,678,000	484,997,000	484,997,000

NATIONAL INSTITUTES OF HEALTH

Management Fund

Budget Authority by Object

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:				
Full-time employment		3,279	3,288	9
Full-time equivalent of overtime and holiday hours		110	101	(9)
Average ES salary		$117,343	$120,770	$3,427
Average GM/GS grade		10.8	10.8	
Average GM/GS salary		$42,091	$43,352	$1,261
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)		$65,827	$66,478	$651
Average salary of ungraded positions		$25,797	$25,947	$150
		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	140,141,000	144,757,000	$4,616,000
11.3	Other than Full-Time Permanent	11,363,000	11,523,000	160,000
11.5	Other Personnel Compensation	12,274,000	12,462,000	188,000
11.8	Special Personnel Services Payments	1,214,000	1,235,000	21,000
11.9	**Total Personnel Compensation**	**164,992,000**	**169,977,000**	**4,985,000**
12.0	Personnel Benefits	36,644,000	37,938,000	1,294,000
13.0	Benefits for Former Personnel	184,000	190,000	6,000
	Subtotal, Pay Costs	**201,820,000**	**208,105,000**	**6,285,000**
21.0	Travel & Transportation of Persons	1,202,000	1,226,000	24,000
22.0	Transportation of Things	689,000	679,000	(10,000)
23.1	Rental Payments to GSA	24,274,000	24,979,000	705,000
23.2	Rental Payments to Others	1,263,000	1,263,000	0
23.3	Communications, Utilities & Miscellaneous Charges	37,624,000	36,693,000	(931,000)
24.0	Printing & Reproduction	2,526,000	2,508,000	(18,000)
25.1	Consulting Services	2,309,000	2,324,000	15,000
25.2	Other Services	62,315,000	59,931,000	(2,384,000)
25.3	Purchase of Goods & Services from Government Accounts	32,455,000	32,258,000	(197,000)
25.4	Operation & Maintenance of Facilities	0	0	0
25.5	Research & Development Contracts	1,700,000	1,455,000	(245,000)
25.6	Medical Care	3,719,000	3,555,000	(164,000)
25.7	Operation & Maintenance of Equipment	21,719,000	21,059,000	(660,000)
25.8	Subsistance & Support of Persons	29,516,000	28,187,000	(1,329,000)
25.0	**Subtotal, Other Contractual Services**	**153,733,000**	**148,769,000**	**(4,964,000)**
26.0	Supplies & Materials	43,467,000	41,653,000	(1,814,000)
31.0	Equipment	17,287,000	18,004,000	717,000
32.0	Land and Structures	7,000	7,000	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	0	0	0
42.0	Insurance Claims & Indemnities	1,088,000	1,094,000	6,000
43.0	Interest & Dividends	17,000	17,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**283,177,000**	**276,892,000**	**(6,285,000)**
				0
	Total, Budget Authority by Object	**484,997,000**	**484,997,000**	**0**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
Management Fund

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	1	1	1
ES-5	1	1	1
ES-4	6	6	6
ES-3	1	1	1
ES-2	1	1	1
Subtotal	10	10	10
Total - ES Salary	$1,137,902	$1,173,431	$1,207,697
GS/GM-15	95	101	102
GS/GM-14	181	186	186
GS/GM-13	191	204	204
GS-12	320	330	331
GS-11	349	359	360
GS-10	371	369	369
GS-9	199	210	210
GS-8	111	114	114
GS-7	278	290	291
GS-6	183	184	184
GS-5	176	179	179
GS-4	101	101	101
GS-3	36	37	37
GS-2	14	16	16
GS-1	5	5	5
Subtotal	2,610	2,685	2,689
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	8	8	8
Director Grade	49	53	53
Senior Grade	54	54	54
Full Grade	44	43	43
Senior Assistant Grade	34	35	35
Assistant Grade	12	12	12
Co-Step	4	3	3
Subtotal	205	208	208
Ungraded	513	510	510
Total permanent positions	3,235	3,314	3,314
Total positions, end of year	6,573	6,727	6,731
Total full-time equivalent (FTE) employment,end of year	3,295	3,279	3,288
Average ES level	4.0	4.0	4.0
Average ES salary	$113,790	$117,343	$120,770
Average GS/GM grade	10.9	10.8	10.8
Average GS/GM salary	$42,250	$42,091	$43,352

NATIONAL INSTITUTES OF HEALTH

Justification

Service and Supply Fund

General Statement

The NIH Service and Supply Fund (SSF) was established on April 11, 1953, under 42 U.S.C. 231. The SSF was created to finance a variety of centralized research support services and administrative activities which are required for the efficient and effective operation of all NIH programs and facilities. The SSF provides a single means for consolidating the financing and accounting of business-type operations involving the sales of services and commodities to customers. The services provided by the SSF include mainframe computing, engineering planning and design, printing, telecommunications, procurement, shipping and receiving, motor pool, research animals, fabrication and maintenance of scientific equipment, and other administrative support services.

A permanent transfer of personnel from the Health and Human Services (HHS) Program Support Center (PSC) to the Division of Computer Research and Technology, funded through the NIH SSF, occurred in FY 1997. The transfer of personnel results from the decision made by the Assistant Secretary for Management and Budget to consolidate data processing centers within the HHS. The action was taken to support the goals for consolidated operations as stated in OMB Bulletin #96-02.

NATIONAL INSTITUTES OF HEALTH

Service and Supply Fund

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Cost of Goods Sold		$39,110		$40,686		$40,686		0
Other	752	134,300	752	137,135	752	136,931	0	(204)
Adminstrative Services - total	752	173,410	752	177,821	752	177,617	0	(204)
Data processing services	216	45,256	232	67,450	232	67,450	0	0
Cost of Goods Sold		4,253		4,618		4,618		0
Other	49	5,319	49	8,479	49	8,479	0	0
Instrumentation - total	49	9,572	49	13,097	49	13,097	0	0
Research animals	47	14,319	47	16,392	47	16,392	0	0
Total obligations	1,064	242,557	1,080	274,760	1,080	274,556	0	(204)
Total, Budget Authority	1,064	242,557	1,080	274,760	1,080	274,556	0	(204)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

Service and Supply Fund

Budget Authority by Object

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:				
Full-time employment		1,080	1,080	—
Full-time equivalent of overtime and holiday hours		50	51	1
Average ES salary		$119,836	$123,192	$3,356
Average GM/GS grade		10.3	10.3	
Average GM/GS salary		$41,639	$42,911	$1,272
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)		$67,422	$69,445	$2,023
Average salary of ungraded positions		$36,420	$37,877	$1,457
		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	48,103,000	49,961,000	$1,858,000
11.3	Other than Full-Time Permanent	986,000	1,026,000	40,000
11.5	Other Personnel Compensation	2,807,000	2,915,000	108,000
11.8	Special Personnel Services Payments	21,000	22,000	1,000
11.9	**Total Personnel Compensation**	**51,917,000**	**53,924,000**	**2,007,000**
12.0	Personnel Benefits	10,029,000	10,435,000	406,000
13.0	Benefits for Former Personnel	207,000	210,000	3,000
	Subtotal, Pay Costs	**62,153,000**	**64,569,000**	**2,416,000**
21.0	Travel & Transportation of Persons	367,000	383,000	16,000
22.0	Transportation of Things	2,532,000	2,466,000	(66,000)
23.1	Rental Payments to GSA	1,330,000	1,330,000	0
23.2	Rental Payments to Others	6,000	6,000	0
23.3	Communications, Utilities & Miscellaneous Charges	24,029,000	23,846,000	(183,000)
24.0	Printing & Reproduction	2,974,000	2,963,000	(11,000)
25.1	Consulting Services	1,209,000	1,203,000	(6,000)
25.2	Other Services	19,431,000	18,987,000	(444,000)
25.3	Purchase of Goods & Services from Government Accounts	62,897,000	61,219,000	(1,678,000)
25.4	Operation & Maintenance of Facilities	128,000	128,000	0
25.5	Research & Development Contracts	2,820,000	2,820,000	0
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	8,857,000	8,113,000	(744,000)
25.8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**95,342,000**	**92,470,000**	**(2,872,000)**
26.0	Supplies & Materials	55,617,000	57,064,000	1,447,000
31.0	Equipment	30,159,000	29,210,000	(949,000)
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	0	0	0
42.0	Insurance Claims & Indemnities	222,000	220,000	(2,000)
43.0	Interest & Dividends	29,000	29,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**212,607,000**	**209,987,000**	**(2,620,000)**
				0
	Total, Budget Authority by Object	**274,760,000**	**274,556,000**	**(204,000)**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
Service and Supply Fund

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	0	0	0
ES-5	0	0	0
ES-4	1	1	1
ES-3	0	0	0
ES-2	0	0	0
Subtotal	1	1	1
Total - ES Salary	$116,008	$119,836	$123,192
GS/GM-15	21	21	21
GS/GM-14	53	53	53
GS/GM-13	155	155	155
GS-12	157	158	158
GS-11	72	72	72
GS-10	7	7	7
GS-9	67	69	69
GS-8	40	39	39
GS-7	116	115	115
GS-6	60	60	60
GS-5	33	33	33
GS-4	34	34	34
GS-3	6	6	6
GS-2	0	0	0
GS-1	0	0	0
Subtotal	821	822	822
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	4	4	5
Senior Grade	6	6	2
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Subtotal	10	10	7
Ungraded	241	241	241
Total permanent positions	988	1,026	1,026
Total positions, end of year	1,073	1,074	1,071
Total full-time equivalent (FTE) employment,end of year	1,064	1,080	1,080
Average ES level	4	4	4
Average ES salary	$116,008	$119,836	$123,192
Average GS/GM grade	10.5	10.3	10.3
Average GS/GM salary	$40,431	$41,639	$42,911

WEDNESDAY, FEBRUARY 26, 1997.

NATIONAL CANCER INSTITUTE

WITNESSES

RICHARD D. KLAUSNER, DIRECTOR, NATIONAL CANCER INSTITUTE
ALAN RABSON, DEPUTY DIRECTOR
HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We're pleased to welcome Dr. Richard Klausner, the Director of the National Cancer Institute, this afternoon. And Dr. Klausner, I'm going to forego an opening statement and so are my colleagues on this side. And why don't you simply proceed.

INTRODUCTION OF WITNESSES

Dr. KLAUSNER. Thank you, Mr. Porter, members of the committee. It's a pleasure to have the opportunity to speak to you.

Before I start, let me introduce, you know the people on my right, but on my left is Dr. Alan Rabson, the Deputy Director of the National Cancer Institute.

OPENING STATEMENT

This past year, we recognized the 25th anniversary of the 1971 National Cancer Act. And it's been for us an historical year as we sought to evaluate this Nation's investment in cancer research and assess the fruits of that investment. This fall, we were able to announce that for the first time since we began to track the constant rise in cancer mortality over 60 years ago, we had encouraging news. Sometime around 1990, we appeared to have reached the peak in the mortality rate and for the past five years, the overall age-adjusted mortality rates have fallen for all cancers. And that's shown here, you can see what we've been able to observe for the last few years.

[See figure 1.]

U.S. Cancer Mortality: 1969-1995

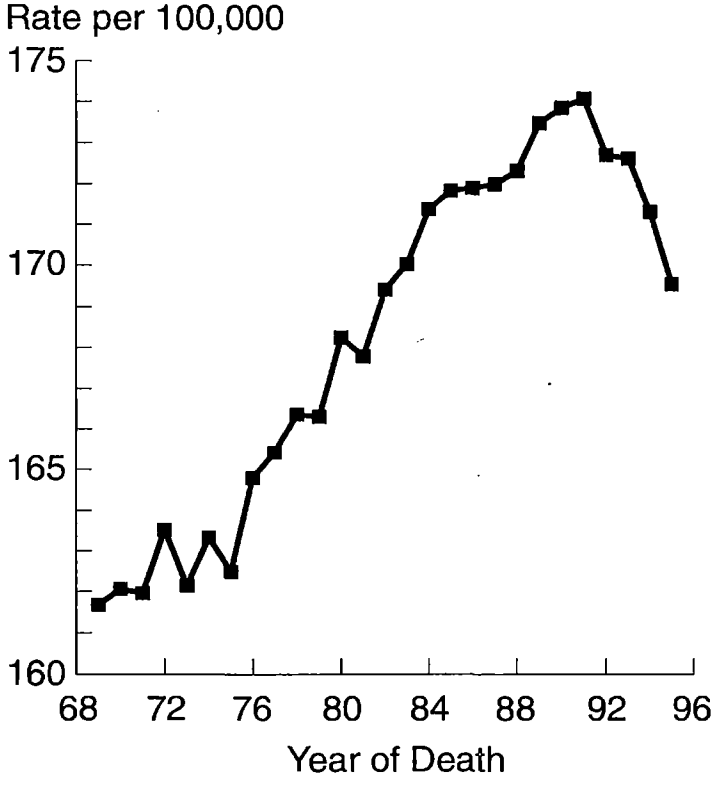


Figure 1

Dr. KLAUSNER. Every 2 percent drop represents 10,000 to 15,000 lives that would have been lost. These include for the first time the most common causes of cancer death, including lung, colorectal, breast, prostate, bladder, head and neck and others. We believe that these encouraging results are the results of the investment we have all made. They are probably the result of multiple factors, including prevention, especially declining tobacco use among American adults, early detection and better therapy.

The burden of cancer, as you all know, is not shared equally among all in our society. African–Americans, for example, experience a 20 to 30 percent excess rate of cancer death compared to white Americans. However, the latest mortality data included again for the first time a significant drop in the cancer death rate in African–Americans. We can see that here. In fact, you can see from looking at this that the percentage drop appears to be larger over the past five years in the African–American community than among all Americans, suggesting if those hold up that this terrible gap in survival may be closing.

[See figure 2.]

U.S. Cancer Mortality By Race and Gender 1971-90 vs. 1991-95

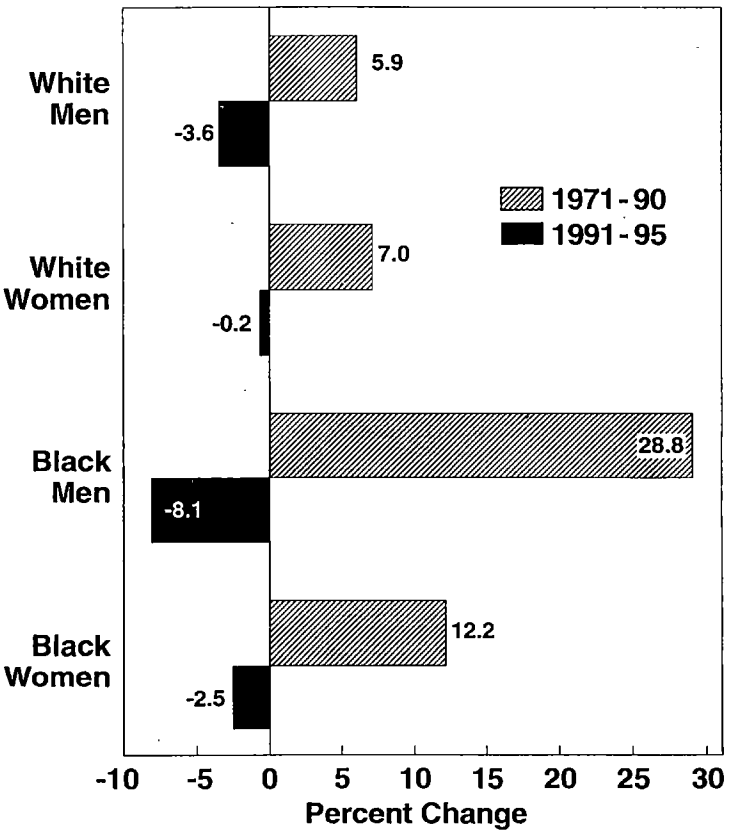


Figure 2

Dr. KLAUSNER. Today over 10 million Americans are cancer survivors. The majority of these were diagnosed over five years ago. In recognition of the many unanswered questions that long-term survivors face, there is a need to do research to answer questions about medical and psychological consequences, of delayed recurrences, second cancers, and long-term effects of treatment. As I announced last year, we're initiating several funding initiatives, in this area. Our fundamental goal is to develop effective interventions to reduce the incidence, mortality and morbidity of cancer.

There is probably not going to be any one intervention or even any one type of intervention that will successfully conquer cancer, or the many diseases, in fact, that we call cancer. Our approach must be and is open and broad-based, identifying those at risk and modifiable risk factors, for developing sensitive and predictive means of early detection, and learning to finally correctly diagnose each cancer so that the diagnosis predicts the course of the disease and dictates the choice of therapy. Cancer is a disease in which one of the trillions of cells in our body gradually changes over time. That cell is a crucible in which the interacting players of genes and environment meet and produce the alterations that drive the behavior, in this case the misbehavior, of each cancer.

The ability to look at genetic changes in cancer cells offers us an interesting twist to the search for external causes of cancer, a type of reverse epidemiology. Scientists are now exploring whether the fingerprint of particular types of carcinogens can be found within the DNA of the cancer cell, much like the thief that leaves incriminating evidence at the crime scene. And to help us use the effects of environmental carcinogens to identify the culprits.

Such an approach has recently been demonstrated for one of the carcinogens, benzopyrene, found in tobacco smoke, as well as a carcinogen that causes liver cancer, and is found contaminating certain foods, for sunlight and for vinyl chloride.

CANCER PREVENTION

Prevention in part explains the drop in cancer mortality rates, and prevention will play an increasingly important role in our approach to cancer in the future. Prevention studies range from evaluating behavioral intervention against tobacco use, and for healthful diets to pharmacologic interventions that include drugs that block the interaction of hormones for breast and prostate cancer, to anti-inflammatory drugs and their ability to prevent the development of colon and other GI cancers, to vitamin derivatives to prevent aerodigestive and other cancers.

In fact, now we're testing 24 agents in over 78 clinical trials aimed at preventing cancer, in approaching cancer not as a single event, which it's not, but as a long and potentially stoppable process. The identification of infectious causes of cancer provides another type of prevention opportunity. Based on major recent breakthroughs at the NCI, we have made a commitment to proceed with the development and testing of a multi-valent vaccine against cancer-causing strains of human papilloma virus. These are the viruses that cause cervical cancer. This is the first such effort to vaccinate against an agent solely for the purpose of preventing cancer.

Early detection remains a critical part of increasing cancer survival and enhancing the possibility of a cure. And I expect we'll be discussing this issue in the question period.

CLINICAL TRIALS

The final component of the decreasing cancer mortality is improved treatment. Clinical trials are the means by which we test and establish the best treatment for cancer. We have continued to work with partners to assure that patients have access to clinical trials by strengthening our cancer clinical trials agreement with the Department of Defense, and conducting a new agreement with the Veterans Administration to integrate the entire VA medical system into the NCI clinical trials and cancer centers network.

We have embarked on a strategic plan to restructure our clinical trials information system, to create a modern informatics base developed in conjunction with the FDA and the International Committee on Harmonization, to develop electronic systems for data on adverse events and the use of common toxicity criteria. A single entry clinical data reporting system will greatly facilitate these trials, and pilot testing for the system will be completed by April. These efforts will improve the speed and accuracy of reporting, produce resource savings, and remove impediments of burdensome and cumbersome paperwork.

Critical to enhancing access to clinical trials is available and useful information. We're currently working with patient and consumer groups to rewrite the NCI PDQ information system to be more inclusive of all trials, to be more user friendly and comprehensible and accessible. The NCI clinical trials evaluation program is currently sponsoring over 750 active clinical trials, including almost 260 phase one trials this year to test new drugs and new therapeutics. Such new approaches include viruses engineered specifically to kill cancer cells, gene therapy, immunologic approaches to cancer, photon based therapy, and new small compound drugs directed against the cancer cells or the blood vessels that nourish those cancers.

In addition, hundreds of other trials are conducted at NCI cancer centers and through other funding mechanisms. This past year, 12 new drugs were approved by the FDA for use in cancer. And we anticipate over 30 new investigational drug applications in 1997.

In the biotechnology industry, over 40 new agents are in clinical trials for cancer. And cancer is the largest beneficiary of this burgeoning industry. Notable results of clinical trials of the past year include the demonstration of a 30 percent reduction in mortality for adjuvant therapy in stage C colon cancer, translating into approximately 4,000 lives saved a year. And as these benefits may also translate, extend to stage B patients, the mortality reduction may prove to be even greater.

Interferon has been demonstrated to be of benefit in at least a subset of patients with advanced melanoma. Remarkably improved survival from combination chemotherapy with radiation for nasopharyngeal cancer resulted in a cooperative trial being stopped early because of the positive results. Other examples illustrate the incremental advances being made, each adding to improved survival for patients with multiple types of cancers.

These trials examine new agents, new combinations of therapy, new ways of delivering therapy such as neo-adjuvant treatment where chemotherapy, for example, is given before rather than after surgery, in order to improve surgical success and even allow less extensive surgery.

One recent therapeutic advance, let me just illustrate, how cancer therapy is being altered by our new understanding of the molecular characteristics of cancer. Recently, investigators at the National Cancer Institute have been studying a particularly aggressive form of lymphoma. And with the previous treatment, using five drugs, we see that about 50 percent of the patients were cured. Those that were not cured relapsed within about the first year.

[See figure 4.]

Tailoring Cancer Therapy to Molecular Diagnosis

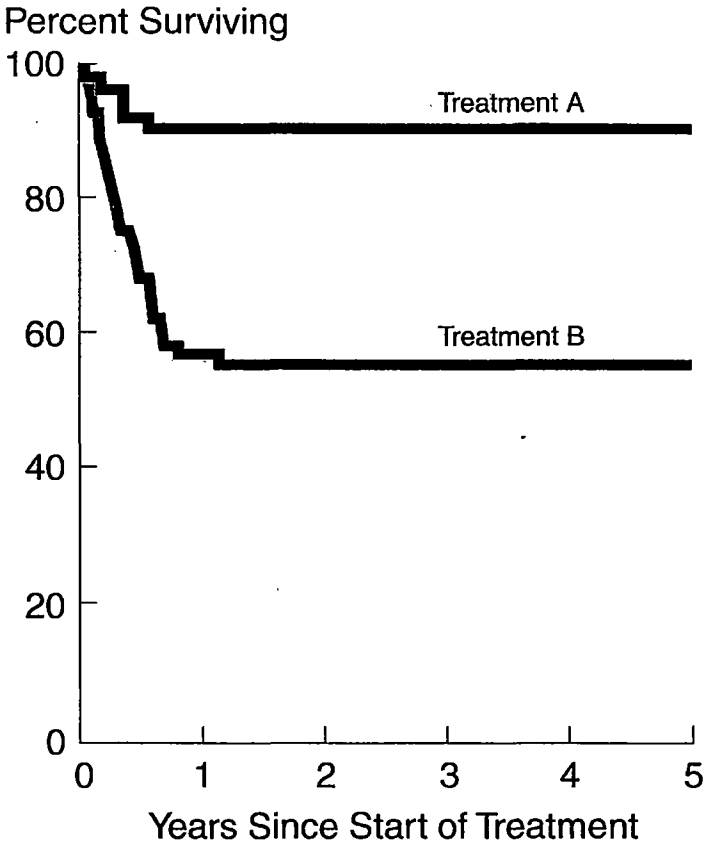


Figure 4

Dr. KLAUSNER. The question was, why 50 percent? What did those other patients have? Well, it turns out virtually all those other patients had a mutation and alteration in one particular gene, *p53,* whose loss of function is involved in over 50 percent of human cancer. So it was actually two different diseases. Now, they developed a new drug regimen, and now we're seeing that for this type of cancer, over 90 percent of patients, including this other category, which we had previously lumped together, are either being cured or at least look like they have long-term remission.

BREAST CANCER—MOLECULAR MARKERS

This illustrates a principle that's guiding a fundamental transformation in oncology. We can begin to identify the defining characteristics of any cancer, leading us to precise and informative diagnoses. Let me give you one example. Breast cancer. One of the most difficult therapeutic decisions we have to make now is an early stage breast cancer without node involvement. Who needs chemotherapy? Who needs adjuvant therapy? Some fraction of these women will relapse or develop evidence that their cancer has spread. And it's very important that we learn to look at these cancers that we've been lumping together and recognize that there will be molecular signatures that will distinguish a cancer that needs a particular therapy from one that doesn't.

This has recently been published, and this shows using two molecular markers that were discovered through studies on understanding the basic properties of moving through the cell cycle, something called *cyclin-E* and an inhibitor called *p27.* And notice these differences. This is the outcome for women with early stage breast cancer, and these are those cancers that have high levels of one of these and low levels of the other. And you see what happens. It's clear that these women are the women we need to focus on for adjuvant therapy.

[See figure 5.]

Molecular Prognosis for Early Breast Cancer

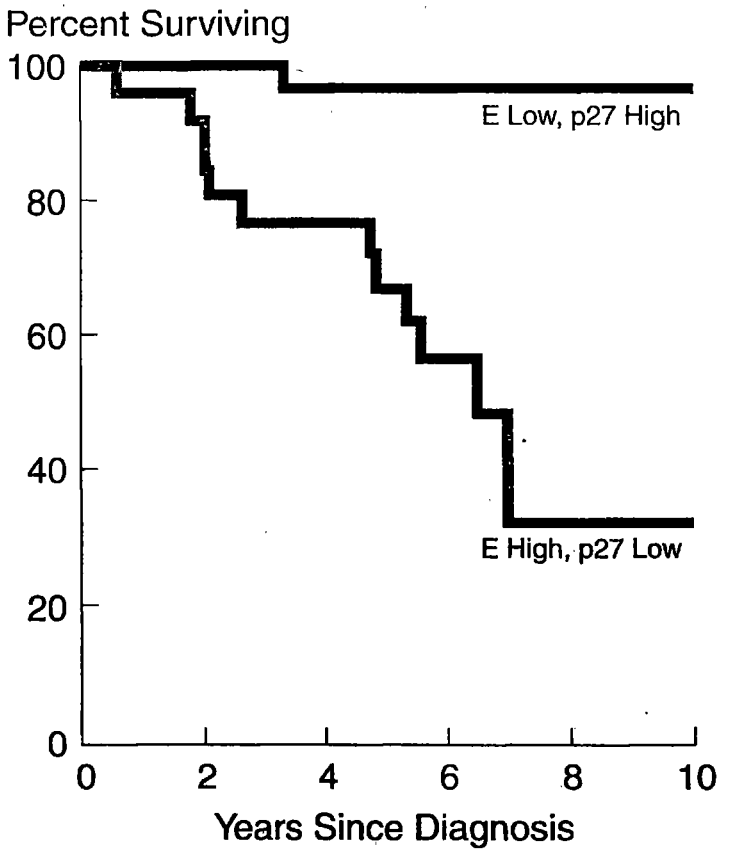


Figure 5

Dr. KLAUSNER. Whereas, look at the outcome for that subset of women which have low *E* levels and high *p27* levels. Again, getting a feeling for how this is going to change in the future.

The molecular profile of the cancer cell will define the actual targets for therapy, therapy that will be designed rather than arrived at empirically as we have done for the past 20 years. It is this molecular distinction between cancers that will allow us to tailor the correct therapy to the correct diagnosis. Because we've made great strides in beginning to understand how we look at the molecular fingerprint of cancer, we've recognized in addition that we can actually accelerate this process. We can do much better.

For that reason, the NCI has embarked on an ambitious project to identify all or almost all the genes expressed in cancer versus normal cells. We call this the Cancer Genome Anatomy Project, and its goals are two-fold: to produce a full index of expressed genes for normal, pre-malignant and malignant cells, to help support the development, dissemination and application of a whole new generation of technologies that will alter our approach to detection, to diagnoses and to choosing therapy.

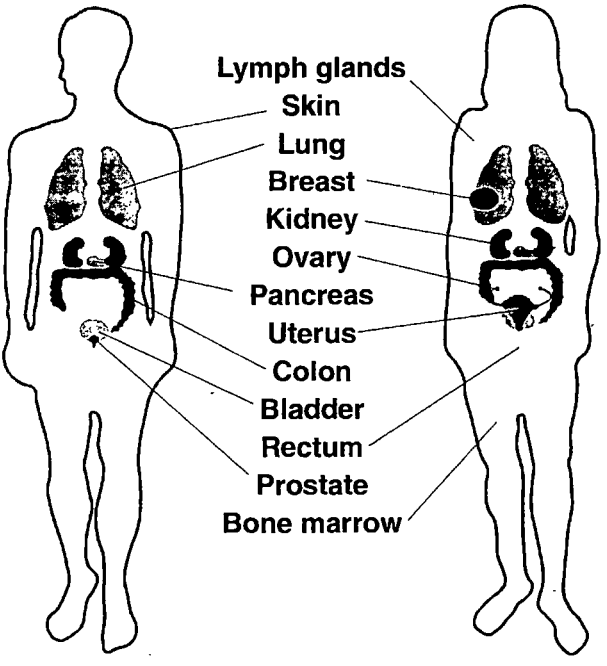
This project, which we call CGAP, both builds on and is complementary to the Human Genome Project, and is being done jointly through collaboration between the intramural and extramural programs. CGAP has been developed with explicit annual milestones, and will be, and already, we believe, is, building a national resource that everyone can tap into via the World Wide Web, and this is the Web page for this new CGAP, you can go to it, click on any particular cancer, and what we hope eventually to fill this with is a description of all possible genes, how one would approach asking diagnostic detection and therapeutic questions.

[See figure 7.]

NCI CGAP National Cancer Institute

Cancer Genome Anatomy Project

Introduction | Libraries | Data Analysis | Methodology | Staff



(click on the name of the tissue)

Figure 7

Dr. KLAUSNER. This will be the way that we will learn to detect cryptic cancers, such as ovarian, pancreatic, stomach and others. Again, CGAP involves a collaborative effort with the National Library of Medicine, the Department of Energy and with a series of industrial partners who are co-funding this.

There of course are many other initiatives that I would be delighted to share with you. But the challenges and opportunities clearly before us are great. To address these, Mr. Chairman, the budget request for the NCI for fiscal year 1998 totals $2,217,482,000, an increase of over $61 million. I am pleased to be able to appear before the committee, and look forward to answering any questions.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Cancer Institute
Richard D. Klausner, M.D.

This past year we recognized the 25th anniversary of the 1971 National Cancer Act. It has been an historical year as we sought to evaluate this Nation's investment in cancer research and assess the fruits of that investment. This fall we were able to announce that for the first time since we began to track the constant rise in cancer mortality rates over 60 years ago, we had encouraging news. Sometime around 1990, we appeared to have reached the peak in the mortality rate and for the past 5 years, overall age-adjusted mortality rates have fallen. This includes the most common causes of cancer deaths, lung, colorectal, breast and others. We believe that these encouraging changes are the result of prevention, especially declining tobacco use among American adults, early detection and better therapy--all of which are the fruits of research. The burden of cancer is not shared equally within our society. African Americans, for example, experience a 20-30 percent excess rate of cancer death compared to white Americans. The latest mortality data include a significant drop in cancer death in African Americans, that may be larger than the decrease reported for white Americans. Despite this good news, we continue to evaluate the causes for differential cancer incidence and mortality among different racial and ethnic groups. Overall, these statistics, I believe, tell us that our investment is paying off. They tell us what we can accomplish but that we have much more to do.

Today, over 10 million Americans are cancer survivors. The majority of these were diagnosed with cancer more than 5 years ago. In recognition of the many unanswered questions that long-term cancer survivors face and the need to do research to answer questions about medical and psychological consequences, late recurrences, second cancers and long-term effects of treatment, we are initiating a series of funding initiatives in this area.

Our fundamental discovery goal is to ultimately develop effective interventions that reduce the incidence, morbidity and mortality of cancer. There is no one intervention or even one type of intervention that will successfully conquer the many diseases we call cancer. Our approach must be open and broad-based, aimed at identifying those at risk and those with modifiable risk factors, developing sensitive and predictive means of early detection, learning to finally correctly diagnose each cancer so that the diagnosis predicts the course of disease and dictates the choice of therapy. Cancer is a disease in which one of the trillions of cells in our bodies gradually changes over time. That cell is a crucible in which the interacting players of genes and environment meet and produce the alterations that drive the behavior of each cancer.

There are two ways to search for the causes of cancer. We can look from the outside and scan the cell's environment for agents of cellular change. Some have been easy to

identify, such as the chemicals in tobacco which cause multiple cancers and are responsible for 30 percent of all cancer deaths, or the sexually transmitted virus, Human Papilloma Virus, responsible for 90 percent of cervical cancers. Environmental factors that can alter the risk of cancer include diet, outside factors such as environmental chemicals and radiation and the internal factors such as hormones and the chemical and physical soup within each cell. We currently employ scores of epidemiologic studies to search for connections between all of these factors and specific cancers, to search out potentially avoidable risks for particular cancers.

More recently, we have learned to look within the cell at the differences between individuals in order to explain why external risks are magnified or reduced in different people. The identification of specific cancer susceptibility genes that explain inherited risks continues to be a focus of discovery. Over the past year, scientists have identified new inherited susceptibility genes for skin cancer and the locus for the first prostate cancer susceptibility gene. We have moved to push beyond the discovery of these genes to fund studies to evaluate the interaction of these genes with environmental, dietary and hormonal factors; to establish more precisely the risk associated with specific alteration in specific genes; and to evaluate chemical or surgical prevention strategies for high risk individuals. We have designed a new research infrastructure called the Cancer Genetics Network aimed at linking centers of excellence throughout the country to work together as a network to develop protocols for critical studies in individuals at genetic risk for cancer to address the many issues that this new aspect of oncology is creating.

The ability to look at genetic changes in cancer cells offers an interesting twist to the search for external causes of cancer--a type of reverse epidemiology. Scientists are now exploring whether the fingerprint of particular types of carcinogens can be found, much like the thief that leaves incriminating evidence at the crime scene, to help us use the effects of environmental carcinogens to identify the culprits. This has been recently demonstrated for one of the carcinogens in tobacco smoke, as well as for a carcinogen that causes liver cancer found contaminating certain foods.

Prevention in part, explains the drop in cancer mortality rates and prevention will play an increasingly important role in the future. Prevention studies range from evaluating behavioral intervention against tobacco use and for healthful diets to pharmacologic interventions including drugs that block the actions of hormones to prevent breast or prostate cancer, anti-inflammatory agents to prevent colon and other GI cancers, vitamin derivatives to prevent aerodigestive cancers, and others. In fact, we are testing 24 agents in 78 clinical trials aimed at preventing cancer, approaching it not as an event but as a long and stoppable process.

The identification of infectious causes of cancer provides another type of prevention opportunity. Based on major breakthroughs at the NCI, we have made a commitment to proceed with the development and testing of a multivalent vaccine against cancer causing strains of human papilloma virus--the first such effort to vaccinate against an agent solely for the purpose of preventing cancer.

Early detection of cancer remains a critical part of increasing survival and enhancing the possibility of cure. The success of early detection depends upon awareness, access and the availability of tests that are sensitive and specific. All of the increase in breast cancer incidence that we saw through the 1980s (now leveled off) was the result of an increased detection of early disease and now 65 percent of breast cancer is found as localized disease compared to less than 40 percent twenty years ago with a 5-year survival rate of 92 percent. We are actually engaged in the evaluation of many new imaging techniques for cancer detection and hope to set up a diagnostic imaging research consortium to, for the first time, establish a stable group of investigators to evaluate innovations in cancer imaging. We are vigorously pursuing the development of better mammography, digital mammography, MRI, and digital ultrasound and other non-invasive techniques, as well as powerful new approaches to image analysis to both provide better sensitivity to the detection of breast cancer and to clarify the majority of abnormal mammograms which detect structures that are not breast cancer, thereby reducing the false positive rate of breast cancer screening.

The final component of decreasing cancer mortality is improved treatment. Clinical trials are the means by which we test and establish the best treatment for cancer. We have continued to work with partners to assure that patients have access to clinical trials, strengthening our cancer clinical trials agreement with the Department of Defense and concluding a new agreement with the Veterans Administration to integrate the VA medical system into the NCI clinical trials and cancer centers network. We have embarked on a strategic plan to restructure our clinical trials information system to create a modern informatics base, developed in conjunction with the FDA and the International Committee on Harmonization to develop electronic system for data on adverse events and the use of common toxicity criteria. A single entry clinical data reporting system will greatly facilitate these trials and the pilot testing for this system will be completed by April. These efforts will improve the speed and accuracy of reporting, produce resource savings and remove the impediments of burdensome and cumbersome paperwork.

Critical to enhancing access to clinical trials is available information. We are currently working with patient and consumer groups to rewrite the NCI PDQ information system to be more inclusive of all trials, more user-friendly and comprehensible and more accessible. The NCI Clinical Trials Evaluation Program is currently sponsoring over 750 active clinical trials, including 258 phase I trials this year to test new drugs and therapeutics. These range from a virus engineered to kill only cancer cells, to gene therapy, to immunologic approaches to cancer, to photon-based therapy, and to new small compound drugs directed against the cancer cells or the blood vessels that nourish them. In addition, hundreds of other trials are conducted at NCI cancer centers and through other funding mechanisms. This past year, 12 new drugs were approved by the FDA for use in cancer and we anticipate over 30 Investigational New Drug Applications in 1997. In the biotechnology industry, over 40 new agents are in clinical trials for cancer. Cancer is the largest single target of this burgeoning industry.

Notable results of clinical trials over the past year include the demonstration of a 30 percent reduction in mortality for adjuvant therapy in stage C colon cancer translating into approximately 4000 lives saved each year and as these benefits may extend to stage B patients, the benefits may be even greater. Interferon has been demonstrated to be of benefit, at least in a significant subset of patients with advanced melanoma. The markedly improved survival of combination chemotherapy with radiation for nasopharyngeal cancer resulted in a cooperative group clinical trial being halted early. Other examples illustrate the incremental advances being made, each adding to improved survival for patients with multiple types of cancer. These trials examine new agents, new combinations of therapy and new ways of delivering therapy such as neo-adjuvant treatment where chemotherapy, for example, is given before rather than after surgery in order to improve surgical success and even to allow less extensive surgery.

One recent therapeutic advance illustrates how cancer therapy is being altered by our new understanding of the molecular characteristics of cancer. Researchers at the NCI, in collaboration with extramural investigators, have been testing new treatment regimens for a particularly aggressive form of lymphoma. A 5-drug regimen resulted in an apparent cure, or long-term remission in about 50 percent of the patients. The remainder either failed to respond or rapidly relapsed. What was different? In virtually all of the relapsed patients, their cancer cells harbored a mutation in the p53 gene, a gene whose loss of function is implicated in over 50 percent of all human cancer. What had been called one cancer was clearly at least two distinct diseases. Recently, the investigators evaluated a newer regimen with three additional drugs and have observed long-term remission, hopefully cure, in 90 percent of all of these patients.

This example illustrates a principle that is guiding a transformation in oncology. We can begin to identify the defining characteristics of any cancer. It is the set of alterations that will define the actual targets for therapy that is designed rather than arrived at empirically and it is the molecular distinctions between cancers that will allow us to tailor therapy to the right disease. In addition, the alterations that distinguish a cancer from a normal cell offer us the set of possibilities for biomarkers for early detection for stealth cancers, such as ovarian, pancreatic, kidney and others. We have made great strides in this critical area of molecular diagnostics but can do more. For that reason, we have embarked on an ambitious project to identify all of the genes expressed in cancer versus normal cells. We call this the Cancer Genome Anatomy Project (CGAP) and its goals are two-fold: 1) to produce a full index of expressed genes for normal, pre-malignant and malignant cells and, 2) to help support the development, dissemination and application of new technologies to apply these indices for the discovery of markers for cancer detection, of discriminators for accurate diagnosis and choice of therapy and of targets for new therapeutics and prevention. CGAP both builds on and is complementary to the Human Genome Project and is being done through joint intramural and extramural efforts. CGAP has been developed with explicit annual milestones and will be a national resource that all can tap into via the world-wide web. CGAP involves a collaborative effort with the National Library of Medicine and the Department of Energy, as well as with industrial partners.

Connecting the profound advances in basic sciences and epidemiology to the clinic has been referred to as translational research. Over the years, the NCI Cancer Centers Program has been a central component of the development and realization of such research. One of my goals was to fully re-evaluate this program to assure it best rewarded outstanding science and best facilitated translational research at the many institutions capable of contributing to the National Cancer Program. To this end, we commissioned and have received a report from a blue ribbon panel which has proposed significant changes in the guidelines, review processes, definitions and funding policies for a revitalized Cancer Centers Program. We are now in the final stages of revising the program to incorporate most of the recommendations of the review group.

Finally, the NCI is committed to fulfilling its role within the larger National Cancer Program and we have strengthened and enhanced our many interactions and collaborations with other agencies and private organizations, with the research and clinical communities, with advocacy organizations and the public.

The challenges and opportunities before us are great. To address these, Mr. Chairman, the budget request for the National Cancer Institute for FY 1998 totals $2,217,482,000, an increase of $61,066,000. I am pleased to be able to appear before the committee and look forward to answering any questions.

Cancer Arises From the Accumulation of Genetic Changes

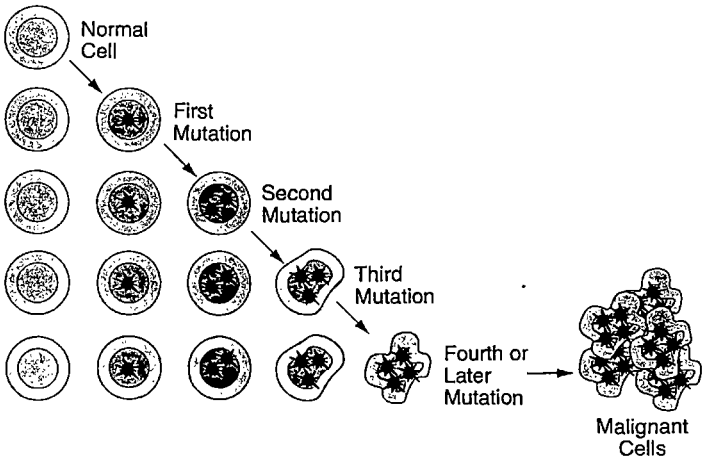


Figure 3

DNA Microarray Analysis of Gene Expression

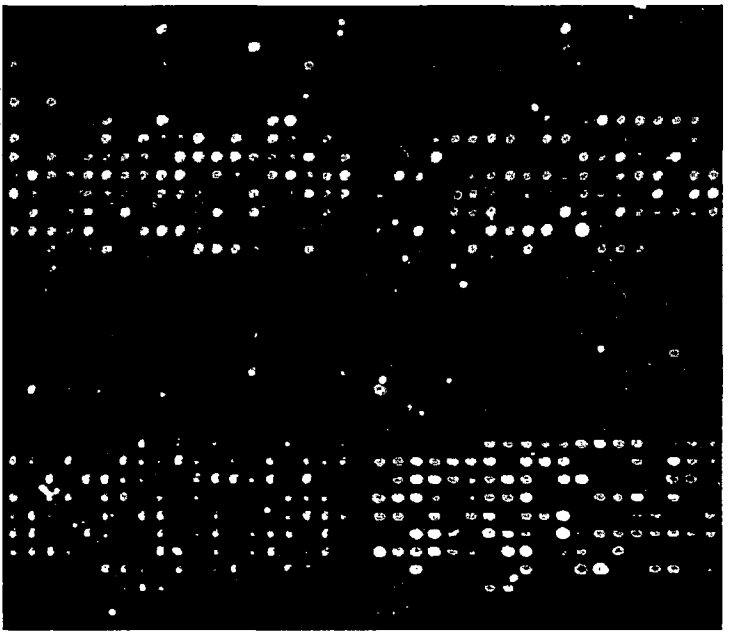


Figure 6

CURRICULUM VITAE
RICHARD D. KLAUSNER, M.D.

Personal: Born - December 22, 1951, New York, NY
Married, two sons

Education:
1973 B.S., Yale University - Summa Cum Laude
Phi Beta Kappa Honors in Molecular Biophysics and Biochemistry
1976 M.D., Duke Medical School - Alpha Omega Alpha

Employment:
1976--1977 Fellow in Internal Medicine, Duke Medical Center, Durham, NC
1977--1978 House Officer, Internal Medicine, Massachusetts General Hospital, Boston, MA
1978--1979 Clinical Fellow in Internal Medicine, Massachusetts General Hospital, Boston, MA
Research Associate, Harvard Medical School, Boston, MA
1979--1981 Research Associate, National Cancer Institute, NIH, Bethesda, MD
1981--1983 Medical Officer, National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD
1981--1985 Attending Physician, Acute Medicine Clinic, National Naval Medical Center
1982--1983 Instructor, Department of Medicine, USUHS
1983--1985 Assistant Clinical Professor of Medicine, USUHS
1983--1984 Senior Research Investigator, National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD
1984--pres. Chief, Cell Biology and Metabolism Branch, National Institute of Child Health and Human Development, NIH, Bethesda, MD
1995--pres. Director, National Cancer Institute, NIH

Panels and Advisory Boards:
1981--1985 Scientific Advisory Board, Sarnoff Foundation for Cardiovascular Research
1983--1985 Cell Biology Study Panel, National Science Foundation
1984--1987 Howard Hughes Education Committee, National Institutes of Health
1988--1994 Advisor to President, W.B. Saunders Company
1988--1990 Consultant to Vice-President, Genentech
1989--1993 Advisory Board, Searle Foundation
1989--1993 Scientific Advisory Board, Cytel
1990--1992 Chairman, Director's Task Force-- Intramural Research Program, NIH
1991--1995 Chairman, Scientific Advisory Board, Ariad Pharmaceuticals
1991--1995 Advisory Board, Pharmacology Research Associate (PRAT) Program
1993--1994 Chair, Committee on Immunohematology, American Society for Hematology
1993--1995 Advisory Board, Albert Einstein College of Medicine
1993--1995 Chair, National Committee on Science Education Standards and

Assessment, National Academy of Sciences
1993--1995 Member, National Delegation for Biomedical Research
1993--1995 Member, Coordinating Council for Education, National Academy of Sciences
1994--1995 Fisher Biotechnology Council, Fisher Scientific International, Inc.
1994--1995 Scientific Advisory Board, Agennix, Inc.
1994--1995 Public Policy Committee, American Society of Cell Biology
1994--1996 Chair, Executive Editorial Committee of the National Committee on Science Education Standards and Assessment, National Academy of Sciences
1994--1995 Scientific Advisory Board, St. Jude Children's Research Hospital
1994--1995 Scientific Advisory Board, Howard Hughes Medical Institute
1994--1995 Elected to Council of the American Society for Cell Biology
1994--1996 Member, NIH Senior Biomedical Research Service Policy Board
1995--pres. Scientific Advisory Board, Jane Coffin Child's Memorial Fund for Medical Research
1996--pres. Member, Institute of Medicine

Editorial Boards:
1983--1988 Assistant Editor, Hepatology
1986--1993 Executive Editor, Analytical Biochemistry
1989--1993 Editorial Board, The New Biologist
1991--1994 Associate Editor, Cell
1991--1994 Monitoring Editor, Journal of Cell Biology
1992--1994 Editorial Board, Annual Review of Cell Biology
1993--1994 Editor, Chemistry and Biology

Honors and Awards:
1986 Meritorious Service Award, Public Health Service
1988 Young Investigator Award, American Federation of Clinical Research
1988 Outstanding Scientist, 1988, Yale Alumni Association Award
1989 New York University Honors Award
1989 American Society of Endocrinology
1990 Charles Smith Professorship - Memorial Sloan Kettering
1992 Damashek Prize, American Society for Hematology
1992 Lederle Award
1993 Distinguished Service Medal, US Public Health Service
1993 Member, National Academy of Sciences, USA
1993 President-Elect, American Society for Clinical Investigation
1994 Alexander Wiener Award, New York Blood Center
1994 Distinguished Scientist Award, University of Oklahoma Medical Center
1994 Distinguished Medical Alumnus Award, Duke Univ. Medical Center
1994 Annual Research Symposium Honoree, Mayo Clinic Foundation
1994 President, American Society for Clinical Investigation
1995 Elected Fellow, American Academy of Arts and Sciences
1996 Cartwright Visiting Professor, University of Utah

1996 Centennial Award for Biomedical Research, Memorial Sloan-Kettering Cancer Center
1996 National Public Leadership Award, National Coalition of Cancer Survivorship
1997 Rabbi Shai Shaknai Memorial Prize Lectureship, Hebrew University, Jerusalem

Lectureships:
1989 Presidential Lecture American Society of Endocrinology
1990 Presidential Lecture Western Medical Society
1990 William Castle Lecture, Harvard University
1991 Marcel Piche Lecture, University of Montreal
1991 ADA Lecture, Duke University
1991 Kroc Lecture, Harvard University
1991 Lamport Lectures, Columbia University
1991 Shannon Lecture, Massachusetts General Hospital
1991 Keynote Address, American Society for Leukocyte Biology
1992 University Lecture, University of Texas - Southwestern Medical Center
1992 University Lecture, Baylor College of Medicine
1992 7th Nycomed Lecture, Norwegian Biochemical Society
1992 5th Abelson Lecture, Washington University, St. Louis
1992 Keynote Address, UCLA Conference on Integrins, UCLA Conference on Growth and Differentiation
1992 Lederle Award Lecture
1993 Merck Centennial Lecture, Harvard University
1993 TY Shen Lectures, MIT
1993 NIH Lecture, NIH
1993 Upjohn Frontiers in Science Lecture
1993 Annual Royal Swedish Academy of Sciences Lecture
1993 Keynote Address, European Frontiers in Science
1993 Dean's Honor Lecture, Mt. Sinai School of Medicine
1993 Keynote Address, The Second Tricontinental Meeting of the Japanese Society for Investigative Dermatology, the Society for Investigative Dermatology and the European Society for Dermatological Research
1994 Distinguished Lecturer, University of Massachusetts Medical School
1994 Honor Lecture, International Conference on the Molecular Biology and Pathology of Matrix, Jefferson Medical College
1994 Maynard M. Dewey Lecture in Biomedical Sciences, State University of New York at Stony Brook
1994 Presidential Lecture, American Society of Hematology
1995 Keynote Speaker, Research Symposium, University of Alabama at Birmingham School of Medicine
1995 Beirne B. Carter Memorial Lecture in Immunology, Univ. of Virginia
1995 Keynote Speaker, Silver Anniversary of the Founding of the Institute of Medicine, National Academy of Sciences, at Duke University
1995 Keynote Speaker, Fifth International Conference on Hemochromatosis and Clinical Disorders of Iron Metabolism, University of Massachusetts

1995 Keynote Speaker, International Conference on Bioiron, North Carolina State University
1995 Keynote Address, American Society for Cell Biology
1995 9th Annual Stewart Lecture, USUHS
1996 Convocation Address, Memorial Sloan-Kettering Research Institute
1996 13th Cartwright Lecture, University of Utah
1996 NCI Director's Address, American Society of Clinical Oncology
1996 Keynote Speaker, American College of Surgery
1996 Keynote Speaker, American Society for Therapeutic Radiology and Oncology
1996 Carl Vernon Moore Memorial Lecture, Washington University
1996 Oberstar Lecture, George Washington University
1997 Presidential Guest Speaker, The Society of Gynecologic Oncologists
1997 Whitemore Lecture, American Urologic Association
1997 Harvey Lecture, Rockefeller University

Societies:
1986 American Society for Clinical Investigation
1986 American Federation for Clinical Research
1989 American Society for Cell Biology
1989 American Society for Hematology
1993 National Academy of Sciences
1993 Sigma Xi
1995 American Association of Physicians
1995 American Association for Cancer Research
1996 American Society of Clinical Oncology
1996 Institute of Medicine

Medical Licensure:
1976 North Carolina
1977 Massachusetts
1979 Maryland #D24497

Research Interests
- The molecular basis of normal and pathological states of iron metabolism in humans.
- Mechanisms of post-transcriptional gene regulation.
- Receptor biology with a particular emphasis on structure function relationships of signaling receptors in the immune system.
- Organelle cell biology
- Tumor supressor genes

MAMMOGRAPHY

Mr. PORTER. Dr. Klausner, let me first say that we believe you're doing a wonderful job at NCI in providing leadership not only for your own institute but for many of the other institutes in how you approach the research that you fund.

Let me also apologize for being late. I was in a meeting with the full committee Chairman and had every intention of starting us off at 1:30 and was unable to do so. So I apologize to you and Dr. Varmus and everyone in the room.

The topic was raised briefly this morning with Dr. Varmus, but I want to begin by discussing the ongoing controversy about mammography guidelines for women in their 40s. NCI initially recommended mammography for this age group, and your predecessor later withdrew the guidelines. You convened a consensus development conference on the subject in light of recent research findings. That group concluded that the evidence was not strong enough to recommend guidelines, and that it should be the individual choice of a woman and her doctor.

The press reports that the conference was acrimonious and even raucous. The impression given in the popular press was that you disagreed with the findings of the consensus conference. Some groups charge that you are now changing your mind and supporting the findings.

Dr. Klausner, I'd like to know not only your own personal views on this, but the course of events in the recent past and what plans there are for the future to address this very, very serious issue.

Dr. KLAUSNER. Absolutely. I think this is a very important, very confusing and, as we've seen, very contentious issue. I think it's the NCI's responsibility to speak clearly about the evidence that we have, to provide guidance to women and their physicians about decision making, guidance that's based upon a clear and balanced description of evidence. And as Dr. Varmus said this morning, the National Cancer Advisory Board, I will be working very closely with them, they have a subcommittee now, we will be working with all due speed in order to provide just that, to provide guidance for us, so that we will, as quickly as possible, communicate a very clear message about what information women and their physicians should use in terms of making decisions about when to begin screening mammography.

The question is not whether to do regular mammography screening, the question and the controversy is about when. We will be coming out with what we believe will be very clear statements that will provide guidance so that individuals and physicians can make decisions about this difficult issue.

Let me just clarify by simply repeating the things that I've said over the past month, including what I said at the time of the consensus conference. The consensus panel, in looking at all of the latest data, said that in their opinion, they did not think a single uniform recommendation to begin screening mammography for all women in their 40s, was warranted by the data.

I think that is not an unreasonable position to take. And what I said is that I agreed with the sentiment of that conclusion. My concern that I said at the time was simply with, and this is impor-

tant, the wording, the balance and the tone in the draft report. Because I want to make sure, if we are to say that women and their physicians need to be informed to make an educated decision, I want to make sure that we provide the most balanced and clear and least confusing answer to the questions of evidence, to the questions of the evidence for benefit, to the questions about limitations, and the question of risk.

And that was where I think some of the confusion comes about who was agreeing and disagreeing. I thought their conclusion was defensible. I was concerned that the draft report, and it is still a draft report, that the draft report did not have the clarity and the balance about the evidence versus the limitations to actually allow women and physicians to make the decisions that they were recommending.

Perhaps I can try to spend a few minutes trying to clarify why this is such a complicated, contentious and difficult problem. Let me just say that whatever guidance the NCI provides, I believe, as I've said all along, must be based upon available evidence. I think the National Cancer Institute must base its statements in science and what we know. And as I said at the time and continue to say, while many of us want extremely clear-cut, yes or no, black and white answers to often difficult problems, we cannot nor should not produce certainty or say that there is certainty where there is not.

So where are we? Why is this so complicated? There is complete agreement from the data that's available that women 50 and above should have regular screening mammography. There is wide agreement that women below the age of 40 should probably not be recommended to having regular mammography. So we're left with 40 to 49. What happens? How do we know?

But why don't we look for data. There have been 8 randomized clinical trials from around the world over the past 30 years that have looked at over 180,000 women who were invited to the trials to begin screening—and this is very important—at some time during their 40s. The average age of women receiving mammograms during those 8 studies is 48. But at some time during the 40s.

None of those studies alone have convincing statistically significant data, have enough deaths from breast cancer to reach a conclusion. So all the data, all the studies have been put together through a process called metanalysis to try to see, do they all say something together. When one does that metanalysis, which is fraught with some uncertainties and difficulties, one, and I think there's general agreement on this, that there is approximately a 15 to 17 percent reduction in mortality for beginning screening mammography at some time in the 40s. The data does not address 40, or 40 and 3 months or 45.

And of course, one of the problems with the controversy is the way we frame the question. Nothing sudden happens to a woman when she turns 50. And certainly, nothing sudden happens to all women when they turn either 40 or 45 or 50. By asking for a yes/no, black/white question that at this birthday, suddenly there is benefit, we get into this very confusing and contentious argument that evidence and data could not directly address, because in fact it does not fit anything we know about the biology of risk of breast cancer, or breast cancer or the performance of mammography.

So there is going to be uncertainty. There will always be some period in which you move and move gradually from when there does not seem to be a benefit that outweighs the limitations and the risks to a period where it clearly does. I think to argue overly about trying to come up with a precise age for all women will keep us in an argument that does not move us beyond an unanswerable question to one that provides useful guidance to women. One size won't fit all. And I think the guidance we will come up with will be based upon the evidence and hopefully will be very useful and clear. I think we can strive for clarity, even when there's not certainty. I think that's what we will be doing over the next month.

SCREENING

Mr. PORTER. Dr. Klausner, correct me if I'm wrong in this, and I may well be, but if this consensus panel had said, and you had agreed, that women should all be screened beginning at the age of 40, have mammographies, then wouldn't that become a guideline that would be widely adopted, particularly in the Medicaid program, for example, and when you say that this is an issue that has to be determined on a case by case basis, aren't you really saying, though, that poor women won't necessarily get screening that might detect cancer early and perhaps save their lives?

Dr. KLAUSNER. Well, remember, the difference between a technique being capable of detecting cancer, even detecting it early, and that translating into a benefit, is something we try to determine by doing studies so that we actually make our decisions based on evidence. My feeling is, if there is evidence that supports benefit in the 40s and we don't have anything more precise than that, but that that evidence would support the decision, for some women it may make sense earlier in their 40s, for some women it may make sense later in their 40s. I think that then we can provide that guidance to make sure that those decisions are supportable.

This is the type of issue that we will be grappling with over the next couple of weeks to months. I hope, and I think it will be very soon, we will work very quickly, so that the position of the NCI is clear, but does not go beyond what we are comfortable that the evidence actually tells us.

Mr. PORTER. But if I understand correctly, you're giving a scientific view, and this issue has tremendous public health consequences. For example, women over 50, I believe, the guidelines show that they will get regular mammography. And those under 50 in public programs probably will get nothing. And what you're saying is that at some point, perhaps in their 40s, they need this additional prevention. But if the guidelines don't provide for it, you can be sure that the funding won't be forthcoming, for poor people. Now, for rich, for a wealthy individual, they can go to their individual doctor and the doctor may well say, well, sure, you're 40, but we think you need this.

Dr. KLAUSNER. Well, again, I wouldn't want to prejudge what the guidance will be. I think that's unfair to the NCAB process that we're doing now. We're very aware of all these issues. We want to make, we want to provide guidance that will be clear and will be helpful. Right now, I believe it's 40 states require insurance companies, now we're talking about insurance companies, to pay for

mammography, I believe it's over the age of 40 or over the age even of 35. And four more states are considering such legislation.

NCAB SUBCOMMITTEE

Mr. PORTER. You say you're going back now to develop this. How long will it take and are additional studies needed to develop the responsive guidelines?

Dr. KLAUSNER. There is a question whether there's need for more studies. And I believe there certainly is a need for more studies in the early detection of breast cancer and new technologies. And perhaps we can talking about that.

But for the process that we started yesterday with the National Cancer Advisory Board, no, we are not looking for new studies. We will be working, there is a subcommittee that has been announced, announced this morning. And they will be working with all due speed. And their expectation is certainly within one or two months to have completed their recommendations to the National Cancer Institute about what message the NCI should communicate to women and providers about this important issue.

Mr. PORTER. Thank you, Dr. Klausner.

Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman.

And welcome, Dr. Klausner. I want to express to you my personal appreciation for the outstanding leadership you have provided at the National Cancer Institute. I can assure you, as former Chair of the Women's Caucus, as the daughter of a victim of breast cancer, as the mother of two daughters in their 30s, I share the anxiety of women across America about the issue of mammography screeing guidelines and we appreciate that this advisory board is meeting. And we are hopeful that there can be clear guidelines.

But most importantly, I would hope that in the absence of a consensus, that the whole issue of insurance can be resolved and that insurance must cover mammograms. I think we're all agreed on that.

Dr. KLAUSNER. Yes.

OTHER DETECTION TECHNOLOGIES FOR BREAST CANCER

Mrs. LOWEY. It seems to me that we've got to provide women in their 40s with clear guidance. I'm hoping that this panel can do just that.

However, I'm concerned, that when you look at the statistics, in women under 40, 25 percent of the cases of breast cancer are not detected by mammograms. So I would like to follow up on my colleague's comments to talk about the possibilities of additional research on other techniques. Improvements in mammography quality, greater access to mammograms, certainly have contributed to the decrease in breast cancer mortality. And there's no question that mammograms save lives. And it's the most important screening tool for cancer that we have.

However, as you have explained to me and to others, there are fundamental reasons why mammogram technology would never be as accurate as we would like it to be. And mammograms are limited in their ability to pick up aggressive tumors.

My concern is, what are we doing about it? Where do we go from here? What alternate technologies is NCI working on that may allow us to detect an aggressive tumor in its earliest stages? Is a blood test for breast cancer, such as the PSA test for prostate cancer, a viable goal? Are there other technologies that hold promise?

Even in women above 50, I believe that 10 percent of those tumors are not detected. And again, as a woman, it's very frustrating to many of us to get a mammogram and speak to a friend who then, because of self-examination a week or two later, discovers a tumor. So perhaps you can enlighten us on where we're going from here.

Dr. KLAUSNER. Sure. Let me just say, the statistics that we have suggest that it's women under 50, where about 25 percent of cancers are missed. And then in older women, it drops to about 15 to 10 percent that are missed.

And as you point out, while mammography is clearly capable of being and is a life saving technology, let me emphasize two things. First of all, in the age groups where we know that regular mammography results in a 30 percent reduction in mortality, still not all women, far from all women, are using, or are availing themselves of access to mammography. And we need to make sure that all women do have access to mammography. Only about 50 percent of women above the age of 50 are having regular mammography. So we need to do much better with that.

We also realize the limitation, a 30 percent reduction in mortality, which is very important that we can ascribe to regular mammographic screening. We can turn it around and recognize that 70 percent of breast cancer deaths in women that never have mammograms will still happen in women that have regular mammograms. So mammography is not perfect. It's the best we have right now. But we need to do much better.

DETECTION TECHNOLOGIES FOR BREAST CANCER

This year, the NCI will be investing over $40 million in studies related to imaging, imaging, as an approach to detection in breast cancer. And I'll come back to molecular approaches like a PSA. These include improving mammography. And we all believe that the most important avenue for improving mammography now is a technology called digital mammography, where instead of using film, you create the image directly through a computer through a variety of sensors, of electronic sensors. And then you can use very sophisticated new techniques of image analysis, can also have telemammography, where you send the images to Centers of Excellence. And we believe that that's a very important area. And much of our investment in mammography development is in this new area of digital mammography.

There are lots of other areas of detection technologies for breast cancer. They include technologies that don't include radiation, such as magnetic resonance, both magnetic resonance imaging and something called magnetic resonance spectroscopy, to look at the characteristics of any possible lesions. There are other techniques, such as PET, SPECT, optical imaging, ultrasound, microwave, photon migration. There's really a proliferation of new ideas.

And in fact, as I think I've mentioned to you, we've just constituted a new think tank, headed by Dr. David Bragg, to advise us on new opportunities in technology detection. We are also proposing for the first time to establish a standing clinical trials group for diagnostic imaging. So we have available to us an infrastructure that will allow us to test clinically new ideas and new approaches in detection technology for breast cancer and other cancers. And we are actually bringing that to our board next week. So there is a lot that we are doing.

But as you said, there are other possibilities for detecting cancer besides just imaging. What do we do when we detect something is important. One of the problems with mammography is most of what we detect is not cancer. And even when we detect something, we're not always sure what to do about it.

The answer there I believe is going to come from what I began with, the sort of approach of the cancer genome anatomy project, that will allow us to look at all of the products of cancer cells, and of different types of cancer cells, so that we can learn as quickly as possible, are there PSAs for breast cancer. And when we detect a lesion, will that lesion be able to be ignored? Because while we call it cancer by looking under the microscope, it may not ever do anything. Such as in Ductal Carcinoma In Situ, we don't know which fraction we need to do something about.

These are the important ways that we need to look at the future, move forward, so we can improve this limited but important technology.

FUNDING ALLOCATION DECISIONS

Mrs. LOWEY. If I may, Mr. Chairman, just following up on that briefly, you mentioned that $40 million was currently being spent on various techniques, mammography, improvements in mammography, etc. Grants are currently reviewed, there's peer review of all grants. However, there are thousands and thousands of grants that are rejected.

One of the questions I've had is, how do you determine what percent of the dollars are put in mammography technology or in other forms of technology or in prevention, or in cures? There are many eager scientists out there working in all of these areas. How do you make these determinations? We all know, and perhaps Dr. Varmus knows one, who recently joined the Strang Clinic. He was doing work on brain research, and now is at the Strang Clinic because of a particular grant, and has made major advances in that direction.

Often, the scientist will be enticed to pursue a certain field because of the availability of dollars. Most of us, including our Chairman, wish we could double and triple the amount of money, if it could prove productive. So perhaps you can shed some light on that.

Dr. KLAUSNER. Well, you're asking an important but, of course, very difficult question. We need to make sure that we're covering in essence all of the bases. We can't choose between prevention or detection and treatment and understanding the basic biology. It's a constant juggling, a constant balance that relates to opportunities, as Dr. Varmus has talked about. When we have a new oppor-

tunity, researchers rush in. And that is a very good use of dollars. Because we know there's an idea, there's an opportunity, there's an inspiration. We're closing in on an opportunity to get a definitive answer.

It is a very dynamic process. And coupled with that is that we depend upon the larger community to come up with their ideas, they're thinking about this all the time. They produce proposals that then are reviewed for their quality and for their importance, for what they can achieve. And our approach is to allow the distributed wisdom of the entire scientific community to, in essence, interact with us, so that we maintain a balanced portfolio. Because we need to approach this and all of these problems from all possible angles. And often we don't know, as you know very well, we don't know exactly where a new advance is going to come. I know you hear that again and again from us. But it is, it has to be a very dynamic process.

Mrs. LOWEY. Thank you, Dr. Klausner, and thank you, Mr. Chairman.

Mr. PORTER. I want to apologize to my colleague, Lou Stokes. We started the year by saying that we would recognize the members in the order in which they arrive at the hearing. But we also said that where you are a ranking member on another subcommittee and have other responsibilities, we would give that member preference. And Mr. Stokes, in VA–HUD, has had a very busy day and had to leave this morning and didn't get a chance to ask his questions. And I'd like to call on him next for that reason.

ADVANCES IN MINORITY HEALTH

Mr. STOKES. Thank you, Mr. Chairman.

Since I didn't get a chance to pose any questions to Dr. Varmus, may I also pose some to him?

Mr. PORTER. Sure.

Mr. STOKES. Dr. Varmus, let me welcome you once again before our subcommittee. It's always a pleasure to have the chance to talk with you.

The NIH programs funded by this Subcommittee are absolutely essential to improving, prolonging and protecting the health and well-being of the American people. As you are keenly aware, the health of African-Americans and other minorities lags dramatically behind that of the general population.

What major advances in diseases and disorders that disproportionately impact African-Americans and other disadvantaged minorities can you report to the Subcommittee this year?

Dr. VARMUS. Mr. Stokes, that's an important question and one to which I've given a lot of thought. Because you know we share this concern, that even when we make advances, we still are failing to close the gap between the health of minorities and the health of majority populations.

But what I don't want to give you a list of the things that we're trying to do. Because that's not satisfactory. But I think this year I can point to a number of advances that affect minority populations in particular, or have special meaning for minority populations. Because the diseases are common in those populations.

Let's start with sickle cell disease. You heard a couple of years ago that we were making significant progress there, because of the drug I mentioned this morning, hydroxyurea, which has a very positive effect on the outcome of the disease, and reduces the episodes of sickle crisis by about 50 percent. In the past year, there's been evidence that bone marrow transplantation can also have a very beneficial effect in quite a significant number of patients. It's a more laborious procedure, but it has been done both in children and in some cases, in fetuses, and had remarkable effect.

The experiments with fetuses, I should say, were not done with sickle cell disease, but the same procedure could be applied in sickle cell.

And the second area I want to draw to your attention is the area of stroke and hypertension. There has been progress in hypertensive medication over the last several years that has a definite effects on the minority population. Because as you know, African–Americans in particular have a very incidence of hypertensive disease. The advances in treatment of stroke that you'll hear about from Dr. Hall again will have particularly beneficial effects on the minority population because of the high incidence of stroke in that population.

You would be right to point out to me that one of the deficiencies thus far in the application of the new treatment of stroke, with tissue plasminogen as an activator, is the need to educate physicians and patients of the urgency of treating stroke. And in many cases, the disparity in health of minority populations can be traced to less aggressive care. And this is one of those situations where it will be particularly important for physicians in rural areas, and physicians treating minority populations to become aware of the advances that have been made in the treatment of stroke.

There have been advances in diabetes, another disease which disproportionately affects the minority populations. Understanding some new genes that are involved in the generation of the diabetic state, and continued advances in the long-term management of diabetes. Again, as you would be quick to point out to me, it's important that we get that message out to the provider community and to the patient community, so that we can adapt readily.

FUNDING FOR NIH

Mr. STOKES. How important, Dr. Varmus, is the research that's done in these various areas throughout the National Institutes of Health?

Dr. VARMUS. Crucial. Every advance that I've described to you is dependent upon NIH sponsored research.

Mr. STOKES. That then brings me to my next question. To my understanding, last year NIH received a percentage increase across the board, did it not?

Dr. VARMUS. Yes, it did. The NIH increase was 6.9 percent, 6.5 percent in program.

Mr. STOKES. Now, did offices such as the Office of Research on Minority Health also receive correspondingly an increase, or percentage increase?

Dr. VARMUS. Let me point out to you, Mr. Stokes, that that office is not the primary source of funding for minority programs. That

office is intended to coordinate the activities, provide stimulus to activities in the institutes. We spend well over a billion dollars a year on projects that we can identify as being highly oriented toward minority health. A very, very small fraction of that goes to the Minority Health Office. Dr. Ruffin's job is to provide a stimulus to those programs. And I believe he does that very effectively.

So the increase in spending for minority programs has gone up.

MINORITIES AND CANCER

Mr. STOKES. Let me switch to Dr. Klausner for a couple of questions before my time expires.

Dr. Klausner, it's always a pleasure to see you. Your cancer mortality by race and gender chart indicates a significant decline in cancer among black men as compared to the rest of the population. Can you elaborate for us on this, that is, which cancers accounted for this decline, what role did prevention play—that is access to health care, early detection and so forth?

Dr. KLAUSNER. That's a very good question. These new numbers, in fact, this is figure 2, which shows the difference between men and women, black and white, you can see the enormous increase in the previous 20 years in the mortality rate, especially black men, from cancer, and then what's happened over the past five years. We've just gotten these numbers. We're very encouraged by them. And we have gotten groups of people together to try to analyze exactly what are the components. We see the drop in mortality across a number of cancers, colorectal, lung, bladder, prostate.

We're trying to understand these. Because I think that's going to be very important. Here we have an opportunity to see a change in the direction we want to go. We need to understand what we're doing right, if indeed it's something that we're doing right, so that we can stimulate that. And we have groups of people now working on the different sites, as well as the different changes among different racial and ethnic groups, so that we can try to understand this data. And that's the first thing that happens, once you get surveillance and epidemiologic data. We now know this, and we need now to try to understand what's behind it.

OFFICE OF SPECIAL POPULATIONS

Mr. STOKES. How is that reflected in the budget before us? Is there built into your budget some means for us to be able to detect how you want to build upon this type of progress?

Dr. KLAUSNER. Well, as I think I mentioned last year, last year in the spring, I was about to receive a report from what's called a Special Actions Committee specifically about what the NCI should do in terms of its research programs vis-a-vis special populations. And over this past year, we've acted on many of those things. We've established a new Office of Special Populations. I think you know Dr. Otis Brawley, I think he's doing a spectacular job. And what he's doing is systematically going through all of our programs. He has an Advisory Committee as well.

He in fact this spring will be making a series of priority recommendations to me. One of the first things that we never had that we're now doing is to create an information base so we know exactly what is going on, what the needs are. It will be setting up

a special what we call Progress Review Group of experts to come in and advise us on what are the areas of need coupled with what we're doing. This year, our programs directed at minority programs have increased. There are over 110 projects and programs specifically oriented towards minority populations. And in fiscal year 1998, the budget for that will increase to about $115 million, that is specifically looking only at issues in minority populations. I can go through many of these.

But I think the major point is that now we have this office to coordinate these activities. It is a real priority for us. And I think the recommendations, considerations and activities in that office are going to be very important.

CANCER SURVIVORS

Mr. STOKES. You mentioned, Dr. Klausner, that over 10 million Americans are cancer survivors. What is the racial and ethnic percentage distribution of these survivors?

Dr. KLAUSNER. I do not know the answer to that, but I will get that.

[The information follows:]

THE RACIAL AND ETHNIC PERCENTAGE DISTRIBUTION OF CANCER SURVIVORS

Of the approximately 10 million Americans who are cancer survivors, approximately 91% are white, 7% are black and Hispanic and 2% are other minorities: Asian, Hawaiian, American Indian, etc.

FIVE-YEAR SURVIVAL RATES

Mr. STOKES. What is the current five-year survival rate for the five leading cancers in African–Americans?

Dr. KLAUSNER. The five leading cancers for African-Americans include, lung cancer is the number one, prostate cancer, colon cancer, breast cancer, and I believe pancreatic cancer is the fifth. The five-year survival rates for lung and pancreatic cancer are and have been and remain dismal. The five-year survival rates are increasing for the other cancers. I may misquote if I try from memory to give you the exact five-year survival rates. But what I will say, we still continue to see a significant disparity between the five-year survival rates between African-Americans and white Americans. We see a disparity in almost all these cancers in terms of the stage of diagnosis and in terms of the outcome.

For example, breast cancer incidence among women over the age of 50 is lower among African-American women than among white women. That's the corrected incidence. And yet mortality rates are about the same. So again, we've seen in each of these cancers, there's now for the first time an improvement. So we're seeing it move in the right direction. Mortality rates are higher. Survival rates are lower for each of those, for colorectal, for breast and for prostate. For lung and pancreas, again, I don't think there's a significant difference in survival, as far as I know.

Mr. STOKES. I see that I am out of time, Mr. Chairman.

Mr. PORTER. Yes, actually you are.

Mr. STOKES. All right, thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Mr. Miller.

NIH REAUTHORIZATION

Mr. MILLER. I'm sorry I missed this morning with Dr. Varmus. In my area of Florida, the Sarasota, Florida area, I don't have a center in my area or district, but Moffitt is not too far away. So I was there this past fall when they celebrated their anniversary, along with Congressman Young of our committee, who is very involved with it because of this committee and because of Defense money that flows into cancer research, and also Congressman Bilirakis who is from that area. So we are all there together, which makes me want to ask the question, where do we stand on reauthorization of NIH? NIH is not authorized right now, is that correct?

Dr. VARMUS. Well, we still have authorization under the original Public Service Act.

Mr. MILLER. Right.

Dr. VARMUS. Last year, a bill was passed by the Senate, after being written by Senator Nancy Kassebaum's committee, but it wasn't taken up by the House, by the corresponding House committee. This year, we are hoping to go through the authorization process. We're working at the staff level to try to make that happen.

Mr. MILLER. Is there a sense that it may be taken up?

Dr. VARMUS. Yes, I think it's very likely.

Mr. MILLER. It's Congressman Bilirakis' committee?

Dr. VARMUS. Yes, that's correct. In the House.

ANGIOGENESIS

Mr. MILLER. But at any rate, I've always been impressed with what they've been doing at Moffitt. I have visited often. They've come a long way.

I happened to see you on ABC news Monday evening, and it raises questions and level of interest about you, you have a very difficult job. You have to cover all the bases of prevention and treatment and detection, and where you allocate your resources. Then all of a sudden, in this case, ABC news picked out one area. And I wonder, what impact does national media has in program selection? You have hundreds of programs. And this one on that special that you were commenting about Monday evening, is this——

Dr. KLAUSNER. I believe this was on angiogenesis?

Mr. MILLER. Yes.

Dr. KLAUSNER. Yes. I didn't see it, but——

Mr. MILLER. You came across very positive and very focused.

Dr. KLAUSNER. Oh, thank you.

Mr. MILLER. And very photogenic on television.

Dr. KLAUSNER. Well, I think the media has tended to pick up things that the scientific community views as interesting or hot. And this is clearly one of those examples. If I can say something about angiogenesis. While we talk about how each cancer is different, one of the things we've realized about all cancers is that in order for them to grow beyond a certain point and to spread, and that's what kills people, that they spread, is that they need to make sure that they establish their own blood supply. The blood supply isn't there for them.

And so cancers, in order to kill people, have to be able to create a new blood supply, which is really pretty extraordinary. And that has led many investigators to recognize a blood supply specific for tumors. It's called angiogenesis for birth of vessel, and is a remarkably attractive target for anti-cancer therapy. Some have even claimed that if all these tumor vessels are the same, maybe all we'd have to do is develop a therapy targeted against the blood vessels. Others say that there will likely never be a single treatment for cancer may not be so accurate.

I think we need to be cautious about that, as I think I was on that show, because there may be many types of blood vessels for different types of cancer. But the point is, this is a whole new approach to the treatment of cancer. And the early studies which are in animals look extremely promising. Right now, the NCI is supporting I think somewhere between 10 and 20 new agents that are being developed that are directed either at killing the blood vessel cells or at clotting the blood vessel, or at preventing the blood vessel cells from growing, or at stimulating those cells to kill themselves. There's a whole bunch of different approaches.

We are in fact very excited about this area. Being excited is wonderful. It helps us keep going. And we'll just have to see how well this looks. But we are putting this new approach on a fast track for development. And in fact, I've just recently asked for there to be a special meeting at the NCI so that we can talk with the investigators, with people who are excited, as well as skeptical about this, to come together and help advise us along with the industry, how we push forward developing these new agents into clinical trials.

Dr. VARMUS. May I comment just briefly about this?

Mr. MILLER. Yes.

Dr. VARMUS. This is a good illustration of an area in which research toward one remedy, that is cutting off the blood supply to a cancer, is also research on other kinds of therapies. Those therapies that are designed to increase the blood supply to organs like the brain and the heart and the kidney and peripheral muscles, because the same principles that are involved in trying to interfere with blood vessel growth to tumors are being exploited to enhance blood vessel growth to the heart, to the brain and to other organs affected by diminished blood supply that frequently accompanies aging.

AREAS IMPACTING ON CANCER

Mr. MILLER. On that line of thought for just a minute, I know Mr. Istook was talking about it this morning, the question of how much money goes to different diseases. Some people question what AIDS gets on a per capita basis to the persons exposed to AIDS, they think it's far too much money compared to cancer. Part of the explanation that Dr. Varmus has made, and I agree, is that, as you just made here, research applies over all areas, it's not just targeted.

Can you, Dr. Klausner, identify areas that research outside of NCI have had a direct impact on types of research? For example, AIDS research, immune system, that has been able to draw from that to be beneficial in the cancer area?

Dr. KLAUSNER. Oh, absolutely. We wouldn't be able to make the progress we think are making in terms of cancer, in any sort of vacuum. And we rely totally on the entire enterprise.

Let me just give you one example that was just published last month that I'm particularly intrigued about, coming from work looking at diabetes and at the development of fat cells. It turns out that there's a critical gene, and this gene is like the gate that determines, as primarily a single gene, whether a cell becomes a fat cell. It's called PPAR gamma. And this is work that's been worked on by Ron Evans and Spiegelman. And what they found is that, they found this particular receptor, and have found drugs that stimulate this receptor. And in fact, some of these drugs have recently been approved by the FDA for treatment of adult onset diabetes.

Now, what does this have to do with cancer? It turns out, the most common type of sarcoma in adults are liposarcomas, that relates to the lineage that relates to fat cells. It turns out what's been recently published, just a month ago, is that all of these sorts of tumor cells have this receptor. And when you give this very nontoxic drug, the tumor cells stop growing, differentiate to just be fat cells.

Now, this is just an experiment in the lab. But in fact, they are now moving and we're talking with them to move very quickly to clinical trials for this currently relatively untreatable form of cancer, these sarcomas. And this is just one example. It goes on and on.

The fact is, we are a very integrated community, and that's very good.

Mr. MILLER. You sound very optimistic about the direction of cancer research, more optimistic than ever, through so many different areas. We see a light at the end of the tunnel, maybe.

Dr. KLAUSNER. We certainly see a lot of light.

Mr. MILLER. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Miller.

Ms. Pelosi.

ENVIRONMENTAL LINKS TO BREAST CANCER

Ms. PELOSI. Thank you, Mr. Chairman.

I too want to join with my colleagues in welcoming you, Dr. Klausner, and thanking you for your leadership. I personally want to thank you for the time you took to come to the Bay area last summer to meet with researchers and breast cancer activists in our community about our high rate of breast cancer. We were all very appreciative of the opportunity to have you come out and speak with our group, but also for you to listen to our concerns regarding the possible environmental links to breast cancer. As you know, that has been one of the questions I keep posing to our distinguished scientists who come before us, is the answer in the lab? Yes. Is part of the answer outside? Let's see.

Dr. Varmus, in fact, testified this morning that the precise changes that occur in genes during our lifetimes are telling us how environmental agents like tobacco and sunlight cause cancer by inducing mutations, and how normal mechanisms for correction of

DNA can fail, allowing harmful mistakes to persist in our genetic material. Is that correct, Dr. Varmus?

Dr. VARMUS. Correct.

Ms. PELOSI. I did better than I think I did with my Transportation Committee and the cloning story.

As you hopefully both know, and I know Dr. Klausner does, the San Francisco Bay area has one of the highest breast cancer rates in the world. You're aware of the great concern.

Dr. KLAUSNER. Yes.

SAN FRANCISCO BAY AREA

Ms. PELOSI. And that there is a concern we have that this high rate is linked to environmental factors. Report language in the fiscal year 1997 bill urges the NCI to work with community groups and the National Institute on Environmental Health Sciences on this concern.

I have a question about the NCI's report to this language in the budget justification. You cite the Long Island breast cancer study project as an example, and I commend my colleague, Congresswoman Lowey, for her success with that project. The studies from the Bay Area cited in the response are not studies of breast cancer in the Bay Area. And only one, which is not funded by the Government, looks at the epidemiology of breast cancer.

Does the NCI intend to study the San Francisco Bay Area with regard to the possible environmental link to breast cancer? I would just, as you answer, also consider in our area possible exposure sources to radiation are plentiful. If you would answer that with a current assessment of the possible role of radiation as an environmental factor in causing breast cancer.

Dr. KLAUSNER. Yes. We've made it very clear that we're interested in supporting studies in areas where there appears to be an excess of any cancer, but certainly breast cancer, that cannot be explained by known risk factors. And in fact, I have met, subsequent to coming out to San Francisco, with researchers from that area who came to the NCI to talk to them about grants that they could put in and our interest in funding such studies. But they have to put in the grants, and we'll see what happens.

What is going on now in the San Francisco area is to analyze the data to actually try to understand whether there is, in fact, an excess and how much of an excess, when one takes into consideration known risk factors. All of the evidence that we have suggests that modifiable factors, whether it's diet or environment, change the risk of breast cancer. We see that from migration studies, we see that from the differences in incidence of breast cancer in different areas of the world, and especially, as I said, when people move.

It's been extremely difficult, despite many, many studies, to pin down specific risks from the environment. It doesn't mean we should stop, we should keep going. I happen to think, as I said in my opening statement, that we need a new approach, such as this reverse epidemiology, where we can look at the breast cells themselves to try to see whether breast cancers in particular areas have a different pattern of DNA damage that might tell us that there's a type of carcinogen that those women are being exposed to.

Certainly, as we've learned over the past year, when we reanalyze the data of local or regional variation in breast cancer incidence, when we correct for known risk factors, and there are, as we know, multiple known risk factors, even though we don't understand all of them, then those regional differences, not entirely, but largely, go away. Seventy percent or more of those differences no longer exist. And this was published last year from researchers at the NCI.

Currently, there are studies at Stanford University specifically to do the same thing in the San Francisco Bay Area. We really need to know that. We need to be able to subtract out known risk factors in order to really get hints that there may be regions that would be amenable to the type of epidemiologic study that would be hopefully useful in tracking down environmental culprits.

Ms. PELOSI. So the status of the study would be, there's an opportunity for a grant, should the grant application be made. But if this Stanford——

Dr. KLAUSNER. This is actually already going on, and we're actually just waiting for the result of this now.

Ms. PELOSI. I understand. But is that a preface to what——

Dr. KLAUSNER. No, absolutely not.

Ms. PELOSI. You said—what I heard, and I might have misunderstood, was that this would decide whether this would be——

Dr. KLAUSNER. I think in order to interpret and understand epidemiologic studies, we need to make sure that we understand the full range of risk factors, so that when we're trying to correlate, the way epidemiologic studies go, you observe peaks of disease and try to correlate that with something you can measure, an environmental exposure, radiation, diet, etc. So you really need to make sure you have a full data set to make sure those correlations are going to be informative.

Ms. PELOSI. I see, okay. So I should tell our folks back home to get their pencils out and——

Dr. KLAUSNER. I think they've already heard that message and are doing that.

Ms. PELOSI [continuing]. That the ball is in their court, and that's where the initiative will come from now.

Dr. KLAUSNER. Yes, ma'am.

BREAST CANCER SURVIVAL

Ms. PELOSI. I appreciate your response. Thank you, Dr. Klausner.

With relation to the continued funding of mammography and the question that has been before the committee this afternoon, in the interest of time, I won't go into that, but to associate myself with the concerns expressed by our Chairman and others, and the statements of Mr. Obey when he said that whatever the decision is about what age, etc., that it should be science-based. But I would add to that, when it is a question that it should come down certainly in favor of women's health. Because it is so that although there's a lower rate of incidence of breast cancer among younger women, there's a lower survival rate, as well, is that not so?

Dr. KLAUSNER. Yes, there is a somewhat lower survival rate for women who are diagnosed with cancer at a younger age. There is

some, it's either a subset, and probably is a subset that changes those statistics of what appears to be more aggressive cancer in younger women.

CLINICAL TREATMENT

Ms. PELOSI. In the past year, dividing the world now since this morning into culminations and inspirations, and I just wondered if there were any culminations in the clinical treatment of breast cancer, is culmination too high a standard to put on that, in the past year?

Dr. KLAUSNER. We'd have to ask Dr. Varmus for exactly his definition. We can get a reading from the Office of General Counsel, I guess, about the exact definition of a culmination.

Ms. PELOSI. Last year we went through this on the word breakthrough.

Dr. VARMUS. I've never felt so influential, Ms. Pelosi.

Ms. PELOSI. Well, you are a man of words, is that not your original training, Dr. Varmus?

Dr. KLAUSNER. There have been advances in the clinical treatment. And we are anticipating the results of some important studies in treatment, just over the next few months.

But I will hasten to add that these advances are incremental. They are not the dramatic changes that we would like to see.

PROSTATE CANCER

Ms. PELOSI. The same thing for prostate cancer as well?

Dr. KLAUSNER. I think for new therapies for prostate cancer, we have not seen any results in the past year that suggest that we are learning to improve mortality through new therapies, therapies that we hadn't had before. Whereas, in breast cancer, we do have upcoming results of, as I said, neo-adjuvant therapy, the value of giving chemotherapy before surgery, with the idea that you can reduce the size of the tumor, perhaps even then significantly reducing the type of surgery that needs to be done.

BREAST CANCER—ABMT

We are finishing accrual, finally, for the first study to look at autologous bone marrow transplantation in advanced breast cancer. And we expect early results by August of 1998. We have a series of results that will be coming out soon, or that have come out, that all suggest that more intensified chemotherapy or combinations of anti-hormonal and chemotherapy improve disease-free survival in different subgroups or survival in different subgroups of women with breast cancer.

What this adds to is unfortunately a slow but a clear incremental set of advances in our understanding of how to approach each woman with breast cancer in terms of making therapeutic decisions.

ACCESS TO CARE

Ms. PELOSI. Thank you, Dr. Klausner.

In closing, Mr. Chairman, I just want to associate myself with the concerns also expressed by Congressman Stokes. I see a big

change in what we're hearing presented by the NIH and the NCI from several years ago before this committee. And I truly believe that what you do there shouldn't be a trickle-down so that minorities and women, for example, eventually reap the benefit of research that you do on white males as concerned as I am about white males as well.

But all that I hear tells me over and over again for the need for universal access to quality health care. Because prevention, I keep saying it, early detection and prevention are so essential. Access to quality health care, if that were increased in the minority community, I'm sure it would reduce the incidence of some of this disease, as well as not only enriching personal lives, but costs to our economy as well.

Thank you, Mr. Chairman.

Dr. KLAUSNER. Can I make one quick comment?

Mr. PORTER. Yes, surely.

Dr. KLAUSNER. About that issue of access to care that relates to what Mr. Stokes asked me. The NCI and the Department of Defense completed a study looking at the outcome of prostate cancer in African-Americans versus whites, where the outcome in general is quite different, as we've said. But now within a system of equal access and equal care, and the outcomes were the same. I think that's a very, very important thing that we've recently learned. And it reinforces that.

I also want to thank you for hosting me in San Francisco and introducing me to a restaurant that I've gone back to many times. [Laughter.]

Mr. PORTER. Thank you, Ms. Pelosi.

Mr. Istook.

Mr. ISTOOK. Well, if you come to Oklahoma, we'll give you good barbecue. [Laughter.]

I was going to inquire, Dr. Klausner, Mr. Stokes beat me to it, you had in your testimony of course the reference to the significantly larger, higher incidence of cancer and cancer mortality in blacks. I share his interest in getting further information from you, not only on the situation, but on the allocation of resources to that. Because that's a very, very major differential that I know you'll want to reflect in your research allocations.

I did want to inquire, I'm also, as Mr. Bonilla is, on the Defense subcommittee. And there are certainly certain aspects of medical research that get significant funding from that. One major one is breast cancer. Where women in the armed forces certainly supply a, base is not the right word, but a population that can be utilized in those studies, for that matter, they could also utilize men in the armed services for prostate cancer research.

Dr. KLAUSNER. Right.

COORDINATION WITH DOD

Mr. ISTOOK. My question on that is, can you describe to me what level of coordination there is or is not, where you think it's sufficient, where you think it may be deficient, in the coordination of cancer research with the significant monies that are being spent on that through the Defense budget?

Dr. KLAUSNER. I think that's an excellent question, and I am very pleased with the level of interaction and communication that we have with the Department of Defense, especially under the leadership of Dr. Joseph. As you know, we established last year a model system, which is an integration of the DOD health care system with the NCI clinical trials system, so that all phase two and three therapeutic trials for the NCI, that there is access to those trials for anyone within the 8.3 million member. It's not just uniformed individuals, 8.3 million member health care system.

We are going to have a day or day and a half retreat I believe beginning March 18th with the Department of Defense specifically to look at how to extend that program and to further coordinate and integrate our research efforts and planning efforts in cancer. So I think the interactions have been really excellent. And we're learning a tremendous amount from this new interaction we have in terms of clinical trials in cancer.

Mr. ISTOOK. I would appreciate, I'm sure there's some documents that describe the relationship, that there's always concerns about overlap in grant application process and research. And you may decide you want to fund a particular program, but they may be interested in funding the same one. There's a lot of elements in coordination.

Dr. KLAUSNER. I'd be happy to provide that.

Mr. ISTOOK. That would be much appreciated.

[The information follows:]

COORDINATION EFFORTS WITH DOD

NCI staff has maintained close contact with the DOD staff of the Breast Cancer Research Program (BCRP) since its inception in 1993. An NCI representative is a member of the BCRP Integration Panel, which is responsible for advising the DOD on the overall direction of the Program and its investment strategy, and provides a second-level review for grants, much as does NCI's National Cancer Advisory Board (NCAB). Other NCI scientists have served as members of many of the scientific review panels convened to review grant applications to the Program and as ad hoc consultants to the Integration Panel at several programmatic meetings. Using the NCI data base resources NCI has performed a portfolio analysis of all its grants and contracts with a breast cancer component. This information includes number of active grants and contracts and level of funding in each of the tracking categories in use by the DOD's grants administration unit. This information is also provided to members of the Integration Panel at the yearly meetings when grant funding recommendations are made to the DOD. The purpose of this information sharing is to avoid unnecessary scientific overlap and duplication and to maximize resources for breast cancer research for both NCI and the DOD Breast Cancer Research Program.

Further coordination is provided through the NIH Inter-Agency Breast and Gynecologic Cancer Working Group, which was established by NCI in 1993. This group, which is chaired by an NCI staff member, serves to coordinate the research of numerous agencies in breast and gynecologic cancer. Representatives from all NIH Institutes with an interest in this area, as well as representatives from DOD, DHHS-Office on Women's Health, Uniformed Services University of Health Sciences, EPA, FDA, and NIOSH attend monthly meetings of this group, which serves as a clearinghouse for information dissemination and scientific exchange.

The NCI has recently established a Breast Cancer Progress Review Group. The Review Group will examine the field of breast cancer research and the current NCI efforts in this field. The results of this analysis will be made available to the DOD Integration Panel.

PROFESSIONAL JUDGMENT BUDGET

Mr. ISTOOK. I also, I recognize of course that each institute, as you indicated before, receives benefit from the research in other in-

stitutes. And there is a lot of crossover in that. Nevertheless, everybody is jealous of their own funding and wanting to maximize that, that they know they can focus on areas most likely to benefit their particular focal area.

I wanted to inquire, and you've probably got this in some documents that you can get to me as well, if the NCI funding were at a higher level, what are the areas in which you would want to increase the cancer research funding? And that could be by type of cancer, that could be by some other descriptive term, but what would those be?

Dr. KLAUSNER. Well, we're asked to provide an annual, essentially professional judgment budget, the so-called bypass budget. And I'd be happy to provide this to you.

But actually, the way we wrote this bypass budget last year, and now we're working on a new one this year, is exactly in terms of delineating new priority opportunities that if there was a sufficient increase of funds, what we would be able to fund. We described them in terms of fairly exact budgets, milestones, accomplishments, explanations, and where the opportunity is. I'm happy to provide you with a copy of this bypass budget, and I think it does explain that process.

Mr. ISTOOK. If you would, and I'll certainly look at it. If there's some very summary fashion overview of what funding is, since it's getting near the NCAA tournament, we ought to say what funding is on the bubble.

[CLERK'S NOTE.—Information submitted was too voluminous to be printed and is available in Committee files.]

Dr. KLAUSNER. I'd be happy to actually give that to you in terms of the types of priorities that we identify.

OPPORTUNITIES

Mr. ISTOOK. Right. There's nothing you'd want to give a quick overview on?

Dr. KLAUSNER. Oh, yes. The way we did it, we first stepped back and established a set of criteria for what was what we call an extraordinary opportunity. And we had a very extensive process of asking the community at large to feed in what are extraordinary opportunities, what we could say reasonably if we had an unexpected increase in available resources, what we might be able to accomplish, that would push forward cancer research.

So we went through that process. And these were clinicians, epidemiologists, basic scientists. And overwhelmingly, there was a confluence on five areas that met those criteria, that we were ready to go if we had the new investment. There wasn't just a fantasy, we were ready to go. And they were areas such as a new approach to developmental diagnostics, how to actually make real this new possibility of molecular diagnostics for cancer, new detection technology, so that we actually can detect things very sensitively and know what we were detecting.

Cancer genetics, an important problem. And in cancer genetics, how to develop the field of the interface between genetics and the environment and diet. And a fourth area was the need for animal models. Or for what we call pre-clinical models, from some of the advances that Dr. Varmus talked about, there's a whole new way

that we can look at organisms, very simple organisms to fairly complex organisms, such as the mouse, to create real understandings of the processes of cancer. So those were some of the examples. They were really infrastructure needs that in fact we feel would advance all cancer.

Mr. ISTOOK. Sure, I appreciate that. And I guess Dr. Varmus, this probably is best for you, the same process that he described of saying where the next steps would be with funding, is that something that each institute does in the same fashion, essentially?

Dr. VARMUS. Not exactly the same fashion. One difference is that the Cancer Institute always has a bypass budget, which provides them with a chance to think about what they would do with a great deal more money than they're likely to get, given the current constraints.

But as I mentioned this morning, I don't believe you were in the room, I was talking about how we put together the request for new money in what I call the areas of NIH research emphasis. That's done by having each institute spend some time with its constituents, its scientists on the outside and the inside, coming then to me with a list of things they would like to emphasize as new research priorities, and reevaluate those together. And we build a series of budgets at different levels of increase, at which we would spend different amounts of money on longer lists of those projects as the amount of money gets greater.

So we are trying to prioritize within those available new opportunities.

Mr. ISTOOK. Okay. And whatever the most parallel document might be from the other institutes, I would appreciate getting a copy of that from the others, too. That would be helpful.

Dr. VARMUS. All right.

[CLERK'S NOTE.—Information submitted was too voluminous to be printed and is available in Committee files.]

Mr. ISTOOK. Thank you very much.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Istook.

Ms. DeLauro.

OVARIAN CANCER

Ms. DELAURO. Thank you, Mr. Chairman.

Welcome, Dr. Klausner.

Just three or four questions. First of all, I'm very excited when we have the opportunity to talk about what you are doing with the genome anatomy project and the focus on ovarian cancer. In last year's report language, the committee asked NCI to provide funding for ovarian cancer research under SPORE. Just a question on whether or not that's been done.

Dr. KLAUSNER. Let me go back and talk a little bit about our advances in ovarian cancer. I think Dr. Varmus did an excellent job of describing what we're doing. I just want to reemphasize what he said, that almost half of 60 clinical trials are looking at new therapies, new agents, from gene therapy to immunologic therapies. And as he said, for the first time, we have agents, that are far from perfect, that are showing responsiveness in advanced ovarian cancer. We have just opened what we think will be an important trial in

looking at bone marrow transplantation and stem cell replacement with much more intensified chemotherapy for ovarian cancer.

But as you pointed out, the problem with ovarian cancer is that it's a secret cancer. It's hidden. And the majority of cases are not diagnosed until they are advanced, when our ability to cure is much more limited, as you pointed out. That's one of the reasons we put ovarian cancer in the first year of the cancer genome anatomy project. We've already begun to make what we call the libraries from ovarian cancer cells, so that we can in a systematic way search for tags, molecules, that can act as flags for us, that will provide us with better detection, hopefully earlier detection, as well as new insight into how to intervene in ovarian cancer. I think that's really going to be a very important investment.

Let me also say that there was another advance that I think is going to be important for ovarian cancer recently reported, and that is the first evidence that one can observe pre-malignant changes in ovaries. Now, for a long time, that's never been seen. These are in individuals at high risk. That is going to be very important, because it's going to give us the opportunity to ask the questions, what are the cells and what are the events that initiate or move forward the progress of the changes that result in ovarian cancer. I think that's an important research advance.

Now, in terms of the SPORE, we did not fund a new SPORE in ovarian cancer. The reason is, the SPORE, or the Specialized Program in Research Excellence program is a new one. As a program, it's experimental. And our advisors have advised us that the program should be reviewed. And we plan to review it. There's much to say that these programs can work very well. So this is not any idea that we're not going to continue this. But we really felt that this specific mechanism required a careful review so we would learn from the first several years what is the best way to organize and fund a SPORE, and whether the SPORE mechanism is the best mechanism for this type of transitional research.

Ms. DELAURO. What's the timing on this?

Dr. KLAUSNER. I think our plan to do that is either next year or the year after. One of the reasons is that we've just completed a very extensive complete review of our whole cancer centers program. I'd be happy to talk about that. And most of the SPOREs are within NCI cancer centers.

HUMAN PAPILLOMAVIRUS

Ms. DELAURO. Also with regard to last year's report language, it encouraged NCI and the NIAID to collaborate in sponsoring basic and clinical research on HPV diagnosis and prevention. Can you tell me if this has been done?

Dr. KLAUSNER. Yes. A lot has happened with HPV—there's several things. First of all, there are at least, I think, six clinical trials going on now or about to go on, on therapeutic vaccines aimed against HPV or HPV gene products. These are vaccines attempting to mobilize the immune system for patients with cervical cancer. Ninety percent of cervical cancer is caused by a series of subtypes of HPV.

As I mentioned in my opening statement, there have been some recent advances in moving towards what may well be an effective

vaccine against oncogenic or cancer-causing forms of HPV. And we are working closely with NIAID, and in fact, researchers from multiple institutes. This is another example where researchers are involved in vaccines from the Child Health Institute and others. And we have made a commitment that we will move forward to develop a multi-valent vaccine aimed at attempting to vaccinate against the subtypes that are responsible for 80 percent of cervical cancer.

OFFICE OF CANCER SURVIVORSHIP

Ms. DELAURO. NCI has established, you said, a new office for cancer survivorship?

Dr. KLAUSNER. Yes.

Ms. DELAURO. What kinds of activities will be performed there?

Dr. KLAUSNER. That office is to coordinate a whole range of activities related to the long-term medical, psychological, psychosocial and biologic consequences of cancer, including looking at second cancers, late recurrences, the effects of the current therapies that we use, psychological aspects of being a cancer survivor, cost and health outcomes issues.

There are four initiatives already. We had a meeting in November, we brought together a large number of people. They created within a month a very good report, which I'd be happy to provide for you, which laid out what a research agenda would look like for long-term survivorship. I then gave the staff about a month to act on that, to create a series of initiatives.

We have four types of initiatives, including a proposal for an RFA that we'll be bringing to our board next week for a whole series of research programs aimed at answering quality of life issues, and that whole range of issues I just described, as well as providing supplemental funding to cancer centers, to cooperative groups, to SEER registry system, and to other national and international registries so that we can quickly get answers to the issue of long-term effects of cancer and survivorship.

Ms. DELAURO. Let me just say that I'm sure all the members on this committee want to work very closely with you on some of these issues—the issue of HPV and what that means in terms of cutting back, and in terms of cervical cancer. You have such good information. I continue to look forward to working very closely with you in seeing how we can move the agenda along as quickly as we can.

Thank you very much.

Dr. KLAUSNER. Thank you.

Mr. PORTER. Thank you, Ms. DeLauro.

We have myriad questions for the record that we would ask that you address for us, Dr. Klausner. By all accounts, you're doing an excellent job at NCI, and the obvious intellect and enthusiasm and energy you bring to that endeavor is just amazing to us. And we very much enjoy working with you and seeing the progress that you are making.

So we thank you for your testimony this afternoon, and appreciate your candor and directness in answering all of our questions.

Dr. KLAUSNER. Thank you very much.

Mr. PORTER. Thank you so much, Dr. Klausner.

The subcommittee will stand in recess briefly.

[The following questions were submitted to be answered for the record.]

INTRAMURAL PROGRAM AT FREDERICK

Mr. Porter: What is the status of your intramural program at Frederick?

Dr. Klausner: The research conducted at the Frederick Cancer Research Development Center has experienced major changes over the last year and a half. This is due to several reasons. First, two of the major research divisions using Frederick have hired new division directors, and under their leadership, programs have been altered and research emphasis have been modified to focus on state-of-the-art needs. Secondly, FCRDC programs have undergone rigorous scientific reviews by the NCI Board of Scientific Counselors (BSC) and as a result of these reviews many reallocations of resources have been recommended and implemented.

The Division of Clinical Science has closed the Clinical Research Branch (CRB) in Frederick and transferred the clinical staff and patient protocols to the NIH campus in Bethesda. All patients enrolled in these protocols are now being seen at the NIH Clinical Center or the NCI Medical Oncology Branch located at the National Naval Medical Center (NNMC) in Bethesda. The research portion of this branch will be relocated back to the Bethesda campus once space constraints are resolved. This type of change permits the NCI to fully utilize the resources at the Bethesda campus while allowing the Frederick operation to be primarily utilized for new initiatives and basic laboratory support.

The reallocation of laboratory space and resources resulting from BSC reviews permits new initiatives to be implemented. The Division of Basic Sciences will be establishing a new multi-disciplinary program on human immunodeficiency virus (HIV) drug resistance.

This program will coordinate exciting, cutting edge programs at FCRDC in a) structural biology of HIV proteins, b) molecular modeling, and c) chemical synthesis. Principal investigators with expertise in informatics and biochemistry will be sought as well. The considerable expertise of FCRDC scientists in computational analysis and structural biology will also be coordinated with clinical researchers in NIH Bethesda laboratories to develop novel strategies and therapeutics for the treatment of HIV-infected individuals and to develop new knowledge on how pathogens like HIV develop resistance to existing drugs.

The overall research effort at the FCRDC has significantly improved as a result of these types of organizational changes and will permit the Institute to move more efficiently toward its new research goals.

Mr. Porter: Do you intend to move additional portions of the program back to the Bethesda campus?

Dr. Klausner: As stated previously, the NCI has closed down the CRB and transferred patients and protocols to NCI programs at the Clinical Center and NNMC,

with relocation of the research lab to follow. The National Cancer Institutes Board of Scientific Counselors has not recommended further relocation of any additional Frederick intramural laboratories to the Bethesda campus. Should future program initiatives warrant it, FCRDC operations could be considered in order to implement these new initiatives.

Mr. Porter: Do you intend to broaden the mission of Frederick to include other NIH Institutes?

Dr. Klausner: Currently, it is not the intention of the National Cancer Institute to recommend other institute relocations involving direct research operations to FCRDC. However, the National Cancer Institute is establishing state-of-the-art core support services which will be available for NCI intramural laboratories and then extended to other NIH institutes in the future.

Mr. Porter: Provide FY '96-98 totals for intramural research, including the research conducted under the Frederick contract.

Dr. Klausner: The following figures represent NCI's FY1996 actual intramural spending, including the intramural amount spent on the Frederick contract, and the FY1997 and 1998 projections:

FY1996 actual spending	$427 million
FY1997 projected spending	$424 million
FY1998 projected spending	$433 million

FTE DECREASE

Mr. Porter: Your Institute has experienced a fairly significant FTE drop since FY '93. In which parts of your program did decreases occur?

Dr. Klausner: This approximate 15% reduction in FTEs has impacted on most of the activities -- scientific and administrative -- of the NCI; our intramural research efforts, cancer control initiatives and the management of scientific programs of the institute. Difficult decisions have been made for all operations and we have been looking at ways to streamline our operations and improve the quality of service. Aiding us for the intramural research program was the initiation of a review of the NCI intramural operations by an Ad Hoc Working Group of the National Cancer Advisory Board. Their recommendations were presented to me and many have been implemented already. The NCI recognizes its responsibilities to function as efficiently as possible and to make difficult decisions about redirecting funds to reflect priorities and opportunities. In that context, eight programs, eight branches, and eighteen sections have been abolished. In addition, six administrative branches have been merged into two organizational components with improved efficiency and service to the research programs. One area of business operations change over the past several years has been in the field of Information Management. In that arena and as a streamlining

and FTE savings initiative we have consolidated our support services from the seven divisions and eight offices into a single management structure.

CONSTRUCTION

Mr. Porter: What share of your construction request is intended for extramural facilities and what portion is designated for the Frederick center?

Dr. Klausner: The NCI 1998 budget request includes $2.6 million for construction funding. Of this amount, almost 60% will be used to fund grants from the extramural community and the remainder will be will be used for repairs and maintenance at the Frederick Cancer Research and Development Center.

RADIATION THERAPY

Mr. Porter: In what percentage of cases is radiation used to treat cancer?

Dr. Klausner: Radiation is one of the most frequently used and successful curative modalities in oncology, and its use continues to expand. It is often used as definitive treatment in a number of diseases -- Hodgkin's disease, early stage non-Hodgkin's lymphoma, gliomas, cervical, lung, head and neck, bladder, anal, prostate, retinoblastoma, and others; for organ preservation following local excision -- breast, soft tissue sarcoma, rectal cancer; to improve local/regional control after radical excision -- breast, rectal, lung, head and neck; and for palliation.

Seventy to eighty percent of cancer patients will be eligible for radiation therapy at some time during their disease. According to the American College of Radiology, fifty percent of all cancer patients actually receive radiation therapy during the course of their disease. The discrepancy is due to multiple factors such as: lack of access, failure to refer patients for treatment, lack of understanding of role of the RT, lack of awareness by the patient, patients' insurance does not cover or limits the patients' access to treatment.

Mr. Porter: How much funding does NCI devote to radiation research?

Dr. Klausner: The NCI spent about $142 million on radiation research in FY 1996 and our current projections are to maintain approximately that level of support over each of the next two years.

Mr. Porter: What is the Institute doing to encourage the generation of meritorious proposals in the area of radiation research?

Dr. Klausner: The NCI has made presentations at radiation oncology meetings. These have included talks on the process of applying for research grants. The NCI staff attended major scientific meetings which have included lectures encouraging applications for funding of meritorious ideas. During this year the NCI has conducted a

workshop on Radiation Molecular Biology which addressed the problems of translating discoveries in the laboratory into benefits for cancer patients treated with radiation therapy. In addition, the NCI will be conducting a future workshop on Treatment Planning which will determine the directions radiation oncology should go in development and research in radiation dose distributions in the treatment volume. Also, a workshop on Radiation Oncology and Tumor Imaging will be held to find frontiers of cancer imaging research as related to diagnosis, treatment and follow-up of cancer patients treated with radiation therapy. Finally, a workshop on Brachytherapy will be held to establish research needs and quality assurance guidelines in the use of radioactive materials in the treatment of patients with cancer.

The Radiation Therapy Oncology Group (RTOG) is a group of physicians, physicists, and statisticians committed to clinical radiation oncology research. This group is funded by NCI. The NCI works with the Radiation Therapy Oncology Group to support and fund clinical research protocols. The RTOG continues to generate meritorious proposals in the area of clinical radiation research on cancer patients. These protocols provide important information on the best methods for improving the survival and quality of life of cancer patients needing radiation therapy.

TOBACCO USE AND CHILDREN

Mr. Porter: What is NCI doing to enhance its research portfolio in the area of tobacco use and children?

Dr. Klausner: Efforts to control tobacco use and tobacco-related morbidity and mortality in the United States have met with reasonable success, at least through the early 1990s. In the 33 years since the publication of the first Surgeon General's Report on Tobacco and Health, adult smoking rates in the U.S. have been reduced by nearly 34%, with reductions among males accounting for much of this success. Other indices of success, such as changing attitudes toward tobacco use in public places, widespread perception of tobacco use as a health hazard, and increasing numbers of laws restricting tobacco use have also been positive.

Controlling tobacco use among U.S. youth, however, has not been as successful. Although there was considerable success in reducing adolescent tobacco use in the late 1970s and early 1980s, tobacco use among high school seniors - for whom data with the longest time trends are available - have remained essentially stable for more than a decade, with just under 20% of seniors reporting daily smoking. Furthermore, high school dropouts smoke at an alarmingly high rate. One study in Minnesota found that 77% of both male and female 16-year old dropouts smoked on a daily basis; a similar study in Ontario, Canada, found a nearly 68% smoking rate among high school dropouts.

When the high school senior tobacco use prevalence rates are considered in tandem with the dropout smoking rates, the smoking prevalence rate among U.S. adolescents nearly equals that among adults, i.e. about 25%. Smokeless tobacco use -

chewing tobacco - among youth, especially among males, also continues to rise. If these trends continue, the prospect for further reductions in national tobacco use prevalence rates - and accompanying tobacco-related disease rates and economic costs - is unlikely to change substantially in the foreseeable future. Nevertheless, a great deal has been learned about tobacco use by children and youth - as demonstrated by several recent reviews of this issue - but there is also a great need to learn more and, especially, to apply broadly and systematically what has already been learned.

In January, 1997, the NCI issued a Request for Applications (RFA) entitled "Prevention and Cessation of Tobacco Use among Children and Youth in the U.S." The stated purpose of this RFA is to support "innovative research which has clear implications for the immediate and significant reduction of tobacco use by children and youth in the United States." This RFA represents the largest and most targeted effort ever undertaken by the NCI and the NIH to reduce tobacco use and its attendant disease burden among our youth. The NCI has budgeted up to $32 million for this initiative between FY1997 and FY2001.

While there is little doubt that it is the combination of effort from many channels, public awareness and commitment, policy change, and research, as demonstrated through the NCI's and American Cancer Society's ASSIST (American Stop Smoking Intervention Study) program, that will likely have the greatest effect on reducing tobacco use among children and youth, this new research initiative can make an enormous contribution to reducing tobacco use among children. Among the questions to be addressed by this initiative are the following:

- What are the characteristics - pharmacological, physiological, and psychological - of nicotine dependence in its early stages and, especially, during the transition between experimental and dependent use? Are there differences in individual susceptibility to nicotine dependence among youth? What is the relationship between the characteristics of different tobacco products and early nicotine dependence? Are there pharmacological treatments from which nicotine dependent children and youth will benefit? What are the characteristics of successful nicotine dependence cessation programs for youth under age 18? How can these programs be adopted on a large scale?

- What are the factors influencing the decline in, or relative lack of involvement in, tobacco use among particular ethnic, social, religious, or racial groups in the U.S., e.g. African-American youth? How can these factors be applied to the larger population of U.S. youth? Conversely, is there need for prevention programs aimed at youth subpopulations at high risk for tobacco use? Can such programs be successfully developed, evaluated, and adopted on a large scale?

- What are the factors that influence youths' responses to advertising, promotional, and warning messages aimed at discouraging tobacco use? What are factors the influence youth's responses to advertising and promotional messages aimed at encouraging tobacco use? What are the ethnic, gender, and

social class differences which influence these responses? What are the characteristics of failed and successful advertising campaigns aimed at discouraging tobacco use by children and youth?

- How do tobacco price increases, especially through higher taxes, affect youth tobacco use in comparison to the effect of prices increases on adult tobacco use, i.e. are youth more, less, or equally price-sensitive to tobacco prices than adults?

- What is the optimal age, and circumstances, at which programs aimed at discouraging tobacco use by children and youth should begin? Is it better to focus on tobacco use alone in these programs or to include other youth-relevant health issues such as diet and exercise? What is the role of the family in discouraging tobacco use among children and youth? What is the role of the health care community, ranging from practitioners - e.g. nurses, pediatricians, dentists, OB-GYNs, family physicians, - professional organizations, and health-care delivery and reimbursement systems?

- What is the optimal way to disseminate and implement successful youth and children tobacco prevention/cessation programs on a large scale?

The results derived from the NCI's new research initiative on children's tobacco use will complement our ongoing research activities in this area. This research includes the ASSIST project and a wide array of investigator-initiated research focusing on such diverse and important issues as the role of school health education in the reduction of youth tobacco use; differences in tobacco use incidence among white, African-American, and Hispanic youth; the role of health care professionals in advising children about tobacco use; youth spit tobacco prevention and cessation; use of multimedia systems for tobacco use prevention among children; and many others.

"FIVE A DAY" PROGRAM

Mr. Porter: How is the "Five a Day" program, which encourages people to eat five servings of fruits or vegetables each day, working?

Dr. Klausner: The 5 A Day for Better Health Program is a national public/private partnership nutrition education program which approaches Americans with a simple, positive message--to eat 5 or more servings of fruits and vegetables every day. The 5 A Day objective mirrors the Healthy People 2000 nutrition objective of increasing fruit and vegetable consumption. The NCI takes the lead in the Program by serving as the credible health source, maintaining scientific integrity, funding research in nutritional behavior change, and organizing and providing technical support to the 55 state and territorial health departments in the 5 A Day infrastructure. The produce industry organized the nonprofit Produce for Better Health Foundation (PBH) to work with the NCI on this endeavor.

The 1991 5 A Day Baseline Survey revealed that awareness of the recommended number of daily servings was low and overall consumption lagged well below recommended amounts. Only 8% of the survey subjects were aware of the need to consume 5 or more servings of fruits and vegetables a day, and over 77% of the U.S. population were not eating the minimum daily amount of fruits and vegetables recommended. From the baseline survey, the median daily intake of fruits and vegetables was about 3.4 servings. As a result of the combined efforts of the NCI, the 5 A Day coordinators at the state level, and the industry partners, the program continues to have a positive effect on the awareness, knowledge and behavior of the American public.

I will attempt to give you a brief overview of the first five years of the program. In 1993, nine four-year grants were awarded to develop and test strategies to help Americans increase fruit and vegetable consumption. Preliminary data show that all nine projects achieved a significant increase in fruit and vegetable intake among populations in specific channels, e.g. worksites, schools, etc. These projects end in the spring of 1997. Additionally, in collaboration with the CDC, the NCI has funded 14 small 5 A Day grants to state health departments to evaluate existing 5 A Day interventions at the community level. Organizationally, the NCI has licensed and provides technical support for 55 of the 56 state and territorial health departments, as well as the health promotion programs of the uniformed services and the Indian Health Service, to conduct 5 A Day interventions at the community level. The Produce for Better Health Foundation has licensed over 1000 industry partners, representing approximately 35,000 supermarkets. Well over 80% of all states have 5 A Day health promotion coalitions, representing over 1600 organizations nationwide. The 5 A Day Program has a formal relationship with the CDC and with the American Dietetics Association to collaborate and disseminate the 5 A Day message. Eleven other countries are implementing similar programs to increase fruit and vegetable consumption, and are using the U.S. 5 A Day Program as a model. I'm pleased to report that consumer awareness of the need to consume 5 or more servings of fruits and vegetables daily has risen from 8% in 1991 to 38% in 1996. Additionally, the most recent (1994) USDA nationwide food consumption survey reveals that average adult consumption of fruits and vegetables has increased ½ serving. However, children and adolescent intake has remained the same at about 3 servings per day.

In the future, the NCI plans to continue set aside funding for 5 A Day nutrition and behavior change research, particularly research projects focused on children, in addition to conducting policy and evaluation research on public/private partnerships focused on improving American diets. Other efforts will include technology transfer research designed to transfer the scientific knowledge gained from our behavior change research to the community level programs, and dedicated funding for state health department 5 A Day demonstration projects at the community level.

SAN ANTONIO CANCER INSTITUTE

Mr. Bonilla: I am proud to say that in my hometown of San Antonio has one of only 28 "comprehensive" cancer centers in the country. The San Antonio Cancer Institute (SACI) is a partnership between the University of Texas Health Science Center and the Cancer Therapy and Research Center. NCI recognized SACI as a comprehensive center last spring.

It is my understanding that for years, the San Antonio group has been among the few authorized by NCI to conduct Phase I clinical trials. These are first time trials of promising anti-cancer agents in humans. Please comment on the effectiveness of the San Antonio program.

Dr. Klausner: Cancer centers vary substantially in the scientific focus of the research which they conduct. This is determined by a number of factors, not the least of which are the areas of interest and expertise of the scientists which they employ. The University of Texas at San Antonio (UTSA) has an extremely successful and productive new drug development program. UTSA has been one of a small number of institutions funded by NCI to do Phase I trials with its IND agents. They have been funded for this purpose since 1985. At that time the NCI funded approximately 8 institutions for this purpose. Currently, 17 Cancer Centers conduct these trials.

COMPREHENSIVE CANCER CENTERS

Mr. Bonilla: Will NCI award additional comprehensive cancer centers?

Dr. Klausner: The NCI has just completed a major evaluation of the Cancer Centers Program using of panel of experts in all areas of cancer research and in outreach and education. The implementation of the panel's recommendations has resulted in substantive changes in the guidelines for cancer centers that should result in an increase in the number of NCI-designated Comprehensive Cancer Centers throughout the nation. We have replaced a cumbersome two-stage peer review system with a simpler one-stage system, for the first time allowing new cancer centers to be evaluated for the comprehensive designation, and are working on novel ways to enhance and sustain high quality outreach and education activities in the communities and regions that cancer centers serve. All of these changes should provide additional incentives for more centers to become comprehensive cancer centers. Within the next 3 to 5 years we could easily see ten additional cancer centers successfully receive the comprehensive designation, raising the total from the current 26 -- out of 55 -- to approximately 36 -- out of 55 or, hopefully, more.

COORDINATION OF THE NATIONAL CANCER PROGRAM

Mr. Bonilla: Dr. Klausner, in the past the Committee has expressed its support for the National Cancer Advisory Board's 1994 report entitled "Cancer at the Crossroads" which concluded that the National Cancer Program suffered from a lack of

coordination of cancer fighting efforts in the public, private and voluntary sectors. As a result the Committee has recommended that NCI take the lead in coordinating the nation's cancer prevention and control programs with the CDC and other Federal agencies to reestablish coordination of the National Cancer Program. Could you update us on your progress in this area?

Dr. Klausner: As I'm sure you know, the NCI was asked following last year's testimony to prepare a comprehensive report addressing the NCI's coordination activities. That report has been forwarded and should be available to you shortly. However, I would be pleased to provide a summary of its contents here.

The reduction in cancer death rates that has occurred since about 1990 is but one very tangible result of the Nation's commitment to cancer research. In addition to improvements in mortality rates for many malignancies, the National Cancer Program (NCP) has achieved important improvements in the quality of life for America's 10 million cancer survivors through less disfiguring and less damaging surgical procedures, better pain control, and more effective medication for the side effects of cancer therapy. Progress against cancer should also be measured in the growth of knowledge about the group of diseases that collectively bear that name. It is upon this knowledge base that the progress of the next century will rest.

This progress will be enhanced by the coordination of the many activities that comprise the NCP, and it is in this coordination that the NCI has and will continue to take the lead. NCI recognizes and stimulates research opportunities through its infrastructure of discovery that leads to understanding of the etiology and biology of cancer and thus provides the means to control and prevent it. NCI facilitates exchange of information, seeks to ensure that overlap and duplication are avoided, and supports the many areas of expertise needed to overcome cancer. NCI's activities in leading the NCP often involve interactions with entities outside of the NCI -- individuals, groups, organizations, and other components of the Federal government. The brief report mentioned above will outline the types of NCI efforts related to coordination of the NCP and provide selected, significant examples of these activities to underscore the progress made in the area of coordination.

ASSIST

Mr. Bonilla: For the record, I would like NCI to submit a copy of their general counsel's response to the Inspector General's inquiry. I believe the document was printed on January 15, 1997 and is entitled, "Inspector General inquiry concerning local lobbying: ASSIST Program."

Dr. Klausner: The NCI response to the Inspector General's inquiry has not yet been finalized. When it is completed and submitted to the IG, a copy will be forwarded to you and to the Committee.

Mr. Bonilla: Has the ASSIST program been extended for another year?

Dr. Klausner: Yes. The ASSIST contractors were recently notified that their contracts would be extended at full funding through September 30, 1999.

Mr. Bonilla: The IG has indicated that one of the difficulties in completing an audit is due to the fact that it is difficult to distinguish between federal and non-federal money once it leaves HHS. What safeguards have been put in place to ensure that federally and non-federal funds are not commingled?

Dr. Klausner: The NCI has been extremely careful to monitor the use of federal funds in the ASSIST program. Redundant monitoring mechanisms are used to assess activities before and after they are completed. NCI receives annually from each contractor a description of all proposed ASSIST activities. These proposed activities are reviewed for adherence to scientific principles and all applicable laws and regulations. In addition, prior approval by NCI is required for each subcontract. Detailed reports of all completed activities and expenditures are required quarterly. Site visits by NCI staff are used to confirm the written reports.

Mr. Bonilla: What procedures does NCI follow to ensure funding is not commingled?

Dr. Klausner: As discussed above, NCI requires detailed reports of all use of federal funds. In addition, the ASSIST contractors have received detailed instruction in allowable uses of federal funds. This instruction included written materials and in-person training. When activities are proposed that are judged to be unallowable, NCI staff inform the contractors and do not approve expenditures of funds for those activities.

Mr. Bonilla: Has NCI ever indicated to the ASSIST contractors what actions would be considered lobbying and which actions are permissible?

Dr. Klausner: The NCI has provided detailed information to the ASSIST contractors regarding permissible use of federal funds. This information was provided prior to the beginning of the intervention phase. The contractors have been reminded of the relevant laws on a regular basis.

Mr. Bonilla: Is one of the goals of the ASSIST program to increase and strengthen public support for certain policy changes?

Dr. Klausner: Yes. Increasing support for public and private policies that are known to reduce tobacco use, especially among children, is a goal of ASSIST. Just like policies that require children to be vaccinated in order to attend public schools, the Department has recognized that public policies are critical to improving the health of the public. In another area of cancer prevention, the NCI has worked to make women aware of the importance of mammograms and the need for mammography quality assurance laws. We are very aware that federal funds can not be used for certain activities related to public policies. We have made sure that ASSIST contractors are in

compliance with all regulations related to this issue. Reducing smoking among children is a major priority of the Department, so the NCI has taken extra care to be sure that the ASSIST project is in full compliance with the law.

ABORTION AND BREAST CANCER

Mr. Dickey: A major emphasis of the NCI is cancer prevention, including the identification of avoidable risk factors. I have seen a paper called, "Induced abortion as an independent risk factor for breast cancer: a comprehensive review and meta-analysis" published last October in the Journal of Epidemiology and Community Health. The authors say they found 23 studies that looked at abortion and breast cancer and found that, overall, there seems to be a 30% increased breast cancer risk due to having an abortion. What is the National Cancer Institute doing to explore the possible link between abortion and breast cancer?

Dr. Klausner: Recent studies with stronger study design have yielded different results than the analysis to which you refer. Because the issue is so important, the NCI continues to explore all leads from epidemiology, clinical and laboratory studies. The Institute has several on-going and planned case-control and cohort studies that collect reproductive history, including induced and spontaneous abortions. Examples of these studies include the ongoing Long Island Breast Cancer Study, the Agricultural Health Study, and the planned study on Breast Cancer Gene-Environment Interaction.

Mr. Dickey: I understand that the recent Danish study has several flaws which could invalidate its conclusion. For example, the study includes all Danish women born from April 1, 1935 through March 31, 1978. However, the study does not take into account tens of thousands of legal abortions performed on women before 1973. So if the Danish study classified a lot of women who had abortions as not having had abortions, and then said that the thousands of women who developed breast cancer had no history of abortion, wouldn't you agree that this misclassification might have affected the study's conclusion?

Dr. Klausner: All epidemiology studies have limitations, and that is why a variety of study designs have been used to explore the complicated issue of abortion and breast cancer. In the Danish study recently published in the New England Journal of Medicine, the lack of data on abortions before 1973 would primarily affect the oldest women in that study, whose reproductive years could have included unrecorded abortions. If the lack of risk observed in the older women was the result of such misclassification, then we would have expected to have seen an effect in women who were born later, if they are followed sufficiently long. However, the investigators reported no effect in those women either. In those women, there was no measurable increased risk of breast cancer associated with previous abortion.

It is important to note that unbiased classification of abortion history is a great strength of the Danish study. This is the only large study that documented which women underwent an abortion and then measured subsequent risk of breast cancer in women who had an abortion compared to those that did not. This study design is the best way to eliminate the well-known possibility of inaccurate recall of past events and exposures in retrospective studies -- so called "recall bias". People affected by life threatening diseases tend to recall and report past risk exposures more accurately than

would healthy control subjects. On balance, therefore, the Danish study yields stronger evidence than the meta-analysis of retrospective studies reported last October in the Journal of Epidemiology and Community Health.

Mr. Dickey: Other problems with the Danish study have been pointed out to me. The study data base was completed as of December 31, 1992. So Danish women who were born between 1968 and 1978 would be between the ages of 14 and 24 at the end of the study. Aren't virtually all women who develop breast cancer older than this age group?

Dr. Klausner: Although the Danish study included some young women who, as you accurately point out, are at low risk of breast cancer, the study included women over a broad range of ages, 14 to 57 years old. Since the study was very large and included more than 10,000 women who developed breast cancer and more than 370,000 women who had undergone abortions the investigators were able to make a statistically secure statement: they found no overall risk of breast cancer associated with abortion. The large data set and range of ages of the women in the study also permitted the investigators to look for any associations between abortion and breast cancer in women of various ages. The investigators did not find any effect on their conclusion of the age at which a woman had an abortion or of the age attained in the study. That is, there was no measurable link between abortion and breast cancer for any age at abortion or any age attained during the study follow-up period.

Mr. Dickey: It is very disturbing to me that Dr. Patricia Hartge at the NCI wrote an editorial in the New England Journal of Medicine, in the same issue in which the Danish study was published, saying, "In short, a woman need not worry about the risk of breast cancer when facing the difficult decision of whether to terminate a pregnancy." As a scientist, can you tell me that, after reading the meta-analysis by Dr. Joel Brind and others which found an increased risk of breast cancer due to having an abortion, and after hearing these questions raised about the Danish study-can you tell me that abortion poses no increased risk of breast cancer to women?

Dr. Klausner: In the meta-analysis to which you refer, studies as early as 1957 were included. Many older studies have well-documented methodologic flaws. This meta-analysis did not take into account the strength of study design. Perhaps even more importantly, even the methodologically strongest studies included in the meta-analysis were prone to the potentially serious problem of recall bias mentioned earlier.

A large body of epidemiologic data, critical reviews and editorials have all commented on this bias. To be precise, the extent of recall bias, which varies somewhat from study to study, has been widely recognized as the greatest problem in the ability of retrospective studies which rely on personal recall to assess reliably any possible association between breast cancer and abortion. The use of meta-analysis, which simply combines data from many individual studies, does not eliminate problems inherent in a study, but rather may propagate or even compound the errors. Statistically combining studies with systematic methodologic flaws and biases will still give biased

results, magnified to the level of statistical significance. In medicine and in public health, one cannot simply count up the number of studies that support one hypothesis or another to determine which hypothesis is correct. As studies of better design are reported, their results should be given more weight.

With respect to the editorial by Dr. Hartge, she was expressing her view as an individual epidemiologist with extensive experience in retrospective cancer case-control interview studies, prospective record-based studies, epidemiologic methodology, and meta-analysis. She judged that the data accuracy, design, and analysis of the Danish registry linkage study provided important new evidence to help resolve the controversy among epidemiologists over this issue. She concluded that the Danish study added to the existing body of evidence critical information in that data collected without recall bias showed no overall effect on breast cancer risk in women who had abortions.

In her editorial, Dr. Hartge noted that there remain unresolved biologic questions in this area that need further study. Such issues are certainly of importance to the understanding of breast cancer. The Danish study points to late abortions as an area that needs further research. The NCI will continue to support research into all areas likely to increase our understanding of breast cancer etiology. As I mentioned earlier, several studies dealing with abortion as a risk factor are underway. However, at present, the best epidemiologic evidence does not indicate that increased risk of breast cancer is posed by abortion.

DIET AND CANCER

Ms. Northup: You mentioned environmental factors which can alter the risk of cancer -- one that was noted was diet. It was my understanding that studies relating to diet have been inconclusive when it comes to cancer. What has NCI done in this regard, and where are we on evidence that diet changes may be helpful to preventing cancer?

Dr. Klausner: Most of the current evidence relating diet and dietary components to cancer has been obtained from epidemiological (observational) studies and animal experiments. Results of such studies suggest that high levels of calories and fat in the diet is associated with an increased risk of a number of cancers and that high consumption of fruits and vegetables, dietary fiber, and some vitamins and minerals is associated with a reduced risk of a variety of cancers. These findings serve as the basis for general dietary guidance for the public. However, because of the inherent limitations of epidemiological and animal studies, the evidence they provide must be considered suggestive rather than conclusive regarding the potential role for diet and dietary components in the prevention of cancer. Controlled clinical trials are needed to establish the benefit of specific dietary patterns and/or components in cancer prevention. A number of such intervention trials of the effects of low-fat and/or high-fiber diets are ongoing.

One is a study to determine whether a low fat, high fiber, high fruit and vegetable dietary pattern will decrease the recurrence rate of large bowel adenomatous polyps. This is a multi-center randomized controlled trial involving 2,000 men and women.

A prospective, multi-site, randomized clinical trial has been initiated to test whether dietary fat reduction as an adjuvant breast cancer intervention will reduce disease recurrence and increase survival for postmenopausal women with localized breast cancer. This study will enter a total of 2,000 postmenopausal women over 50 years of age who have a dietary fat intake of greater than 25 percent of calories at baseline assessment.

A randomized controlled clinical trial of the Women's Health Initiative is enrolling approximately 63,000 postmenopausal women aged 50 to 79 years of age. This trial, which is supported by the NIH, has three intervention components; one will evaluate the effect of a low-fat dietary pattern on the prevention of breast and colon cancer and coronary heart disease.

Trials of individual dietary components have also been conducted and some have been completed.

The Physicians' Health Study, the Alpha-Tocopherol, Beta-Carotene (ATBC) Lung Cancer Prevention Study, the Carotenoid and Retinoid Efficacy Trial) found that

beta-carotene was not effective in decreasing the incidence of lung cancer, whether administered alone or in combination with vitamin A or vitamin E.

An intervention trial in Linxian, China, showed that a supplement of selenium, vitamin E, and beta-carotene resulted in a decrease in stomach cancer mortality. In another study, selenium supplementation failed to reduce the incidence of skin cancer, but did reduce the incidence of prostate cancer.

Vitamin E supplementation in the ATBC Study resulted in a significantly lower incidence of prostate cancer in male smokers. The ongoing Women's Health Study is examining the effects of vitamin E supplementation on cancer incidence in women.

The NCI is also supporting human metabolic studies designed to improve understanding of the mechanisms of action by which components of plant foods and dietary fats may modulate cancer risk. Results of such studies will be useful in guiding plans for additional dietary intervention trials and in helping to refine dietary guidance for the public.

CANCER GENETICS

Ms. Northup: In your testimony you mentioned the ability to more precisely determine the risk associated with specific alteration in specific genes. Could you go into greater detail about the work which is being done in this area and what types of cancer this research may address?

Dr. Klausner: We have developed an entire program of studies to investigate the risk of cancers associated with specific alterations of genes. The ability to define and understand whether variations in genes within the human population will allow us to better predict sensitivity to specific causes of cancer is one of our great challenges. There are two broad categories of genes being evaluated: those that confer high risk of cancer but are relatively rare in the population, and those that confer much lower risk but are much more frequent. Studies of alterations in these two types of genes are being conducted for almost every type of cancer.

Examples of the high-risk relatively rare genes are *BRCA1* and *BRCA2*. In families with multiple members with breast and ovarian cancer, it is estimated that those family members who have alterations in these genes are at a very high risk of developing both breast and ovarian cancer. It is not known, however, whether alterations in the genes confer the same magnitude of risk in the general population, and it is difficult to test for alterations throughout these large genes. Knowing the cancer risks associated with specific alterations is essential for adequate genetic counseling. Among the Ashkenazi Jewish population, two specific alterations in *BRCA1* and one alteration in *BRCA2* have been found at a total frequency of about 2%. The technical feasibility of only looking for three specific alterations and the frequency of 2% in a defined group make it possible to try to assess the risk of breast and ovarian cancer associated with these specific changes. We have recently conducted a large study of

these three specific alterations in the Jewish population in the metropolitan Washington area. We are still finalizing the results of these studies, and hope to have the manuscripts published this summer.

Examples of genes in which common variations may influence cancer risk are ones involved in clearing out the toxins from cigarette smoking. One of these genes, *GSTM1,* has a variation present in about half of the general population. In heavy smokers, this variation has been found to confer about a 2-fold increased risk of lung cancer. In a similar fashion, a common variation in another gene, ADH_3, has been associated with a 5-fold increased risk of oral cancer among people who are heavy alcohol drinkers. Although the risks of cancers seen with these common variations is much lower than with genes like *BRCA1* or *BRCA2*, the effect in the general population may contribute to a greater percentage of cancers.

CANCER GENETICS NETWORK

Ms. Northup: It is intriguing the role that genetics play in cancer. Please describe the funding you plan to give to the Cancer Genetics Network and how many centers of excellence will be involved in preparing protocols for individuals at genetic risk.

Dr. Klausner: Capitalizing on advances in the area of hereditary cancer predisposition requires scientific resources and study populations that are currently unavailable to most human genetics programs. The purpose of the Cancer Genetics Network is to support the formation of a multicenter, interdisciplinary cooperative which will serve as an infrastructure for collaborative research investigations into the genetic basis of human cancer susceptibility, explore mechanisms for integrating this information into medical practice, and identify means to address the psychosocial, ethical and legal issues associated with human cancer genetics.

The Cancer Genetics Network will also facilitate the exchange of human cancer genetics information and resources within the larger cancer genetics community. The Network will develop mechanisms to broaden access to genetic services and educational materials by both the public and health care professionals. It will establish a clearinghouse of human cancer genetics resources and develop means to extend access to and connections between cancer genetics researchers, providers of genetic services, and the general public.

Thus, the Network will be a hybrid between the traditional models of Cancer Centers -- with recognized scientific excellence -- and the cooperative clinical trials groups -- with efficient multiline recruitment. Through this research infrastructure, potential study populations are preassembled through multiple participating centers and linked to a collective scientific expertise in cancer genetics. It is envisioned that groups participating in the Cancer Genetics Network consortium will have access to resources, information, and expertise that are beyond the scope of any single institution or organization.

Initially, a maximum of eight Network participating centers will be funded. If this pilot is successful, additional funds will be sought to expand the number of participating Network centers. In addition, an Informatics and Information Technology Group will be supported to serve as a resource in helping to meet the information management needs and requirements of the Network. This Group will help develop and maintain an internet-based data management system, which will expand and enhance the heterogeneous computer capabilities of the individual participating centers. Data security and confidentiality will be of primary importance in the design and implementation of this information system. Individual participating centers must demonstrate competency in electronic management of data that will become part of the larger Network repository.

The Network will provide funds for the development of pilot studies in all aspects of cancer genetics research, including the psychosocial, ethical, and legal impact of genetic testing, and will seek to foster collaborative research among Network centers and between Network and other researchers to encourage optimal utilization of this national resource.

GENETIC TESTING

Ms. Northup: What ethical considerations do you intend to accompany genetic risk testing development?

Dr. Klausner: There are a number of complicated scientific and ethical issues in genetic testing for cancer susceptibility. Questions related to rights to privacy and protection from discrimination on the basis of genetic testing must be addressed. But these are not simple questions. Do family members who may share genes have a right to know the results of another family member's test? The uncertainty involved in the scientific issues has a profound bearing on theses ethical issues, so I would like to focus on the scientific issues.

My remarks pertain to genetic testing for the relatively rare genetic variations that confer substantial risk. The common variations in genes that are associated with smaller risks in combination with specific exposures like cigarette smoking have completely different implications for genetic testing, because they frequently have little medical implications for disease risk without the relevant exposure. With respect to the genetic alterations associated with high risk in selected families, it should be pointed out that almost all of the current risk estimates are derived from the rate of cancer in families selected because many members have cancer. These families are essential for finding cancer susceptibility genes, but the risk in these families is very likely different than the risk associated with exactly the same alteration in other people. Before reasonable genetic counseling about risk associated with a specific alteration can be done, the risk has to be evaluated in an unselected group that is more like the general population, as we have done in the study in the Washington metropolitan area of the specific changes in *BRCA1* and *BRCA2* genes in the Jewish population. These large efforts are very expensive and time consuming, since many people need to be studied to

identify a very few with alterations in a specific gene. Investigators all over the world are planning and conducting the large, long-term investigations in the general population which will give us the needed information to adequately assess risk of cancer associated with these alterations.

Another major scientific issue relates to most of the genes we have currently identified. For these genes, we need to evaluate whether we can change risks associated with a specific genetic alteration by modifying other risk factors. The development of cancer is a complex process that occurs over many years, and perhaps can be arrested at several points. For instance, since oral contraceptive use has been shown to lower the risk of ovarian cancer, investigators are trying to establish if their use can decrease the risk of this cancer type associated with alterations in *BRCA1*. In a different example, we think the risk of melanoma in members of melanoma-prone families can be reduced by protecting them from sun exposure. These types of interactions with other risk factors may well modulate the risk associated with specific genetic alterations.

These levels of scientific uncertainty have implications for genetic testing. Individuals need to know about the levels of uncertainty prior to deciding whether or not to have genetic testing. At this time, the best way to educate people about genetic testing and to deliver test results are unclear. Both education and risk notification are being systematically evaluated in a number of research studies funded by the NCI and the National Human Genome Research Institute (NHGRI) at NIH. In addition, we do not yet fully understand the risks and possible benefits of genetic testing, which will differ depending on the specific test and type of cancer. Ensuring the privacy of genetic test results is also a major ethical issue because of the potential for discrimination in employment, insurance, or other areas. Finally, there is the dilemma of how to proceed once the results of the testing are known. We are working on developing reliable screening tests for early diagnosis and preventive interventions for many of the cancers for which we have identified susceptibility genes. We also need to establish whether the cancers occurring in people with a genetic susceptibility respond to various treatments in the same way as other cancers.

It is clear that the ethical, legal and social implications of genetic testing for cancer are profound and cannot and should not be separated from the conduct of genetic research. In this respect, the work of other NIH funded groups, such as the NCI Cooperative Family Registries for Breast and Colon Cancer Studies and the NHGRI Cancer Genetics Studies Consortium in establishing guidelines for informed consent and counseling procedures and in exploring the psychosocial impact and adverse outcomes associated with genetic testing, provide a starting point for consideration of these critical issues within the Cancer Genetics Network.

CANCER VACCINES

Ms. Northup: In regard to infectious causes of cancer, could you please provide the time line for testing of the multivalent vaccine against cancer that you referred to in your testimony (related to human papilloma virus).

Dr. Klausner: Several commercial groups around the world are pursuing different time lines for testing vaccines against human papillomavirus infection. With regard to NCI's effort, we are expecting to spend about three years on the Phase I and Phase II trials needed to establish the safety and optimal dose of the vaccine components. On a parallel track, we are busy organizing the full-scale Phase III population trial, which will determine the usefulness of the vaccine. Once the proper dose is known, we will be able to start the full-scale Phase III trial without delay. The Phase III trial will require the long-term follow-up of thousands of women randomized according to whether or not they receive the vaccine. We expect to be able to draw the first conclusions from the Phase III trial about 3-4 years after we begin, although genital malignancies take much longer to develop. Initially, we will be able to look for reductions in the rate of new infection and cancer precursor states, not just a reduction in the rarer cancers which will take years longer to prove definitively. In summary, if the safety and dosage experiments proceed without significant problems, we should have some important answers about the vaccine in about 6 years, but it will take about a decade to determine its longer-term effectiveness.

Ms. Northup: In addition, is this vaccine addressing a certain population which is susceptible to this virus, and who are these individuals?

Dr. Klausner: The rates of infection with genital papillomaviruses are so high that it appears that nearly all women are susceptible. The virus is spread primarily by sexual intercourse with an infected partner. Poorer populations tend to have higher prevalence rates of infection, but this association with income level has been weakening over the past few decades. The same viral types are found everywhere in the world among women with cervical cancer, indicating that no population is particularly immune or susceptible. It is worth noting that most women are able to spontaneously clear the viral infection. Men also get the same infections, but almost never develop cancer as a consequence. In summary, all sexually active people seem to be at risk of infection, since we have not yet found anyone who is naturally immune.

IMAGING

Ms. Northup: In working on imaging research, are you working with other agencies such as the Food and Drug Administration to develop new innovations? I imagine the FDA hears a lot from the field during its certification program, especially in regard to mammography.

Dr. Klausner: Since early 1990, NCI established collaborative efforts with FDA in all stages of technology innovation and transfer: concept development, technology evaluation, and implementation.

The joint NCI/FDA efforts in the development of new ideas for innovations are reflected in the active and extensive FDA participation in numerous conferences and workshops held by the NCI in diagnostic imaging and devoted to the identification and support of new promising areas of science and technologies in diagnostic imaging. In particular, NCI staff has been closely working with FDA on the development and testing of novel breast imaging technologies, such as digital x-ray mammography and Magnetic Resonance Imaging of the breast. Since May 1993, NCI has joined efforts with the FDA to facilitate transfer of defense and space technologies to digital mammography. Since July 1994, NCI has joined efforts with the DHHS Office on Women's Health and the FDA to establish a Joint Working Group with the CIA for transfer of intelligence technologies to breast imaging.

In March 1996, encouraged by this experience, NCI joined efforts with the DHHS Office on Women's Health to formalize these collaborations by establishing a Federal Multi-Agency Consortium of Imaging Technologies to Improve Women's Health. The goal of the Consortium is to foster identification, evaluation and transfer of intelligence, space, defense, energy and other relevant technologies to advance the state-of-the-art in medical imaging critical for women's health. Under the leadership of this Consortium, many Federal agencies have been brought together to join efforts, expertise, and resources in the area of imaging technologies. In addition to the Office on Women's Health, FDA, and NCI, this Consortium includes such organizations as the Department of Defense, CIA, NASA, DOE, NSF, and the Department of Commerce.

Ms. Northup: Who will be involved in the consortium to evaluate innovations?

Dr. Klausner: The NCI is planning to issue a Request for Applications for the establishment of a multicenter clinical trials consortium expert in the evaluation of imaging innovations. The devices or pharmaceuticals that will be tested by the consortium will be products of development in industry, government or academia. We expect that the consortium will include both academic health centers and community sites with the requisite technical expertise and patient volume. Responsibility for the governance of the consortium will be in the hands of the principal investigators, and the research will be investigator-initiated.

Ms. Northup: Are you working with businesses such as Kodak and professional groups as well in this endeavor?

Dr. Klausner: The NCI will act as a partner in this effort and will have responsibility for protocol review and general oversight. It is expected that many private companies involved in imaging research and development will wish to partner with this consortium for clinical trials of novel devices. The NCI has had extensive discussions with industry representatives from many companies about the desirability

of a clinical trials consortium of this type, and there seems to be a great deal of interest in industry.

MAMMOGRAPHY IMAGING

Ms. Northup: In mammography imaging you mentioned the ability to reduce the number of false positives. What percentage of false positives are due to the quality of imaging versus human error in interpreting mammography?

Dr. Klausner: There are no data to directly address the question of what percentage of false positives are due to the quality of imaging versus human error in interpreting mammography. False positives may be largely due to the fact that the radiographic signs of some early breast cancers are indistinguishable from some benign abnormalities. In fact, the question is likely to be less one of quality of imaging versus human error but rather more the inherent conservatism of medical practitioners who do not want to miss a cancer if it is present. Improvements in image quality have resulted in a reduction of false positive mammograms in the last few years. The characteristics of the population being screened -- such as family history, estrogen use, menopausal status, and breast density, etc.-- are considered important in determining false positive rates. Additionally, published studies have shown modest variation in false positive rates among radiologists in the first few years of interpreting mammograms. However, after the initial period these differences in false positive rates disappear and false positive rates drop to a fairly constant and low rate. This finding is commonly interpreted as indicating that early in practice radiologists are more conservative, and as they gain experience with interpretation and learn of subsequent diagnoses they become more comfortable in interpreting the mammogram as normal without additional work-up — i.e. their false positive rate declines. Ongoing research at NCI may provide more information to address this question in the future.

We do know, however, that human error is known to account for about 40% of false NEGATIVE mammograms, which themselves occur in about 15% of breast cancers. Since October 1, 1994, all facilities performing mammography must be certified by FDA as meeting quality standards, in accordance with the Mammography Quality Standards Act (MQSA). Today, 10,000 facilities are certified.

CLINICAL TRIAL AGREEMENT WITH THE DEPARTMENT OF DEFENSE

Ms. Northup: Please go into more detail on how you are working with the Department of Defense and the Department of Veterans Affairs to ensure that patients have access to clinical trials.

Dr. Klausner: In March 1996, the National Cancer Institute (NCI) and the Department of Defense (DoD) signed an agreement that authorized TRICARE/CHAMPUS to cover beneficiary participation in NCI-sponsored clinical trials. Under the terms of this three year demonstration project, TRICARE/CHAMPUS

now provides coverage for participation in Phase II or III, NCI-sponsored, treatment clinical trials.

This agreement marks the first public commitment to provide coverage for NCI-sponsored clinical trials by a single payer organization. TRICARE/CHAMPUS beneficiary participation in this demonstration project extends clinical trials opportunities beyond the military treatment facility (MTF) system into private practices, community hospitals and comprehensive cancer centers.

In support of the NCI/DoD agreement, PDQ, the NCI's computerized cancer and clinical trials database, has been expanded to list all clinical trials included under this agreement. PDQ now has a search field for "sponsorship" where all NCI-sponsored treatment studies can be located under one subheading providing the most comprehensive listing of NCI peer-reviewed studies.

To assist physicians seeking an appropriate clinical trial for a patient, the NCI offers clinical trials case management support for physicians. Based on the physician's request, NCI staff can conduct a nationwide search for NCI-sponsored trials that meet the criteria set forth by the NCI/DoD demonstration project. To date, a number of TRICARE/CHAMPUS beneficiaries have participated in the demonstration project as a result of this service.

Promotion of the NCI/DoD agreement is currently underway. Key civilian and military audiences have been targeted for promotional mailings including: the Surgeon Generals of three of the armed services, TRICARE/CHAMPUS managed care medical directors, military oncologists, civilian oncologists, and CHAMPUS beneficiary groups. Following these general mailings, more specific promotional activities will be undertaken with these audiences.

CLINICAL TRIAL AGREEMENT WITH THE VETERAN'S ADMINISTRATION

The most recent clinical trials partnership was signed in October 1996 and began implementation in January 1997. This partnership resulted in an agreement between the NCI and the Department of Veterans Affairs (VA) to provide eligible veterans participation in the full range of NCI-sponsored studies. Under terms of the three year demonstration project, eligible veterans will have access to all phases of NCI-sponsored clinical trials in diagnosis, treatment and prevention.

Most of the eligible veterans that will be participating in this demonstration project will be treated within the VA's primary-care delivery system as VA facilities conduct many NCI-sponsored trials on site as affiliates of NCI cooperative groups and as participants in the NCI's early clinical trials program. Support structures for this agreement will be similar to the structures already in place for the NCI/DoD agreement and implementation plans are currently underway. The PDQ database will expand its current listing of prevention trials and will begin to list diagnostic clinical trials.

CLINICAL TRIAL EDUCATIONAL EFFORTS

Ms. Northup: In regard to all clinical trials, what type of outreach is NCI doing to ensure that physicians are aware of clinical trials in cases where a patient might be appropriately referred?

Dr. Klausner: The NCI uses multiple resources to educate physicians and patients about clinical trials including state-of-the-art electronic technology, print media, and partnerships with health professional organizations and patient advocacy groups. PDQ, the NCI's comprehensive, computerized cancer information and clinical trials database represents the most comprehensive source of information on clinical trials. Physicians can access PDQ directly through the NCI's web site, online through commercial and non-profit vendors, by joining the NCI's member service (Information Associates Program), or indirectly, by utilizing NCI's toll-free PDQ physician search service (1-800-345-3300). Information is also accessible to patients via the NCI home page on the World Wide Web.

Another source of information for physicians, patients and health professionals is the NCI's Cancer Information Service- a national network of regional offices which, through its toll-free telephone service (1-800-4-CANCER), provides up-to-date information on cancer and clinical trials.

The NCI has developed an extensive inventory of educational materials for health professionals, patients and the public. Among these materials are a health professional newsletter highlighting cancer clinical research activities and high priority clinical trials- distributed to approximately 3,500 individuals --including health professionals and organizations -- and a clinical trials information booklet specifically designed for patients which physicians may provide to patients as part of their treatment discussions.

Recognizing that sustained media coverage over a period of years is essential to raising awareness of clinical trials, the NCI regularly disseminates press materials on new clinical trials-related issues to many major and local media outlets.

The NCI has developed partnerships with many professional organizations including the American College of Physicians (ACP) and the American Association of Family Physicians (AAFP) to disseminate NCI clinical trials information to their members. Presentations at professional organization meetings such as American Society of Clinical Oncologists (ASCO) and ACP also heighten physician awareness of cancer clinical trials and research.

Because patients frequently seek out their own information about clinical trials , the NCI has developed partnerships with many patient advocacy groups. One such partnership between the NCI and the National Alliance of Breast Cancer Organizations (NABCO) has resulted in the creation of easy-to-read summaries of all of the breast cancer clinical trials currently listed in PDQ. These summaries are available on both

the NCI and NABCO web sites and can be easily downloaded for review with physicians. Eventually, all of the NCI clinical trials summaries on PDQ will be available on the NCI's web site in a similar format for patients.

NEW CANCER DRUGS

Ms. Northup: You mentioned 12 new cancer drugs approved by the FDA for use in cancer. Are these drugs a result of NCI research or research done in the private sector?

Dr. Klausner: The National Cancer Institute collaborated directly in the clinical development of 6 of the twelve approved drugs in that we held INDs (Investigational New Drug Applications) and sponsored cancer clinical trials which contributed to the evaluation and determination of efficacy of the agents. In one case, the pivotal study used as the basis for approval was conducted by a NCI funded Cooperative Group, Southwest Oncology Group. In two other cases, NCI was substantially involved in preclinical development of the drug, for example, with topotecan, a soluble active analog of camptothecin, NCI was critically involved in initial preclinical work. In fact, discovery of topotecan occurred through the NCI-funded National Cooperative Drug Discovery Group Program. It was developed subsequently by the corporate partner in that program (Smith, Kline, and Beecham). With gliadel, NCI was critically involved in funding initial studies of gliadel through its National Cooperative Drug Discovery Group Program.

MEASURE OF SUCCESSES

Ms. Northup: Do you measure the outcomes of NCI research in relation to drug approval by the FDA, or how do you measure NCI outcomes?

Dr. Klausner: NCI sponsors research covering virtually the entire spectrum of biomedical and biobehavioral science relevant to cancer. The approval of cancer drugs by FDA is, therefore, only one measure of success and it is relevant only to a restricted segment of NCI programs. For example, the success of NCI's large investment investigator-initiated basic research would be more appropriately measured by the new scientific insights produced by the research. Certainly some of these insights might eventually translate into the discovery of new drugs that gain FDA approval, but other might have practical significance in other, equally important ways: for example, the identification of a new carcinogen, a new cancer-control research would generally not result in new FDA approvals but might result in the improved strategies for cancer-avoiding behavior, such as smoking cessation. Ultimately the success of NCI research will be best measured by reductions in the national morbidity and mortality from cancer, as has already occurred dramatically for many pediatric and some adult malignancies.

CANCER GENOME ANATOMY PROJECT

Ms. Northup: What is the status of the Cancer Genome Anatomy Project and how many federal agencies and personnel (FTE) are involved in this project?

Dr. Klausner: The two primary components of the Cancer Genome Anatomy Project (CGAP) are to establish an index of all genes that are regulated during tumor formation and progression and to support the development and dissemination of new technologies that will allow high through analysis of gene and protein expression as well as mutation detection. With respect to the tumor gene index the program is coordinated through the NCI intramural program with significant collaborative contributions from the National Center for Biotechnology Information (NCBI) and the Department of Energy. The NCI and NCBI currently have three and two FTEs assigned to CGAP, respectively. In addition, cDNA libraries are being prepared at Columbia University and two private companies, and DNA sequence analysis is being performed at Washington University. It is expected that additional collaborators will participate in the project during this fiscal year.

The technology development goals of CGAP are primarily being addressed through extramural initiatives although advances from the NCI intramural program are also expected. Already two Requests for Applications (RFAs) and one Program Announcement (PA) have been issued to stimulate technology development and facilitate the interface of new technologies with clinical cancer research.

Ms. Northup: What level of funding do you propose for this effort?

Dr. Klausner: In the NCI Budget Proposal for FY 1997/98 several extraordinary opportunities for investment were identified. Because of the enormity of the opportunity and the need to act promptly, the NCI has provided seed funding to initiate CGAP with FY 1997 funds. The current total funding for CGAP, excluding funds for the intramural FTEs, is approximately $21 million for FY 1997 and full implementation during FY1998 would require an additional investment of about $15 million included in the President's Budget Request.

CANCER CENTERS PROGRAM REVIEW GROUP

Ms. Northup: When did the blue ribbon panel come out with its recommendations on guidelines regarding NCI, what are the recommendations, and what are you doing to address these suggestions?

Dr. Klausner: The Cancer Centers Program Review Group, a blue ribbon panel of experts asked to evaluate the NCI Cancer Centers Program and make recommendations that will prepare us for the next decade of cancer research, submitted its Report in October 1996 after a year of deliberation. The report clearly recognized that NCI Cancer Centers were particularly well-positioned to be the leaders of the future in translational cancer research; that is, the bidirectional process of discovery in

moving laboratory findings into patient and population research settings and the reverse. There were three general themes to the Review Group's recommendations if centers were to function in this capacity more effectively: (1) the time spent by cancer centers satisfying the rigid record keeping requirements of the NCI had to be reduced significantly if centers were to have more time to do innovative research; (2) there needed to be increased flexibility in the use of cancer center funds to ensure that the most exciting new research opportunities could be pursued without delay; (3) the peer review system had to be modified in order to attract reviewers who are the most knowledgeable about cancer centers and have experience in taking advantage of research opportunities that have had an impact on preventing and curing cancer. The report was reviewed by the National Cancer Advisory Board and the Board of Scientific Advisors at their November meetings. In response to the Review Group's recommendations, the NCI has completely revamped it's cancer center guidelines and will implement a completely new approach to cancer centers starting in June 1997.

DECLINE IN CANCER MORTALITY

Mr. Stokes: According to your opening statement, "Sometime around 1990, we appeared to have reached the peak in the mortality rate, and for the past 5 years, overall age-adjusted mortality rates have fallen." To what extent did this encouraging finding hold true for African Americans, and for other minorities that disproportionately suffer from cancer?

Dr. Klausner: The decline in overall cancer mortality was seen for both white Americans and black Americans. While the rates for Americans of races other than white or black did not decline, their overall cancer mortality rate (107 per 100,000) was less than half that for black Americans (222 per 100,000) and approximately one-third less than that for white Americans (167 per 100,000).

EXCESS CANCER DEATH RATE

Mr. Stokes: As you have indicated, African Americans experience a 20 to 30 percent excess rate of cancer death compared to white Americans. Specifically, how is the FY 1997 appropriation being used to address this problem, and how will the FY 1998 budget request allow you to build on that effort?

Dr. Klausner: The NCI remains committed to reducing the burden of cancer in all segments of the population. Toward this end an internal Special Actions Committee was formed at the request of the NCI Director to review NCI's activities and program mechanisms to ensure that the cancer problems of minorities, the undeserved, and persons age 65 and over were being adequately addressed. The Special Actions Committee issued its report and recommendations in May 1996. The report was intended to identify the specific efforts to deal with the cancer problems among these populations and to indicate opportunities for further action. Issues addressed by the Special Action Committee include the definition of minority and special population activities, monitoring of minority training, organization of NCI programmatic data on minority/special population activities, leadership and coordination of minority and special population activities, input of NCI staff into management of minority and special population activities, and identification of research opportunities.

As a tangible outcome of this analysis, the Office of Special Populations was established within the Office of the Director, NCI in June 1996. The Office of Special Populations will serve as a focal point to provide leadership and coordination on research related to minorities and special populations. The office will coordinate NCI programs addressing scientific questions pertinent to these populations. Important elements of this office are the evaluation of current NCI programs and planning new initiatives. Through its evaluation function the office will determine what questions are important to special populations, what questions are being addressed through NCI's programs and portfolio of grants, and what research questions should be raised. Established epidemiologic data bases and current research findings will be used to define scientific questions pertinent to special populations. The office will develop

concepts for new programs that need to be implemented by the scientific divisions of the NCI. An advisory committee of NCI staff will help define these questions. The expertise of individuals from the community will also be called upon.

The mortality data cited is derived from data developed by the NCI Surveillance, Epidemiology and End Results Program. NCI has expanded its surveillance efforts in tracking cancer rates for minorities. The institute has sponsored a number of patterns-of-care studies looking at the differences in cancer care among regions and among racial groups in the U.S. The NCI Black-White study reviewed differences in cancer biology, treatment, and outcomes in Blacks and Whites with bladder, uterus, breast, and colon cancer in several regions of the U.S. Several outreach initiatives have been established including the National Black Leadership Initiative on Cancer, the Hispanic Leadership Initiative on Cancer, and the Appalachian Leadership Initiative on Cancer providing grants to non-government agencies to provide information concerning cancer prevention, early detection, and treatment to some special populations. For NCI treatment clinical trials, minority representation among the individuals enrolled reflects their representation among individuals with the disease under study. The NCI has also sponsored a national conference, concerning the accrual and retention of minorities in clinical trials. Additional regional conferences on this topic will be held in the coming year utilizing NCI support.

Mr. Stokes: In your professional judgement, what must we do to effectively address this continuing health disparity?

Dr. Klausner: There is a definite association between poverty and cancer. Cancer mortality rates are the highest among the poor. To some extent, statistics from the NCI Surveillance, Epidemiology, and End Results Program about the high mortality of minorities relate to poverty, since minorities are over-represented among the poor. While it is our responsibility to study and describe the causes or etiology of cancer and the causes of cancer mortality, many of the solutions to the cancer problem are ultimately beyond the NCI.

It is also important to remember that cancer is not the only disease that disproportionately affects minorities. Indeed, heart disease, obesity, hypertension and other diseases disproportionately affect minority cancer patients. These diseases often complicate or even prevent desired treatments and increase the chances of mortality which will be attributed to cancer. The cancer disparity cannot be fully addressed until we address co-morbid disease. NCI programs such as 5-A-Day for Health, designed to encourage an increase in the consumption of fruits and vegetables and decrease the amount of fat in the diet may also decrease rates of cancer, diabetes, and heart disease.

CANCER SURVIVORS

Mr. Stokes: You mentioned that today over 10 million Americans are cancer survivors. What is the racial and ethnic percentage distribution of these survivors?

Dr. Klausner: Of cancer survivors approximately 91% are white and 7% are black. The U.S. population is approximately 83% white and 12.5% black. Whites are over-represented among cancer survivors because of differences between the races in cancer incidence rates, survival rates for cancer, and overall mortality rates.

ADVANCES AGAINST CANCER

Mr. Stokes: As we look back over the 25 years of the National Cancer Act, what do you consider to have been the most significant advances that have brought us to where we are today, — to be able to say that mortality rates have fallen?

Dr. Klausner: The past quarter century has seen remarkable advances against cancer, many coming as a direct or indirect result of passage of the National Cancer Act in 1971. Among them, as you mentioned, are the drop in several cancer mortality rates. There have also been significant developments made in the technologies available in the field of cancer research. The last twenty-five years has seen an explosion in cancer genetics which has helped lead to important progress in treatment - including several promising drugs, detection and diagnosis and prevention. A number of significant epidemiological studies have also been released. Advances have been made in information technology that have strengthened our information dissemination programs. The following is a list of some of our most important advances in carrying out the National Cancer Program in the past twenty-five years.

Cancer Mortality Rates (from analysis available by January 1997)

- Overall cancer death rates fell 2.6 percent from 1991 to 1995
- Lung cancer death rates for men fell 6.7 percent from 1991 to 1995
- Death rate for colorectal cancer dropped 18.6 percent from 1973 to 1993, and 5.4 percent between 1991 and 1995
- Death rate for breast cancer fell 2.9 percent from 1973 to 1993, and 6.3 percent between 1991 and 1995
- Testicular cancer death rate dropped 65.7 percent from 1973 to 1993
- Hodgkin's disease death rate fell 58.4 percent from 1973 to 1993
- Death rate for cancers in children -- up to age 14 -- fell 44.4 percent from 1973 to 1993; leukemia, the most common childhood cancer, decreased 52.9 percent in that period

Technologies

- Recombinant DNA techniques developed for cloning genes, mid-1970s
- Hybridoma technology developed for production of monoclonal antibodies, 1975
- Southern blot technique developed to identify DNA fragments, 1975
- Methods developed to sequence DNA fragments, 1975 to 1976
- Restriction fragment length polymorphism (RFLP) technique used in cancer, 1983
- Polymerase chain reaction technique (PCR) developed, mid-1980s
- Severe combined immunodeficiency (SCID) mice developed, mid-1980s

- Techniques developed to manipulate the genetic makeup of laboratory animals, facilitating the study of the effects specific genes and gene alterations on tumor development, 1980s
- Fluorescence in situ hybridization (FISH) technique developed, about 1990

Cancer Genetics

- First of some 50 now-known human proto-oncogenes discovered (*src*), 1976
- Most frequently mutated gene in human cancer, *p53*, discovered, 1979
- First of some 20 now-known tumor suppressor genes cloned (*RB1*), 1986
- First human gene therapy for cancer (melanoma), 1991
- First of the hereditary nonpolyposis colon cancer genes cloned (*hMSH2*), 1993
- Isolation of VHL gene, associated with familial and non-familial kidney cancer as well as other tumors, 1993
- RET gene, linked to thyroid and adrenal cancers and to multiple endocrine neoplasia, cloned, 1993
- Inherited breast cancer genes cloned *(BRCA1 and BRCA2)*, 1994 and 1995
- CDK4 gene, associated with melanoma, identified, 1996.
- Cloning of gene, called *patched or PTC,* linked with an inherited basal cell carcinoma of the skin, 1996

Epidemiology

- Surveillance, Epidemiology, and End Results (SEER) Program established, 1973
- Statistical methods developed to control simultaneously for several factors in the analysis of studies and to quantify cancer risks, 1970s and 1980s
- Studies in human populations link cancer risk to infectious agents, such as human papillomavirus (cervical cancer) and Hepatitis B (liver cancer), 1970s and 1980s
- Studies link cancer risks to hormonal drugs, such as diethylstilbestrol (DES) taken during pregnancy and hormonal replacement therapy, 1970s and 1980s
- Studies clarify the patterns of cancer risk following exposure to ionizing radiation, 1970s and 1980s
- Studies associate risk of certain cancers with dietary and nutritional factors, such as low intake of fruits and vegetables, obesity, and sedentary lifestyle, 1980s
- Biochemical and genetic assays integrated into epidemiologic studies (molecular epidemiology), 1980s
- Precursors, such as specific moles as precursors to melanoma, linked to several forms of cancer, late 1970s and early 1980s
- Statistical genetic techniques developed to define modes of inheritance, localize genes, and evaluate gene-environment interactions in cancer risk, 1970s through 1990s
- Several common genetic variants linked to the risk of lung and other cancers, 1990s

Treatment

- Limb-sparing surgeries developed for sarcomas of the extremities, late 1970s
- Development or intensive multi-drug treatments, followed by long-term oral chemotherapy, bring dramatic improvements in survival rates for childhood leukemia, 1970s.
- Bone marrow transplants proven to effect long-term survival and cures in certain leukemias and lymphomas, 1970s
- Development of the highly curative regimen, cisplatin, vinblastine, and bleomycin (PVB) for testicular cancer, 1970s
- Interleukin-2 discovered, 1976
- First human testing of a biological therapy (alpha interferon), 1978
- Total mastectomy replaced radical mastectomy for breast cancer, 1979
- Continuous pain medication infusion pumps developed, early 1980s
- First effective anti-nausea drugs developed to alleviate side effects of chemotherapy, early 1980s
- First human cancer vaccine developed (Hepatitis B virus vaccine for liver cancer), 1981
- Lumpectomy plus radiation found equivalent to mastectomy for breast cancer, 1985
- Modified prostatectomy designed to preserve potency and urinary continence introduced, 1986
- Adjuvant chemotherapy proven to increase disease-free survival in early breast cancer, 1988
- Adjuvant chemotherapy found to increase survival in colon cancer, 1989
- Larynx-sparing surgery for laryngeal cancer developed, 1990s
- Adjuvant radiation and chemotherapy found to improve survival in rectal cancer, 1991
- Combination chemotherapies proven effective, first for Hodgkin's disease and later for a variety of cancers

Anticancer Drugs (year of FDA approval)

- Doxorubicin (1974)
- Cisplatin (1978)
- Tamoxifen (1978)
- Levamisole (1990)
- Paclitaxel (1992)
- Topotecan (1996)

Prevention

- Flexible sigmoidoscopy and colonoscopy developed to help detect and remove precancerous growths, 1980s
- Dietary guidelines to reduce cancer developed, 1984
- First chemoprevention trial to show efficacy (vitamin A analogue against mouth and throat tumors), 1990
- ASSIST, largest tobacco prevention and control project in United States, launched, 1991

- National Cancer Institute-sponsored studies in China show importance of nutrition in preventing cancer, 1991
- Prevalence of adult cigarette smoking dropped from 37 percent in 1971 to 24 percent in 1993

Detection and Diagnosis

- Computed tomography introduced to the United States, 1973
- Positron emission tomography (PET) developed, mid 1970s
- Magnetic resonance imaging (MRI) introduced, early 1980s
- The Bethesda System conference developed system for standardized reporting of Pap smear results, 1988
- Transition from film-based radiology to digital computer-assisted medical imaging, 1990s
- Molecular diagnostics developed, using immunological, chromosomal, DNA, and protein markers, 1990s
- Mammography Quality Standards Act passed, 1992

Cancer Concepts

- Established that proto-oncogenes play important roles in normal cellular control, 1970s
- Cytochrome P450 enzyme system shown to activate many carcinogens, 1970s
- Genes identified that are involved in deactivating the metabolism of carcinogenesis, 1970s
- Metastatic cells shown to arise from pre-existing subpopulations in primary tumors, 1978
- Metastatic cells shown to arise from a unique subpopulation of cells within the primary tumor, 1978
- Discovery of multiple steps by which cancer cells metastasize and invade other tissues and organs, 1970s-1980s
- Development of laboratory animals with specific genetic makeups to serve as models of human cancers, 1980s
- First tumor suppressor genes identified and shown to be critical in control of cell growth, 1980s
- Apoptosis shown to be a critical mechanism in tumor suppression, tied to specific genes, 1990s
- Carcinogenesis linked to discrete events in the cycle of cell division and replication, 1990s
- Multistep nature of carcinogenesis documented and correlated with genetic changes, 1990s
- Understanding of how angiogenesis — the growth of new blood vessels — supports tumor growth and spread, offering a potential target for treatment, 1990s

Information Transfer

- CANCERLINE, a national database of published cancer research, established, 1974

- Cancer Information Service (1-800-4-CANCER) opened, 1976
- First national cancer patient education program (I Can Cope) founded, 1977
- First major DNA sequence databases established in United States (GenBank) and Germany, 1982
- PDQ (Physician Data Query) database established, 1984
- Human Gene Mapping database established, 1989

Cancer Specialists

- Certification in medical oncology (6,550 certified to date) first offered, 1973
- Certification in gynecologic oncology (559 now certified) first offered, 1973
- Society for Surgical Oncology (1,600 members now) established from earlier group, 1975
- Oncology Nursing Society (24,000 members now) established, 1975
- Certification in radiation oncology (3,130 new certified) first offered, 1989
- Number of medical oncologists certified annually grew from 351 in 1973 to 597 in 1995
- Membership in the American Society of Clinical Oncology, established in 1964, grew to about 10,500 in 1996

ROLE OF STRESS IN CANCER

Mr. Stokes: As researchers examine cancer's risk factors some are more tangible than others, how is the impact of stress on disease assessed?

Dr. Klausner: Research on the role stress may play in either developing or ameliorating the effects of cancer is usually grouped within the broad field of psychoneuroimmunology, which is the study of the role social and psychological factors may play in the alteration of human neurological and immunological systems. Research on the role of stress in cancer may be divided into two parts, i.e. whether controlling stress plays any part in preventing cancers from developing and whether controlling stress can ameliorate the effects of any cancers once they have been diagnosed.

Mr. Stokes: Do we know what role stress plays in cancer?

Dr. Klausner: The complex relationship between physical and psychological health is not well understood. As you might imagine well-controlled studies comparing individuals with a high level of stress with those with lower stress are difficult to design and conduct. Reduction of stress is likely to be beneficial in terms of certain quality of life issues, but there is little evidence that stress plays a role in cancer. Some studies have focused on hormone levels and the immune system, but these involve complex networks whose activities are affected by a number of factors. It has not been shown that stress-induced changes in the immune system is relevant to cancer formation or progression. One NCI-sponsored study suggested that there is no important association between breast cancer and stressful life events such as the death of a loved one or

divorce. The NCI is continuing to support additional work in the field of psyconeuroimmunology.

PROSTATE CANCER

Mr. Stokes: I understand that scientists have identified the locus for the first prostate cancer susceptibility gene. Can you tell us what this means in terms of furthering advances in the treatment, prevention and early detection of the disease?

Dr. Klausner: The identification of a region of chromosome 1 that contains candidate genes for prostate cancer susceptibility immediately suggests that the potential exists for identification of individuals at high risk for this disease. These individuals may then undergo intensive surveillance and be enrolled in chemoprevention trials. Moreover, the protein products of these susceptibility genes may provide a handle on the molecular mechanisms leading to prostate cancer and may lead us to targets for therapeutic intervention.

CLINICAL TRIALS

Mr. Stokes: How critical are clinical trials to furthering advances in the treatment, prevention, and early diagnoses of cancer?

Dr. Klausner: A clinical trial is an experiment that attempts to answer a medical question, most often about the effect of a therapeutic intervention on the outcome of a disease, or of an intervention to prevent the development of the disease. Clinical trials are absolutely essential to furthering advances in the treatment, prevention, and early diagnoses of cancer. While interventions, such as new medical treatments or diagnostic techniques, may appear to be promising based on scientific rationale, evidence obtained in animals, or anecdotal usage in patients, clinical trials are critical to reliably establish their benefit and define their toxicities. The need to reach accurate conclusions about the benefit of toxic and expensive interventions is self-evident and requires systematic use of clinical trials. Nonexperimental approaches, in which reasoning rather than observation is used to reach conclusions, or flawed experimental research, in which the intervention is inconsistent or uncontrolled, can severely restrict progress toward the cure of cancer by erroneously supporting the value of what are actually useless or harmful interventions.

Mr. Stokes: What is the extent of the participation of women and minorities in NCI trials?

Dr. Klausner: The NCI has at any one time almost 3 million subjects enrolled in clinical studies concerning the detection, diagnosis, treatment, prevention or control of cancer. These subjects, which are predominately healthy individuals, are composed of 71% women and 45% minorities. NCI has vigorously pursued on its own and with its grantees recruitment of women and minorities in all studies, and conducts many trials specifically targeted at gender-specific cancers of high prevalence and impact.

NCI has been extremely successful in ensuring representation in trials with therapeutic intent and with population-based data collections. For NCI treatment clinical trials, minority representation among the individuals enrolled in the trial reflects their representation among individuals with the disease under study. For treatment clinical trials approximately 183,000 individuals are participating, of which nearly 88,000 are women and about 95,000 are men. The NCI has also sponsored a national conference, the topic of which was the accrual and retention of minorities in clinical trials. Additional regional conferences on this topic will be held in the coming year utilizing NCI support.

NCI's internal assessment of the fulfillment of meeting the inclusion requirement has assured compliance with the NIH Revitalization Act of 1993: Women and Minorities as Subjects in Clinical Research. A grant application that fails to meet the standard for inclusion receives an unacceptable gender or minority code, which results in an administrative bar-to-funding. This bar may be removed upon receipt of additional information. Program staff has some flexibility to work with an applicant and resolve problems the may prevent award of highly meritorious projects.

On February 26, 1997, based upon the review of the data presented to the National Cancer Advisory Board (NCAB), the NCAB concurred with the NCI's compliance in implementing the NIH Guidelines on the inclusion of women and minorities in clinical studies.

Mr. Stokes: How much is included in the FY 1998 budget request for clinical trials, and how does this compare with FY 1997 and FY 1996?

Dr. Klausner: In the FY1998 budget request, $412,618,000 is included for both treatment and prevention clinical trials. This represents an $8.6 million increase, or 2.1%, over FY 1997 and an increase of $18.8 million, or 4.8%, over the FY 1996 amount.

Mr. Stokes: Over the 25 years of the National Cancer Act, what clinical trials have given the nation the biggest payoff and explain why?

Dr. Klausner: It should be noted that over this period, clinical trials numbering in the tens of thousands have been conducted. Collectively, they have significantly improved the prognosis for patients with many types of tumors. I will highlight only a tiny fraction of these trials. A series of trials conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) established that lumpectomy (breast-sparing surgery) with breast irradiation results in overall survival comparable to that achieved with mastectomy for women with early invasive breast cancer confined to the breast and axillary lymph nodes and for women with non-invasive (ductal in-situ) breast cancer. These trials demonstrated that women with breast cancer can choose to avoid mutilating surgery without fear of reducing their life expectancy.

A trial by the NSABP has demonstrated that tamoxifen administered daily for five years is an effective and well tolerated adjuvant hormonal therapy in pre- and postmenopausal women with breast cancer who have negative axillary lymph nodes and whose tumor is positive for the estrogen receptor. This seminal trial demonstrated a near 20% reduction in the risk of death from breast cancer, or an absolute improvement in survival of nearly 5%, compared to a placebo. Tamoxifen was also shown to reduce the risk of new contralateral breast cancers; a finding that laid the foundation for the NSABP's Breast Cancer Prevention Trial (BCPT) in which tamoxifen is used as a preventive agent. Based in large part on the results of this trial, tamoxifen has become a mainstay of therapy for women with hormone sensitive tumors and has prolonged the lives of many women world-wide.

A series of breast cancer adjuvant trials conducted within the Clinical Trials Cooperative Group Program established that combination chemotherapy results in a 20-30% reduction in the risk of death compared to pre- and post-menopausal women receiving surgery alone and compared to surgery and tamoxifen therapy alone in postmenopausal women. These trials established that chemotherapy is effective in pre- and postmenopausal women as well as in women with positive axillary lymph nodes and in certain subsets of women with negative axillary lymph nodes. These Cooperative Group trials have made a major contribution to the overview analysis of world-wide chemotherapy trials in breast cancer. This overview analysis has demonstrated that chemotherapy results in a near 10% absolute improvement in survival which translates to the prolongation of about 10,000 American lives annually considering that over 100,000 women are candidates for chemotherapy every year in the U.S.

Hodgkin's disease represents one of the major successes of contemporary oncology. The MOPP combination chemotherapy regimen developed at the NCI was able to achieve complete remissions in two-thirds of patients with advanced disease, half of whom were cured. Unfortunately, this regimen had a number of serious associated toxicities, including secondary acute leukemia and infertility. In an attempt to improve on the results with MOPP, several combination regimens were developed which included the anthracycline drug, adriamycin, while eliminating the drugs in MOPP implicated in the secondary leukemias. In a randomized trial involving almost 400 patients, three anthracycline-based regimens were compared to MOPP. More than 80% of patients treated with the newer regimens achieved a complete remission, and two thirds of these remained free of disease. Overall survival was also better with each of the newer programs compared with MOPP. Of critical importance is the fact that these newer regimens are also associated with a significantly lower risk of secondary leukemia and infertility compared with MOPP

A series of colorectal cancer adjuvant studies conducted within the Clinical Trials Cooperative Groups established a 33% reduction in risk of death in patients receiving adjuvant chemotherapy compared to those receiving surgery alone. For stage III colon cancer alone, there are about 25,000 cases diagnosed each year in this country, so that the results translate to potentially 4,000 additional lives saved among these

patients. As the results appear to apply in roughly equal proportions to stage II colon and to rectal cancers as well, the overall benefit is even greater.

A series of trials conducted by the Gynecologic Oncology Group have established the optimal combination of surgery and chemotherapy for women with ovarian cancer. These trials have shown that women who undergo effective surgical staging and cytoreductive ("debulking") surgery live longer than those who have less extensive surgical procedures. In addition, these trials have helped identify the best chemotherapy regimen to use after initial surgery. The best chemotherapy regimen currently available is a combination of platinum and paclitaxel (taxol). Paclitaxel was originally identified and developed by the NCI as an anticancer drug. Thanks to these trials, the treatment of choice, which combines effective surgery and chemotherapy, has prolonged the lives of many women with ovarian cancer.

A trial of limited surgical resection versus removal of the entire lobe of the lung for early stage lung cancers demonstrated that limited resection was associated with a 75% increase in overall deaths, a 30% increase in overall deaths, and a 50% increase in deaths with cancer as compared to patients treated with the more extensive surgery. This was important in maintaining lobectomy as the surgical approach of choice in early stage lung cancer, and prevented the adoption of a less successful surgical approach which would have led to thousands of needless deaths.

Nasopharyngeal cancer is a malignancy of the part of the throat which sits just above the soft palate. An NCI-sponsored intergroup trial has demonstrated that combined modality treatment -- chemotherapy plus radiotherapy — is superior to standard radiotherapy alone in patients with advanced nasophayrygeal cancer in terms of both progression-free and overall survival, thus establishing combined modality therapy as the treatment of choice. The impact of this trial result has world-wide application. While this type of cancer occurs most frequently in China and Southeast Asia, North Africa, the Middle East, and among Eskimos, the incidence of nasopharyngeal cancer in the United States may increase with immigration from these other areas. Chinese-Americans have the highest statistical risk for nasopharyngeal cancer in the U.S. -- six times higher than that of any other ethnic group.

Over the past 25 years, bone marrow transplantation (BMT) has emerged as an important therapeutic advance in the treatment of diseases such as the acute and chronic leukemias. Prior to this therapy, chronic myelogenous leukemia was an incurable disorder. If transplanted within a year of diagnosis, as many as 60% of patients in the chronic phase of the disease can now be cured. Whereas combination chemotherapy can cure 20-30% of patients with acute myeloid leukemia (AML), and 40% of adult patients with acute lymphoblastic leukemia (ALL), there is no satisfactory treatment upon disease recurrence; however, BMT can cure about 25% of such patients. Similarly, there is no cure for patients with myelodysplastic syndromes, yet 40% of select patients are cured with BMT. Other diseases in which BMT is showing promise include multiple myeloma, chronic lymphocytic leukemia, and the non-Hodgkin's lymphomas. The major problem with BMT has been the high rate of treatment-related

mortality, ranging from 20-50% of patients, depending on age, disease, and other factors. However, continued research is focusing on reducing the complications of this treatment, which should increase the number of patients cured by BMT.

Acute promyelocytic leukemia (APL) accounts for 15% of adult patients with acute myeloid leukemia. This disease is characterized by a specific chromosome abnormality, severe bleeding, and with most patients dying from the disease despite aggressive chemotherapy. In 1988, Chinese investigators published a paper suggesting that all-trans-retinoic acid, administered orally, could reduce the hemorrhagic complications of the disease and was able to induce complete remissions in more than 80% of patients. Subsequently, a small trial from France confirmed these observations. The NCI coordinated a North American trial in 401 pediatric and adult patients with APL. Although response rates were the same whether or not ATRA was included, the estimated disease-free survival was 54% with chemotherapy alone compared with 92% with ATRA. Subsequent follow-up also noted a survival advantage to the incorporation of ATRA. This study led to approval of ATRA by the FDA. Importantly, these clinical observations opened a whole new area of research into the biology and genetics of leukemia and the function of retinoids.

A sequence of clinical trials carried out through the NCI clinical trials network in the 1970s demonstrated remarkable but temporary antitumor activity for several individual chemotherapeutic agents in advanced (metastatic) testicular germ cell cancers, and then that combining these in the PVB regimen (cisplatin, vinblastine and bleomycin) was curative in most patients with testicular cancer. The following generation of NCI-sponsored trials established that substitution of etoposide for vinblastine reduced the toxicities while maintaining the efficacy, and that bleomycin could not be eliminated from the regimen. Currently, about 90 percent of all patients with testicular cancer are cured while approximately 80 percent of patients with advanced disease are cured. Clinical studies are continuing to maintain the high cure rates and decrease the side effect resulting in an improved quality of life.

The most important contributions of the pediatric Cooperative Groups to the treatment of children with acute lymphoblastic leukemia (ALL) have come not from single trials, but from series of trials conducted over the past 25 years which have resulted in successive incremental increases in survival rates. For example, children with ALL treated on Children's Cancer Group treatment protocols in the years from 1968-72 had event-free survival (EFS) rates of only 10-20%. Event-free survival rates improved to approximately 60% by the mid-1970s and to approximately 70% by the mid-1980s. With current therapy, EFS rates approach 80%, which is a dramatic improvement in outcome from that possible 25 years ago. The most important improvements in treatment identified in these Cooperative Group studies have included: (I) the importance of effect central nervous system treatment and the ability to prevent central nervous system recurrences without the use of cranial radiation for many children; (ii) the benefit for "delayed intensification" therapy following achievement of remission; and (iii) the benefit for the use of "intermediate-dose" methotrexate.

As in childhood ALL, outcome for children in the United States with Wilms' tumor has improved over the past 25 years as a result of clinical trials conducted by the NCI-supported National Wilms' Tumor Study Group. The major conclusions of these studies are that: (I) the two drug combination of vincristine and dactinomycin gives better results than either agent used alone; (ii) routine, post-operative radiation therapy is not necessary for most children with localized tumors that are resected; and (iii) a three-drug combination plus radiation therapy is curative for most children with localized, but not fully resectable tumors. With current therapy, the vast majority of children with Wilms' tumor -- greater than 90% -- are long-term survivors.

Osteosarcoma and Ewing's sarcoma are the two primary types of bone cancers that occur in children and adolescents, and the NCI-supported pediatric Cooperative Groups have made important contributions in both. Pediatric Oncology Group investigators conducted a randomized controlled trial to determine whether intensive multi-agent adjuvant chemotherapy improves relapse-free survival in patients with nonmetastatic high-grade osteosarcoma of the extremity. After undergoing definitive surgery, patients were randomly assigned to adjuvant chemotherapy or to observation without adjuvant treatment. The 2-year RFS rate was 17% for those not receiving adjuvant therapy and 66% in the adjuvant-chemotherapy group ($P < 0.001$). This trial clearly documented the benefit of adjuvant chemotherapy following complete surgical resection and established a standard of treatment for osteosarcoma.

The Children's Cancer Group and the Pediatric Oncology Group collaborated in a study for Ewing's sarcoma to evaluate the role of the ifosfamide + etoposide combination. The impetus for this clinical trial was reports from phase II studies in the 1980s showing that the ifosfamide + etoposide combination had significant activity for Ewing's sarcoma and for other pediatric solid tumors. The study clearly demonstrated that the addition of the ifosfamide + etoposide combination to standard therapy improved outcome, with the 3-year survival rate increasing from 56% to 80%. As a result of this clinical trial, the ifosfamide-based regimen of this trial has become the standard therapy for children with Ewing's sarcoma.

Mr. Stokes: How many clinical trials are currently being funded and how much of the budget is invested in clinical trials?

Dr. Klausner: For this year the NCI is projecting to spend $403 million to support therapeutic and prevention clinical trials. Within the clinical trials site on the NCI's Web site (CancerNet) over 1,500 NCI clinical trials are listed with a description of each trial. Approximately, two-thirds are NCI sponsored. Besides studying new anticancer drugs, clinical trials study new combinations of drugs already used in cancer treatment, new ways of giving treatment, and how changes in lifestyle can help cancer patients or prevent cancer from occurring including studies of the psychological impact of the disease and ways to improve the patient's comfort and quality of life -- including pain control. Other clinical trials compare the best known standard therapy with a newer therapy to see if one produces more cures and causes fewer side effects than the other.

Mr. Stokes: How does this compare with the number and funding level in the FY 1998 budget request?

Dr. Klausner: The request for next year includes $412 million, an increase of approximately $9 million over FY 1997. I would expect that the number of trials would increase slightly above the current level.

DISSEMINATION OF CLINICAL TRIAL RESULTS

Mr. Stokes: How well are we doing with regard to rapidly disseminating clinical trial results?

Dr. Klausner: The NCI has a variety of procedures in place to inform the public, patients and health professionals about results obtained from cancer clinical trials. One method of informing the public is through the national media, using television, radio, or print materials such as newspapers or magazines. When new scientific information is available, an investigator who is familiar with the study or the NCI Director may be identified as a spokesperson who makes an announcement to the national media at a press conference. In addition, a press release is written containing scientifically accurate information about the results of the clinical trial. Those who typically disseminate this information through the national media are able to directly phone staff at NCI's Office of Cancer Communication (OCC) to confirm the trial results. In addition, staff members of the OCC may write news releases or articles to be placed in appropriate scientific journals or magazines. They also provide a list of *Questions and Answers* to help media personnel to understand the results of the clinical trial. In addition, a newsletter, *UPDATE,* is written by OCC specifically to focus on issues related to cancer clinical trials and is sent bi-annually to approximately 3,500 health professionals and related organizations.

Another important means of disseminating this information is through NCI's Cancer Information Service (CIS), a national network using two complementary program components, the 1-800-4-CANCER telephone service and the regional outreach program. The CIS meets the information needs of patients, the public, and health professionals. Specially trained staff provide the latest scientific information about the results of the clinical trial in understandable language. OCC provides each of the nineteen regional CIS offices with the appropriate information concerning the results of the clinical trials, including information on the study prior to any national announcement. In this way the results are disseminated to those who phone in for information as well as to regional partners identified in each region.

OCC also has lines of communication, such as newsletters or electronic methods, with staff at cancer treatment institutions and organizations, including advocacy groups, and NCI-designated comprehensive, clinical and consortium cancer centers. OCC also disseminates clinical trials results to sister DHHS agencies.

Use of electronic methods to disseminate results of clinical trials has become a popular means of informing the public and health professionals about the most up-to-date cancer information. Specific up-to-date information is available through CancerFAX® (301-402-5874) and CancerNet™. CancerNet™ can be accessed using E-mail at the following address: cancernet@icicc.nci.nih.gov or via the Internet through the World Wide Web (http://cancernet.nci.nih.gov) and Gopher (gopher://gopher.nih.gov) servers.

The NCI also uses the PDQ as a resource to educate physicians and patients about clinical trials. PDQ is NCI's comprehensive cancer database which includes a registry of summaries of trials that are open or approved for patient accrual, including protocols for cancer treatment, supportive care, screening and prevention. In addition, you can reference more than 8,000 summaries of protocols that have been completed or are no longer accepting patients. All protocols supported by the NCI are listed in PDQ. Clinical trials not sponsored by the NCI, including foreign protocols, are included in PDQ after review and approval by the PDQ Voluntary Protocol Review Board.

Mr. Stokes: Please provide for the record a list of clinical trials that are underway and of those that are ready for implementation in FY 1998?

Dr. Klausner: As a part of the NCI's efforts to rapidly disseminate the latest information on cancer research, the NCI developed the PDQ as a comprehensive, computerized cancer information database. A wide variety of cancer information is available from PDQ including details on over 1,500 ongoing clinical trials is now available through the World Wide Web (WWW). PDQ contains an extensive register of clinical trial protocols, with information from studies around the world, full-text information statements describing the latest advances in cancer treatment, supportive care, screening, and prevention, as well as information about selected anti-cancer drugs currently under clinical evaluation, and directories of over 23,000 physicians and over 11,000 organizations active in cancer treatment and care. Most information statements appear in two versions, a technical version for the health professional and a lay version that is in English and Spanish. The database is updated monthly by editorial boards of oncology experts.

CancerNet, the World Wide Web site of the NCI's International Cancer Information Center (ICIC), provides health professionals and the public access to PDQ cancer information. Individuals can search for specific trials by a variety of criteria including cancer type, geographic region, and sponsorship -- including NCI sponsorship. Studies conducted at the NIH Clinical Center can be identified as well. The clinical trials information in CancerNet is updated each month to reflect the frequent changes in the details of these trials. For example, when trials are closed to patient accrual they are removed, the design of a trial may be modified through an amendment process resulting in a revision of the description of the trial, and the specific institutions and investigators participating in a specific trial may change. Up-to-date listings and detailed information about cancer clinical trials are now available to members of the public as well as health care professionals on the CancerNet. It is

preferable that anyone interested in information about cancer clinical trials get it directly from the CancerNet web site directly since a printed listing of the trials included in CancerNet would soon be out of date.

To access CancerNet one can point a Internet browser to ICIC's Web site by entering the following Internet address: http://cancernet.nci.nih.gov in the place where the browser calls for a location or address. To use CancerNet to search for clinical trials, once you have reached the CancerNet homepage, click on "Patients and the Public"; then click on "Clinical Trial Information"; next, click on "PDQ --- Comprehensive, International Clinical Trial Information"; next, click on "Search PDQ for Comprehensive, International Clinical Trials Information". You will then see the PDQ Clinical Trial Search Form. Complete the form, and click on "Search"; the results of your search will be returned momentarily. Click on the title of each clinical trial to view the full PDQ protocol summary.

In addition, the NCI homepage, accessible through http://www.nci.nih.gov, contains significant other information relevant to the operation of the National Cancer Institute.

CLINICAL TRIALS IN FY 1998

The following list represents NCI sponsored trials that are ready to be implemented in FY 1998:

1. A Phase I pilot study of Recombinant IL-2 in children and adolescents with Human Immunodeficiency Virus Infection

2. A Phase I and Pharmacologic study of a Three Drug Combination of Chemotherapy Drugs (Idarubicin, ARA-C and Etoposide) in conjunction with the Multi-drug Resistance Modulator PSC-833 in patients with refractory acute leukemia.

3. A Phase I and Pharmacological study of Penclomedine (NSC#338720, IND#43409) administered daily by mouth for five consecutive days in patients with Advanced Solid Tumor Malignancies

4. A Phase I Clinical and Pharmacologic Evaluation of Phenylbutyrate in patients with Refractory Solid Tumors Study of Continuous Exposure Oral Phenylbutyrate on a three times daiiy schedule

5. A Phase I Clinical and Pharmacologic Trial of Irinotecan Hcl (Irinotecan, Cpt-11) by Chronic Low-dose Daily Injections in patients with Advanced Solid Tumor Malignancies

6. A Phase I Pilot Study of 5-azacytidine in HIV Patients with Relapsed and /or Refractory EBV-associated Malignancies

7. A Phase I Pilot Study of Paclitaxel/Cyclophosphamide and High Dose Melphalan/Etoposide with Autologous Progenitor Cell Transplantation for the Treatment of Metastatic and High Risk Breast Cancer

8. A Phase I Pilot/dose-finding Study of the Toxicity, Anti-kaposi's Sarcoma (KS) Activity, and Immunologic Activity of Interleukin-12 administered to patients with AIDS-associated KS

9. A Phase I Study of a Human Papillomavirus E7 Lipopeptide Vaccine for the Treatment of Recurrent or Persistent Cervical Cancer

10. A Phase I Study of active Immunotherapy with Carcinoembryonic Antigen Peptide (CAP-1)-pulsed, Autologous Human Cultured Dendritic Cells in patients with Metastatic Malignancies Expressing Carcinoembryonic Antigen

11. A Phase I Study of Continuous Infusion Immunotoxin IGG-RFB4-SMPT-DGA in Refractory Cd22-positive B-cell Lymphoma

12. A Phase I Study of Depsipeptide in Patients with Advanced Cancer

13. A Phase I Study of Irinotecan (Cpt-11) Administered as a Prolonged Infusion in Adult Patients with Solid Tumors

14. A Phase I Study of Levamisole in Children and Adolescents with Advanced Human Immunodeficiency Virus Infection

15. A Phase I Study of Perillyl Alcohol in Patients with Refractory Malignancies (NSC #641066)

16. A Phase I Study of Prolonged Low Dose Topotecan Infusion Combined with Taxol

17. A Phase I Study of Pyrazoloacridine given as a weekly 24 Hour Continuous Intravenous Infusion in Adult Cancer Patients

18. A Phase I Study of Recombinant Vaccinia Virus that expresses Prostate Specific Antigen in Adult Patients with Adenocarcinoma of the Prostate

19. A Phase I Study of the Combination of CAI and Paclitaxel in Adult Patients with Refractory Cancers or Lymphoma

20. A Phase I Study: FdDA Therapy in Children Infected with HIV

21. A Phase I Translational Study of Chronobiologic Timing of Intravenous IuDr(NSC#39661) in the Treatment of Advanced Malignancies

22. A Phase I Trial of a Recombinant Vaccinia-CEA (180-kd) Vaccine delivered by Intradermal Needle Injection Versus Subcutaneous Jet Injection in Patients with Metastatic CEA-expressing Adenocarcinoma

23. A Phase I Trial of Perillyl Alcohol (NSC 641066) administered on a Two Weeks On, Two Weeks Off Schedule

24. A Phase Ib Study to Evaluate the Safety and Tolerance of Repetitive Daily Intravenous Doses of RSR13 Administered to patients receiving Cranial Radiation Therapy for Glioblastoma Multiforme

25. A Phase Ib Vaccine Study of Recombinant ras Protein combined with Adjuvant Qs-21 in patients with Adenocarcinomas Expressing an Activated ras Oncoprotein

26. Phase I and Pharmacokinetic Trial of Phenylacetate given as a 28-day Continuous Infusion in Pediatric Patients with Refractory Malignancy

27. Phase I and Pharmacokinetic Trial of Phenylbutyrate given as a Continuous Infusion in Pediatric Patients with Refractory Malignancy

28. Phase I and Pharmacologic Study of Sequences of Pyrazoloacridine (NSC 366140; Pd115934) and Cisplatin Without and With Granulocyte-colony Stimulating Factor (R-METHG-CSF) in Patients with Advanced Cancer

29. Phase I Cancer Vaccine Studies

30. Phase I Clinical and Pharmacokinetic Study of Diethylhomospermine (Dehspm) Administered by Subcutaneous Injection

31. Phase I Clinical and Pharmacokinetic Study of Oral 9-aminocamptothecin (Nsc-603071) on a 5 Days Every 2 Week Schedule

32. Phase I Evaluation of a Protracted Daily Bolus Schedule of 9-amino-20(s)-camptothecin [Colloidal Dispersion Formulation] in patients with Advanced Solid Tumors

33. Phase I Evaluation of Krn5500 (NSC-650426)

34. Phase I Protocol for the Administration of 2'-beta-fluoro-2',3'-dideoxyadenosine (F-DDA) to Patients with HIV-associated Diseases

35. Phase I Study of a Human Papillomavirus E7 Peptide Vaccine with Incomplete Freund's Adjuvant for the Treatment of Cervical/Vulvar Squamous Intraepithelial Neoplasia

36. Phase I Study of Adoptive Cellular Therapy of Solid Tumor Malignancies with Tumor-draining Lymph Node Cells Activated and Expanded in Vitro with Bryostatin 1, Inonomycin, and Interleukin-2

37. Phase I Study of ANTI-TAC(FV)-PE38 (LMB-2), a Recombinant Single-chain Immunotoxin for Treatment of TAC-expressing Malignancies

38. Phase I Study of IL-6, GM-CSF and CBDCA in Patients with Recurrent Ovarian Cancer

39. Phase I Study of SMS 201-995 PA LAR (NSC 685403) with/without Tamoxifen in Patients with Osteosarcoma

40. Phase I Study of Taxotere in Patients with Advanced Malignancies and Varying Degrees of Liver Dysfunction

41. Phase I Study to Determine the Safety and Pharmacokinetics of Farnesyltransferase Inhibitor, R115777, in Advanced Cancer

42. Phase I Study to Evaluate the Safety and Immunogenicity of HIV-1 Immunogen in Children with HIV-1 Infection

43. Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the gp100 Melanoma Antigen

44. Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Fowlpox Virus Encoding the gp100 Melanoma Antigen

45. Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Fowlpox Virus Encoding the Mart-1 Melanoma Antigen

46. Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Vaccinia Virus Encoding the gp100 Melanoma Antigen

47. Phase I Trial of 9-Cis Retinoic Acid (Alrt1057,NSC #659772) and Interferon-alpha-2b in Patients with AIDS-Associated Kaposi's Sarcoma

48. Phase I Trial of Adriamycin Combination with Suramin for the Treatment of Patients with Advanced Androgen-independent Prostatic Carcinoma

49. Phase I Trial of Combined Treatment with Ch14.18 and R24 Monoclonal Antibodies and Interleukin-2 For Patients with GD2+/GD3+tumors

50. Phase I Trial of Irinotecan and Tomudex in Combination on an Every Three Week Schedule

51. Phase I Trial of Rhizoxin (NSC 332598) Administered as a 72 Hour Continuous Intravenous Infusion Every 21 Days

52. Phase I Trial of Tomudex and 5-iodo-2'-deoxyuridine (IdUrd) in Patients with Advanced Cancer

53. Phase I, Open Label, Multicenter Dose Escalation Study of Gliadel in Patients with Recurrent Malignant Glioma

54. Phase I-II Study of Fluorouracil in Combination with Phenylbutyrate in Advanced Colorectal Cancer

55. Phase I/II Trial of Estramustine and Vinblastine Plus 3-d Conformal Radiation Therapy in Patients with Poor Prognosis Non-metastatic Prostate Cancer

56. A Phase I Pilot Study 5-azacytidine given as a 7-day Continuous Infusion Patients with Relapsed and/or Refractory EBV-Associated Malignancies

57. A Phase I Treatment of Patients with Advanced Epithelial Ovarian Cancer using Anti-CD3 Stimulated Peripheral Blood Lymphocytes Transduced with a Gene Encoding a Chimeric T Cell Receptor Reactive with Folate Binding Protein

58. A Phase I Study: vaccination of Follicular Lymphomas with Tumor-derived Immunoglobulin Idiotype Combined with Qs-21 Adjuvant

59. A Phase I Trial and Pharmacokinetic Study of the Sequential Administration of Carmustine (BCNU) and Temozolomide in Patients with CNS or Systemic Tumors Refractory to Standard Therapy

60. A Phase II Pilot Study of the Recombinant Vaccinia-CEA (70 Kd) Vaccine in Patients with Low Tumor Burden Adenocarcinoma of the Colon/rectum

61. A Phase II Randomized Study of Epoch II Versus Epoch II and Immunotherapy in Lymphomas

62. A Phase II Study of 9-aminocamptothecin in Patients with Refractory Breast Cancer

63. A Phase II Study of Chemoimmunotherapy in Patients with Mullerian Carcinoma Utilizing Intravenous Paclitaxel and Cisplatin Followed by Intraperitoneal rIL-2 Expanded TIL and a Low Dose Schedule of rIL-2.

64. A Phase II Study of CI-958 (NSC #635371) in Refractory or Recurrent Ovarian Cancer

65. A Phase II Study of Intravenous Phenylacetate in Metastatic, Hormone Refractory Prostate Cancer

66. A Phase II Study of Oral CAI in Patients with Androgen-independent Prostate Cancer

67. A Phase II Study of Suramin in Patients with Platinum-resistant Epithelial Ovarian Cancer

68. A Phase II Study: Familial Renal Carcinoma

69. A Phase II Trial of Bryostatin-1 in Low Grade Non-Hodgkins Lymphoma

70. A Phase II Trial of CI-980 in Patients with Stage D2, Hormone Refractory Prostate Cancer

71. A Phase II Trial of Phenylacetic Acid for Recurrent Malignant Glioma and Primitive Neuroectodermal Tumors: a Clinical and Pharmacokinetics Study of the North American Brain Tumor Consortium

72. A Phase II Study of Combined Modality Therapy for Good Prognosis Patients with Extensive-stage Small Cell Lung Cancer: Efficacy of Alternating Chemotherapy with Etoposide/cisplatin and an In-Vitro Best Regimen

73. A Phase II Study: CWRU 1296: Biochemical and Pharmacokinetic Predictors of Colon Cancer Response to a Topoisomerase I Directed Treatment with Irinotecan

74. A Phase II Study: Evaluation of CI-958 (NSC #635371) in Patients with Hormone Refractory Metastastic Prostate Carcinoma

75. A Phase II Study: Interleukin-12 and Epoch Chemotherapy in Untreated and Interleukin-12 in Previously Treated AIDS-related Lymphoma

76. Phase I/II Clinical and Pharmacologic Study of 9-amino-20(s)-camptothecin (9-AC) Administered as a 72 Hour Infusion in Adults with Recurrent or Progressive Malignant Glioma

77. Phase II Clinical Evaluation of Bryostatin 1 in Patients with Relapsed Multiple Myeloma

78. Phase II Clinical Evaluation of Bryostatin 1 in Patients with Relapsed Non-Hodgkin's Lymphoma and CLL

79. Phase II Evaluation of CI-980 in Untreated Extensive Stage Small Cell Lung Cancer

80. Phase II Study of All-trans Retinoic Acid and Subcutaneous Cytosine Arabinoside in Unfavorable Myelodysplastics

81. Phase II Study of Chemotherapy of Non-Hodgkin's Lymphoma arising in the CNS or Eye

82. Phase II/I Clinical and Pharmacologic Study of Pre-irradiation 9-amino-20(s)-camptothecin (9-AC) Administered as a 72 Hour Infusion in Adults with Newly Diagnosed Glioblastoma Multiforme

83. A Phase II Study: Pilot Study for the Evaluation of Rhgm-CSF Before Induction Chemotherapy in Hairy Cell Leukemia

84. A Phase II Study: Treatment of Patients with Metastatic Melanoma Using Peripheral Blood Lymphocytes Sensitized in Vitro, to the Gp209-2m Immunodominant Peptide

85. A Phase II Study: Treatment of TAC-expressing Cutaneous T-cell Lymphoma (CTCL) and Adult T-cell Leukemia (ATl) with Anti-TAC-h, a Humanized Antibody that Binds to the IL-2 Receptor

86. A Phase II Study: Use of Safety-modified Retroviruses to Introduce Chemotherapy Resistance Sequences Into Normal Hematopoietic Cells for Chemoprotection during the Therapy of Breast Cancer.

87. A Phase III Cell Kinetic Examination of Tumors in Patients Entering The Trial: Conventional Fractionation vs Continuous Hyperfractionated Accelerated Radiotherapy (w/wo Mitomycin C) in Advanced Head and Neck Cancer

88. A Phase III Current Practice Study of Antibiotic Treatment of Gastric Malt Lymphoma

89. A Phase III Study Comparing Cisplatin, Dacarbazine, Carmustine and Tamoxifen with Dacarbazine Alone in Patients with Advanced Melanoma

90. A Phase III Study: Prostate Cancer Intervention Versus Observation Trial (PIVOT): a Randomized Trial Comparing Radical Prostatectomy Versus Palliative Expectant Management for the Treatment of Clinically Localized Prostate Cancer

91. A Phase III Study: Randomized Multi-institutional Phase III Trial of Bep and High Dose Chemotherapy Versus Bep Alone in previously Untreated Patients with Poor and Intermediate Risk Germ Cell Tumors

92. A Bioavailability and Bioequivalence Study of Three Oral Formulations of Tretinoin Capsules (Ro 01-5488/109;/108; C 160449-01) and an Oral Solution in Healthy Volunteers

93. A Feasibility Study of Budr Labelling of Human Breast Cancer DNA in Vivo: Determination of Proliferation Fraction and Cell Viability in Individual Tumors

94. A Pilot Trial of Sequential Chemotherapy with Antimetabolite Induction, High-dose Alkylating Agent Consolidation with Peripheral Blood Progenitor Cell Support, and Intensification with Paclitaxel and Doxorubicin for Patients with High-Risk Breast Cancer.

95. A Study of the late Cardiac Effects of Two Different Adjuvant Chemotherapy Regimens in Women with Node Negative Breast Cancer Treated on SWOG-8897

96. A Study of The Prognostic Value of Flow Cytometric Data in Primary Colorectal Carcinoma

97. A Trial to Evaluate the Worth of Tumor Biomarkers Obtained by FNA or Core Biopsy in Predicting Response to Preoperative Chemotherapy & Long-term Outcome in Patients with Operable Breast Cancer who are Participating in NSABP Protocol B-27

98. Coagulation Studies in Acute Promyelocytic Leukemia

99. Colorectal Cancer Screening in First Degree Relatives of Colorectal Cancer Patients

100. Effect of Stem Cell Factor Presentation on AML Blasts

101. Estimation of Potential Doubling Time (TPDT) in Vivo by Iodo-deoxy-uridine

102. Fractionated Mixed Proton: Photon Radiation Therapy for Malignant Gliomas: Analysis of Local Control, Morbidity, and Patterns of Failure

103. Functional and Biomechanical Assessment of Selected Limbsparing Patients with Endoprosthesis

104. Gastrointestinal Tumor Repository Protocol

105. Human Immunodeficiency Virus and Cervical Cancer in Zambia

106. In Vitro Assay of Hematologic Tumors from Human Bone Marrow Samples

107. In Vivo Administered Iododeoxyuridine (IdUrd) as a Tool to Measure Tumor Cell Kinetics and Drug Distribution in Breast Cancer Tissue in Patients

108. Intracellular Rbc Thiopurine Pharmacokinetics in All Patients Receiving Oral 6mp vs Oral 6tg: Companion Study to CCG 1952

109. Laparoscopic Retroperitoneal Lymph Node Sampling Followed by Immediate Laparotomy in Women with Cancers of the Cervix

110. Local Excision Alone for Selected Patients with DCIS of the Breast

111. Minimal Residual Disease in Relapsed Acute Lymphocytic Leukemia: a Companion Study for CCG 1941

112. Molecular Biology of Pediatric Brain Tumors

113. Monitoring First Dose Recombinant Human Granulocyte-Macrophage Colony Stimulating Factor Toxicity

114. Positron Emission Tomography (PET) of Tumor Glucose Metabolism as an Indication of Tumor Response to Radiation Therapy

115. Prognostic Factors in Chemotherapy-treated Patients with Non-small Cell Lung Cancer

116. Prognostic Significance of Ki-67 Proliferative Index Utilizing the Mib-1 Antibody in Low Grade Gliomas in Young Children

117. Proliferative Potential of Primary Human Brain Tumors with Particular Reference to Intracranial Meningiomas and Pituitary Adenomas

118. Self-care Outcomes in Adolescents with Cancer

119. The Role of Salvage Prostatectomy for Radiation Failure in Prostate Carcinoma: a Phase II Trial

120. Validating PET Scan Measurements of Glucose Utilization in Human Extremity Sarcomas

INFECTIOUS CAUSES OF CANCER

Mr. Stokes: What is the extent of the infectious causes of cancer in the United States?

Dr. Klausner: The major types of virus-associated cancers in the United States are cervix (human papillomavirus), liver (hepatitis B and C viruses), Kaposi's sarcoma (human immunodeficiency virus and human herpesvirus 8), and lymphomas (Epstein Barr virus and human immunodeficiency virus). Stomach cancer also is common in the United States, and is strongly related to bacterial infection with *Helicobacter pylori*.

Two other cancers are clearly caused by viruses, anal cancer (human papillomavirus) and nasopharyngeal cancer (Epstein Barr virus), but these are uncommon in the United States.

The following table summarizes the number of cases of these cancer types in the United States during 1995 and the proportion attributed to an infectious cause:

Cancer type	Total U.S. cases in 1995	Est. No. (%) due to infectious cause
Cervix	15,800	15,010 (95%)
Liver	18,500	7,400 (40%)
Kaposi's sarcoma	10,000	10,000 (100%)
Non AIDS-Lymphomas	56,300	16,890 (30%)
AIDS-Lymphomas	2,400	2,400 (100%)
Stomach	22,800	13,680 (60%)
Total	125,800	65,380 (52%)

Mr. Stokes: What is the possibility of developing a vaccine against these types of cancers?

Dr. Klausner: A safe, highly effective vaccine is on the market against hepatitis B virus (HBV), which is a major cause of liver cancer worldwide. Although HBV is not a major cause of liver cancer in the United States, HBV vaccination will also reduce acute, life-threatening hepatitis and cirrhosis. Vaccines against human papillomavirus and *Helicobacter pylori* appear feasible and development of prototype vaccines against these agents is underway. Progress in developing a human immunodeficiency virus (HIV) vaccine has been slow. However, in addition to steady advances in understanding the nature of an effective immune response to HIV, the past year saw a breakthrough in the discovery of HIV "co-receptors" that are likely targets for a vaccine. Hepatitis C virus (HCV), which is unrelated to HBV but also contributes to liver cancer in the United States, presents serious obstacles to vaccine development, including no clearly defined, effective immune response to natural infection and great molecular diversity in the infecting strains. Vaccines against Epstein Barr virus and human herpesvirus 8 are possible, but as with HIV and HCV, there is no prototype of an effective vaccine against this class of viruses.

MAMMOGRAPHY

Mr. Stokes: In your opening statement, you state that "the success of early detection depends upon awareness, access and availability of tests that are sensitive and specific. All of the increase in breast cancer incidence that we saw through the 1980s [now leveled off] was the result of an increased detection of early disease and now 65 percent of breast cancer is found as localized disease compared to less than 40 percent twenty years ago with a 5-year survival rate of 92 percent." With this type of evidence

in hand, what was the rationale for the recent determination with respect to regular mammograms in women in the 40 to 49 year old age group?

Dr. Klausner: Stage shift, that is finding localized cancer versus late stage cancer is a necessary but not sufficient condition for reductions in mortality. A decrease in late stage incidence is a critical factor relating to reductions in mortality. The National Cancer Advisory Board, the chartered body responsible for advice to, and oversight of, the NCI is currently deliberating on this and other facts. It is anticipated that they will complete these deliberations in the next few weeks.

Mr. Stokes: How does this mesh with the recent decision of the consensus panel?

Dr. Klausner: The National Institutes of Health Consensus Development Conference panel examined all relevant studies on the subject of screening mammography in women ages 40-49. Studies in this analysis also included indicators of sensitivity and specificity. Several published studies have shown a statistically significant reduction in mortality for women who have mammography beginning some time in their forties, while other studies have not. The panel analyzed nearly 150 published research papers and more than 300 research abstracts over a period of two months, and listened to more than 30 oral presentations at the Consensus Conference. In its initial draft statement, the panel concluded that the available data do not warrant a single recommendation for mammography for all women in their forties. This draft statement and the data presented at the consensus development conference are being considered by the National Cancer Advisory Board in its deliberations regarding mammography.

Mr. Stokes: What major improvements have been made in mammography and other breast cancer screening technologies over the past few years, and how does this compare with what is currently being used by the majority of health care providers?

Dr. Klausner: There continue to be incremental -- but measurable -- improvements in conventional (film-based) mammographic systems that are available in the market place. These improvements are based on physical and chemical progress in silver-halide (film) technology.

Significant technological improvements in high-definition diagnostic and Doppler ultrasound now allow this modality to go beyond its traditional role of making the solid vs. cyst determination. One company claims that their high-definition ultrasound can work adjunctively with mammography to incrementally improve the benign vs. cancer determination, and this claim was supported by a clinical study and recently approved by the FDA.

Computer-assisted "back-up" or "second-read" image processing and display tools for mammography continue to make incremental improvements in performance. It was recently announced that new image analysis software may be capable of

maintaining high sensitivity while reducing the false-cues per image from the neighborhood of two to less than one per image in mammographic screening.

IMAGING TECHNOLOGIES

Mr. Stokes: Is there anything new on the shelf that is ready to go, and if so, how far away are we from having that technology widely used?

Dr. Klausner: It appears from public discussions that several manufacturers of digital mammographic systems are close to seeking Food and Drug Administration approval to market these systems. Digital mammography generates images directly on a computer rather than on traditional X-ray film. There, the images can be digitally enhanced perhaps allowing radiologists to detect smaller lesions. Another attraction of digital mammography is its use in telemedicine. Digital images can be readily transmitted from community clinics and remote areas to academic centers for expert radiologic consultation. This feature is of particular value to women in isolated or underserved areas by providing access to experts nationwide who can assist in the interpretation of their mammograms.

To optimize our efforts in breast cancer, NCI has established a Progress Review Group, to assess research opportunities in breast cancer, including those related to imaging, and to place the current activities of the NCI in the context of these opportunities. The Breast Cancer Progress Review Group along with the Prostate Cancer Progress Review Group represent the first uses of this mechanism. The Breast Cancer Progress Review Group will work with NCI staff in conducting an in-depth evaluation of the current state-of-knowledge regarding this area, survey the literature and related fields of science, and recommend to the NCI, through the National Cancer Advisory Board and the Board of Scientific Advisors, how the Institute can optimally respond to and stimulate research opportunities related to breast cancer including the improvement in detection technologies. This exercise will help set the NCI's research agenda in breast cancer by identifying and prioritizing those scientific opportunities that are most likely to expand our knowledge base and that will ultimately reduce the burden of this cancer. An important feature of the Progress Review Group is its linking of planning at NCI with a comprehensive program analysis and with all of the institute's program implementation mechanisms.

This year the NCI will be investing over $40 million in studies related to imaging in breast cancer. This includes improvements to X-ray based mammography, but also includes Several other technologies with potential for breast cancer detection that do not involve the use of radiation. These include magnetic resonance, both magnetic resonance imaging and something called magnetic resonance spectroscopy, to look at the characteristics of any possible lesions. There are other techniques as well, such Positron Emission Tomography—the PET scan, ultrasound, microwave, and photon migration. There is a proliferation of ideas that are beginning to be tested.

The NCI has created a new think tank to advise us on new opportunities in detection technologies. We are also proposing for the first time to have a standing group for clinical trials of diagnostic imaging procedures. I believe that the real break through in detection will come as we have more molecular diagnostics whose meaning we understand. Here, I think that the Cancer Genome Anatomy Project will yield tremendous return on our investment. As we identify the molecular characteristics of breast cancer cells that define their behavior, we will be able to develop increasingly "smart" diagnostics that may enable us to distinguish those breast cancers that are more aggressive from those that are less aggressive.

I have stated before and will restate for the record that it is very important to develop new means for early detection of breast cancer. However, while early detection improves prognosis, it does not guarantee a cure. We much not lose sight of the need for improvements, not only in detection, but also in therapies.

Mr. Stokes: Given that the data used to make determinations about the use of mammography is taken from trials conducted in other countries, have we compared follow-up treatment in those countries to the clinical and psycho-social care provided in the United States?

Dr. Klausner: The conduct of the randomized mammography screening trials around the world spanned the three decades of the 1960's, 1970's, and the 1980's. Over this period, the practice of follow-up treatments such as adjuvant chemotherapy and hormone therapy after initial surgery changed substantially. For example, the only trial performed in the United States, the HIP study, was conducted in the 1960's, well before the proof of benefit of adjuvant therapy had been tested and put into common use. Likewise, at the recent National Institutes of Health Consensus Development Conference, the Swedish investigators reported that very few women diagnosed with breast cancer received adjuvant therapy in their trial. In contrast, adjuvant therapy for women with breast cancer which had spread to regional lymph nodes was standard practice in Canada during the period in which the Canadian National Breast Screening Study (NBSS) was conducted. In this regard, Canadian practice was more similar to that of the United States than was Swedish practice. In the NBSS, investigators examined the medical records of women who died of breast cancer. They found that adjuvant therapy, surgery, and radiotherapy had been given appropriately to both women in the screened group as well as control women. This may have contributed to the relatively good survival rates in both arms of the NBSS trial. None of the screening trials directly addressed psycho-social issues after diagnosis of breast cancer.

The HIP study was the only study to include substantial numbers of African-American women (about 18%) of study participants). In that study, the overall effectiveness of screening was about the same for African-Americans as for the white majority. While not direct proof, this offers some evidence that similar outcomes are achievable in both racial/ethnic groups.

Finally, it is clear that the follow-up of mammograms differs from country to country. In Sweden, the ratio of breast biopsies to cancers found is generally lower than in the United States. This suggests that there is room to improve upon the biopsy:cancer ratio in our country so that fewer surgical biopsies would be needed to diagnose the same number of cancers. The efforts of the American College of Radiology to give specialty training to mammographers and of the Food and Drug Administration Mammography Quality Standards Act (MQSA) are likely to improve this aspect of quality control in breast cancer screening in our country.

AFRICAN AMERICAN WOMEN AND CLINICAL TRIALS

Mr. Stokes: There has been an appallingly low accrual of African American women to clinical trials, particularly randomized clinical trials. What do you plan to do differently to recruit African American women to the mammography screening trial and what message will you send to African American women that is different from what the message given to white women.

Dr. Klausner: Actually, the NCI has a very good history of racially and ethnically proportional representation on randomized clinical treatment trials. Indeed in certain diseases such as breast and prostate cancer we disproportionately over accrued Blacks to cancer treatment trials. The Institute published its accrual figures in the Journal of the National Cancer Institute in June of 1996. Among women enrolling on breast cancer treatment trials 10% of participants were African American while only 8.4% of breast cancer patients in the U.S. are African American and 3.2% of participants were Hispanic compared to 3.3% of breast cancer patients in the U.S. who are Hispanic.

The Institute has had difficulty enrolling minority women into many prevention and screening studies. The institutions that provide us with proportional representation on treatment trials are the same institutions that are unable to accrue minorities to prevention trials. The Division of Cancer Prevention and Control and the newly formed NCI Office of Special Populations have published on and continue to study the dynamics of accrual to clinical trials. A key theme among participants in prevention trials is they tend to be highly educated and of higher than average socioeconomic status.

For NCI treatment clinical trials, minority representation among the individuals enrolled in the trial reflects their representation among individuals with the disease under study. For treatment clinical trials approximately 183,000 individuals are participating, of which nearly 88,000 are women and 95,000 are men. The NCI has also sponsored a national conference, the topic of which was the accrual and retention of minorities in clinical trials. Additional regional conferences on this topic will be held in the coming year utilizing NCI support.

One major NCI research effort that has been successful in recruiting minority women is the Breast Cancer Screening Consortium. It is evaluating community-based

mammography screening. Two sites have significant percentages of black or Hispanic women in their study samples: Los Angeles with 27% black and 37% Hispanic women and North Carolina with 15% black women.

The NCI Office of Special Populations is convening meetings of persons interested in breast cancer in special populations -- both advocates, medical and public health professionals. These experts are being asked to help shape the message we should send to minority women about the importance of participating in these non-therapeutic studies as well as help determine how to convey that message.

PROSTATE CANCER INITIATIVES

Mr. Stokes: Last year alone, more than 314 thousand new cases of prostate cancer were projected to be diagnosed, and 41 thousand deaths from the disease. African American males have the highest rate of prostate cancer than any other segment of the world's population. What progress do you have to report with regard to the institutes' prostate cancer initiative in general, and also as it relates to African American males?

Dr. Klausner: NCI research efforts concerning prostate cancer, and this specific population, are and have been vigorous and varied encompassing development of new treatments, epidemiology and prevention research, the study of practice patterns, and basic science studies to understand the disease at a molecular level. A Prostate Cancer Progress Review Group is being established. It along with the Breast Cancer Progress Review Group represent the first use of this mechanism. The Prostate Cancer Progress Review Group will assess research opportunities in prostate cancer and the activities of the NCI in the context of these opportunities. The Prostate Cancer Progress Review Group will work with NCI staff in conducting an in-depth evaluation of the current state-of-knowledge regarding this area, survey the literature and related fields of science, and recommend to the NCI, through the National Cancer Advisory Board and the Board of Scientific Advisors, how the Institute can optimally respond to and stimulate research opportunities related to prostate cancer. This exercise will help set the NCI's research agenda in prostate cancer by identifying and prioritizing those scientific opportunities that are most likely to expand our knowledge base and that will ultimately reduce the burden of this cancer. An important feature of the Progress Review Group is its linking of planning functions at NCI with a comprehensive program analysis and with all of the institute's program implementation mechanisms.

NCI has recently established the Urologic Oncology Branch within the Division of Clinical Sciences. One of the major areas of emphasis of this branch will be prostate cancer. In addition, NCI has established a new fellowship program in urologic oncology that will also have as a major focus NCI's commitment to reduce the burden of prostate cancer in all segments of our society.

The NCI recently conducted a large interview-based study of prostate cancer in African Americans and whites. Analysis of the results have not thus far revealed any

specific factor that could explain the racial differences in risk. However, further studies are underway, including an extensive evaluation of the role of different components of the diet. In addition, since a number of molecular alterations have been reported recently in prostate tumors, stored tumor specimens from these study subjects are being obtained to look for tumor-stage and race differences in these molecular markers, and the potential relation of the markers to possible risk factors. The molecular events associated with the initiation and progression of prostate cancer are poorly understood, and NCI researchers continue to initiate research aimed at learning more about these changes.

The NCI has issued a Request for Applications which was co-funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Institute of Environmental Health Sciences (NIEHS) in order to stimulate innovative molecular epidemiologic research into the origins of prostate cancer. Eleven epidemiologic studies were funded or co-funded by NCI in September 1995 for three years. Eight of the 11 studies include an assessment of risk factors among African American men.

A consortium of investigators is being formed to collaborate on interdisciplinary studies following the recent discovery localizing the prostate cancer susceptibility gene on chromosome 1. Leads from this effort may help to clarify genetic and gene-environment interactions responsible for black-white difference in risk. NCI plans to support physical mapping of a region of chromosome 8 thought to contain a gene involved in prostate cancer, and to isolate and screen candidate tumor suppressor genes on this chromosome.

Researchers continue to evaluate anti-cancer agents that appear to inhibit tumor growth though novel mechanisms. One agent which has shown clinical promise is suramin. In the mid-1980's, suramin was tested as an antiviral agent in patients with AIDS because of its ability to inhibit reverse transcriptase *in vitro*. During this trial, it was noted that some AIDS-associated malignancies, e.g., Kaposi's sarcoma and high-grade B-cell lymphomas, regressed under suramin therapy. Suramin has since been tested as a treatment for a variety of human solid tumors. The greatest potential benefit of suramin appears to be in the treatment of patients with advanced prostate cancer. Other agents currently being evaluated clinically are high-dose tamoxifen, thalidomide, and CAI in patients with hormone-refractory prostate cancer.

NCI clinical studies in prostate cancer have significant African-American participation. A recent NCI study shows that 14.7% of men enrolled onto NCI sponsored prostate cancer treatment trials are Black while 10.3% of Americans diagnosed with prostate cancer are Black. Serum and tissue samples from NCI sponsored treatment, prevention and screening trials are being used to study racial differences. To date NCI sponsored studies have shown that increased length of the trinucleotide CAG repeat on the androgen receptor gene seem to correlate with decreased prostate cancer risk. NCI sponsored studies have also shown that blacks

have shorter CAG repeats than whites. This may be a biologic reason explaining, in part, why blacks have a higher incidence and mortality from prostate cancer.

NCI is planning to study CAG repeat differences among black and white men in the Prostate Cancer Prevention Trial. The major goal of the trial is to determine if a drug finasteride can prevent prostate cancer. By following these men over the next decade the hypothesis that shortened CAG repeat length confers greater risk of prostate cancer may be validated. These studies, though preliminary, are the first to link a specific germline genomic polymorphism and prostate cancer risk. The ability to stratify men according to prostate cancer risk by a relatively simple genomic test could potentially alter current approaches to prostate cancer screening and/or prevention efforts.

An NCI funded researcher is studying the enzyme 5-alpha reductase in a special population in the Dominican Republic. There is a suggestion that individuals with lower 5-alpha reductase activity have a lower risk of prostate cancer. It is known that individuals who genetically lack 5-alpha reductase do not develop prostate cancer. There is also some evidence of a racial variation in 5 alpha reductase activity. Some studies suggest that blacks have a higher average 5-alpha reductase activity than whites. Working in collaboration with Howard University, NCI scientists will analyze a large number of stored prostate samples from African American patients with prostate cancer. This will compare those results to tissue available from non-African American patients, looking at a series of molecular endpoints. Samples from patients currently being treated at Howard University and NCI will also be obtained for analysis.

The NCI has begun the Cancer Genome Anatomy Project (CGAP). The first two goals of CGAP are designed to build an infrastructure of resources, information, and technologies that will provide a platform for the establishment of an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. An early component of CGAP is the preparation to tumor sample for generation of cDNA libraries. During the first year of CGAP libraries will be produced from tissues derived from prostate tumors -- as well as from breast, colon, lung, and ovarian tumors -- and from corresponding non-tumor tissue samples. This project is aimed at accelerating our ability to develop new markers for prostate cancer and to provide accurate and predictive diagnostic tests. Prostate cancer is not one disease, and the CGAP is intended to identify the molecular characteristics that distinguish one prostate cancer from another in ways that will guide future approaches to the design and choice of effective interventions.

PROSTATE CANCER TREATMENT AND EARLY DETECTION

Mr. Stokes: Where are we with regard to reaching some consensus on treatment and early detection?

Dr. Klausner: The value of any screening test used in a healthy population is dependent upon the incidence of the disease, the mortality associated with that incidence as well as on the performance characteristics, shortcomings, and risks of the screening procedure. More than fifteen organizations in the U.S., Canada, and Europe have expressed concern that the benefits prostate cancer screening is unproven and only three organizations have recommended routine screening of the population using the currently available procedures. Screening for prostate cancer is widespread only in the U.S. The studies to determine definitively if prostate cancer screening saves lives such as the NCI-sponsored Prostate, Lung, Colon, and Ovarian Cancer Screening Trial will take still a number of years to complete. Since the results of these essential trials are not yet available, the data on which the three organizations have recommended screening is very soft. A true consensus about the efficacy screening and treatment can only reached after completion of well-designed clinical trials. There is clear consensus in support of these trials.

The efficacy of radical prostatectomy as a treatment of low stage disease also continues to be a question. It is being addressed by the Prostate Cancer Intervention Versus Observation Trial. This high priority NCI study is being run in a number medical centers across the country. The NCI and its cooperative groups are also a discussing a trial comparing radiation therapy and observation for men with low stage disease. Because men in these trials have to be followed for some time, the answers will not be available for five to ten years. There is less controversy in the treatment of advanced disease, current studies are focusing on whether hormonal therapy is better early in the course of disease versus later in the course of disease. The NCI is committed to providing men with accurate, up-to-date information regarding the pros and cons of prostate screening so that individuals can make an informed decision in conjunction with their physician.

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In addition, NCI has recently established the Urologic Oncology Branch within the Division of Clinical Sciences. One of the major areas of emphasis of this branch will be prostate cancer. In addition, NCI has established a new fellowship program in urologic oncology that will also have as a major focus NCI's commitment to reduce the burden of prostate cancer in all segments of our society.

AFRICAN AMERICANS AND PROSTATE CANCER

Mr. Stokes: With respect to African Americans, what is the institute doing to ascertain why this segment of the population is more prone to prostate cancer, and why the mortality rate from the disease is exceedingly high?

Dr. Klausner: Of the studies described above several are specifically aimed at defining the etiology of prostate cancer and may help explain why Blacks have a higher mortality. Among them are ongoing projects such as: the case control interview study which is intensively looking at diet and prostate cancer; the search for a prostate cancer gene; and studies of hormonal differences such as the 5 alpha reductase study in the Dominican Republic. There are new projects such as the study of CAG repeat length and the Cancer Genome Anatomy Project which is likely to prompt other studies that may answer the question "Why do Blacks have a greater incidence and mortality from prostate cancer?"

The study that compares prostate cancer tissues taken from Black and White patients may lead us to better understanding of the differences in biologic behavior, if differences do exist. Staff from the NCI and the Department of Defense have collaborated in a study of treatment data from an equal access system (the DoD) and shown that equal treatment yields equal outcome within stage. This finding suggests that all NCI efforts to improve prevention, diagnosis and treatment of this disease benefit all patients equally. However, NCI staff analyzing SEER Program data have shown that there are tremendously differing patterns of care among black and white Americans with prostate cancer.

Mr. Stokes: What major community-based programs focusing on prevention, detection, diagnosis, and treatment are underway, and what is planned for FY 1998?

Dr. Klausner: The Prostate Cancer Prevention Trial (PCPT) began in 1993. This trial is assessing whether hormonal manipulation with finasteride will prevent prostate cancer. It involves more than 18,000 men from more 220 medical centers in the U.S. Two-thirds of these sites are community medical centers involved in either the NCI Community Clinical Oncology Program or the NCI Community Group Outreach Program.

Other studies with significant community involvement are the Prostate Intervention Versus Observation Trial (PIVOT) and the Prostate, Lung, Colon and Ovarian Cancer Screening (PLCO). PIVOT is an NCI high priority trial to determine if radical prostatectomy is effective and is currently being run in nearly one hundred

medical centers across the country. The PLCO study is designed to answer the question "Does prostate cancer screening save lives?" and is being run in ten centers around the country.

The nature of the disease is such that the PCPT, PIVOT, and PLCO, which all began more than three years ago, are not likely to give us definitive answers for several years, perhaps early in the next century. This does not mean that we are not learning important information now.

The NCI Office of Cancer Communications has developed a productive working relationship with the "Us Too", a prostate cancer support group. Over the next year there are plans to develop objective information for men considering screening and for men considering prostate cancer treatment options. The NCI funded National Black Leadership Initiative on Cancer is also planning a major community effort aimed at explaining the significant questions concerning prostate cancer and prostate cancer screening in 1998. Our goal is that men will have the information to make informed decisions with their physicians.

CANCER GENETICS AND MOLECULAR BIOLOGY

Mr. Stokes: What major activities are underway to further the understanding of cancer genetics and molecular biology?

Dr. Klausner: Recent discoveries have enhanced our understanding of how tumors develop. We now know that cancer is a disease caused by mutations in key target genes that give selective advantage to the growth of a tumor cell. The accumulated mutation allows the cells to grow out of control. The most direct and ultimately the most effective approach to preventing, detecting, diagnosing, and treating cancer is to learn the properties of responsible genes. Genes those dysfunction accounts for cancer are being rapidly identified. These genes ultimately determine the behavior and the relentless growth of cancer cells. Although our knowledge about these genes is growing daily, it is still incomplete, and many cancer genes remain to be found. Ideas abound on ways to use the new information for cancer prevention, diagnosis, prognosis, detection, and treatment. In short, the whole field of cancer research has been revolutionized and energized by this recent and continuing genetic revolution.

The research programs of the NCI take place in three settings: the laboratory, the clinic, and the community. In the laboratory, research is pursued on the biology of cancer, the fundamental properties of cancer-causing agents and processes, and the body's defense against and response to cancer. In the clinic, patient-oriented research is carried out concerning prevention, detection, diagnosis, treatment, and rehabilitation. In the community, research is carried out on the causes, risks, predispositions, incidence, and behavioral aspects of cancer. Each of these settings has been profoundly affected by the genetics revolution. In FY1996, the NCI expended over $1.06 billion in support of over 3,600 separate research projects. Many of these projects are aimed at understanding genetic factors related to cancer predisposition, genes involved in

tumorogenesis, genes involved in the fatal consequences of oncogenesis, as well as gene-gene and gene environment interactions.

In addition, several new and highly interesting projects have been identified by the NCI as principle targets for expansion in this area. The NCI has begun its ambitious Cancer Genome Anatomy Project (CGAP) to convert emerging biological knowledge into clinical tools. The growing understanding of the roles of specific genes in the development and behavior of cancer offers an unprecedented set of opportunities to fundamentally alter our approach to cancer. NCI has identified a new set of initiatives to produce a new generation of knowledge and technology to read the molecular fingerprint of cancer cells to aid in early detection, diagnosis, prevention and treatment of cancer. These programs are intended to provide us with the tools to unravel the critical interactions of genes with diet, hormones and the environment that have eluded us for so long.

The first two goals of CGAP are designed to build an infrastructure of resources, information, and technologies that will provide a platform for the establishment of an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. An early component of CGAP is the preparation of tumor samples for generation of cDNA libraries. During the first year of CGAP, libraries will be produced from tissue derived from tumors--breast, colon, lung, ovarian, and prostate tumors-- and from corresponding non-tumor tissue samples. This project is aimed at accelerating our ability to develop new markers for cancer and to provide accurate and predictive diagnostic tests. Cancer is not one disease—even cancers that share site and appearance differ from one another at the molecular level. The CGAP is intended to identify the molecular characteristics that distinguish one cancer from another in ways that will guide future approaches to the design and choice of effective interventions.

Another major new initiative of the NCI is the Cancer Genetics Network. The recent discovery of specific genes that are predictive of predisposition to cancer will only benefit people if we rapidly move to provide interested individuals with an expanded opportunity to seek information, counseling and testing at centers of excellence. In addition, we must establish the best surveillance and interventions to reduce the chances that individuals at risk will develop cancer. This will require additional clinical research. The Cancer Genetics Network will address these issues by establishing a network of centers of excellence in human cancer genetics to enhance our ability to answer the many pressing questions that these new discoveries raise.

While recent advances in the understanding of the genetic basis of tumor development represents an extraordinary opportunity for investment in cancer research, the need is critical for an integration of basic, clinical, and epidemiologic research in this area. The aim must be not only to identify and characterize genes which modify inherited predisposition to cancer, but also to assess the efficacy of risk-reduction strategies. The NCI intends to facilitate the construction of the Cancer Genetics

Network as a dynamic informatics and research infrastructure linking institutions that test individuals for hereditary cancer susceptibility and provide counseling and intervention to these individuals.

Mr. Stokes: What investment opportunities are built into the FY 1998 budget request to further work in this area?

Dr. Klausner: The area of Cancer Genetics was identified as an area of extraordinary investment opportunities and it is a field that we are moving rapidly. The NCI deems that, furthering the study of cancer genetics and molecular biology, will greatly enhance our ability to understand and control cancer.

We desire to identify and characterize every major human gene responsible for inherited predisposition to cancer and, with this knowledge, transform medical practice. The discovery that the development of cancer is driven by mutations in our genes, the identification of certain genes that predispose individuals to cancer, and recent advances in our understanding of human genetics and molecular biology make this a compelling area of research.

Since each cancer is ultimately defined by its particular pattern of altered gene activity, these patterns will define what each cancer is and how many different cancers there are. By defining these molecular patterns, we will be able to distinguish each cancer from its normal counterpart. Advances in our ability to detect, diagnose, and treat each cancer will most likely be found in these differences.

Therefore, the NCI seeks to establish a comprehensive genetics initiative. This will give us insight into cancer at its most fundamental levels. This will allow us to identify high-risk individuals and develop new interventions, both preventive and therapeutic, for people with, or at high risk for, cancer.

COLLABORATIVE EFFORTS

Mr. Stokes: As I am sure you would agree, the cancer research field is broader than the NCI. Would you bring the committee up-to-date with respect to collaborative efforts that the institute have underway with other agencies?

Dr. Klausner: As I'm sure you know, the NCI was asked following last year's testimony to prepare a comprehensive report addressing the NCI's coordination activities. That report has been forwarded and should be available to you shortly. However, I would be pleased to provide a summary of its contents here.

The reduction in cancer death rates that has occurred since about 1990 is but one very tangible result of the Nation's commitment to cancer research. In addition to improvements in mortality rates for many malignancies, the National Cancer Program (NCP) has achieved important improvements in the quality of life for America's 10 million cancer survivors through less disfiguring and less damaging surgical

procedures, better pain control, and more effective medication for the side effects of cancer therapy. Progress against cancer should also be measured in the growth of knowledge about the group of diseases that collectively bear that name. It is upon this knowledge base that the progress of the next century will rest.

This progress will be enhanced by the coordination of the many activities that comprise the NCP, and it is in this coordination that the NCI has and will continue to take the lead. NCI recognizes and stimulates research opportunities through its infrastructure of discovery that leads to understanding of the etiology and biology of cancer and thus provides the means to control and prevent it. NCI facilitates exchange of information, seeks to ensure that overlap and duplication are avoided, and supports the many areas of expertise needed to overcome cancer. NCI's activities in leading the NCP often involve interactions with entities outside of the NCI -- individuals, groups, organizations, and other components of the Federal government. The brief report mentioned above will outline the types of NCI efforts related to coordination of the NCP and provide selected, significant examples of these activities to underscore the progress made in the area of coordination.

Mr. Stokes: Why are these efforts critical to the fight against cancer?

Dr. Klausner: These efforts are necessary to expedite the nation's fight against cancer. While NCI is the primary Federal agency whose mission is cancer research, we have extensive collaborations. The key is to communicate all our efforts to avoid overlap and duplication between the NCI and the larger community of cancer researchers, cancer care providers, cancer patients, and cancer survivors. I believe we have a very effective process and good working relationships with our many collaborators. Many research questions deal with issues that are also related to the mission of other ICDs within the NIH or other entities within the Federal government. This includes numerous collaborations with other Federal entities in the form of Working Groups, Task Forces and collaborations on areas of mutual interest.

COMBINATION THERAPIES

Mr. Stokes: What major studies are underway to determine and evaluate the benefits of combinations of therapy including combination chemotherapy with radiation?

Dr. Klausner: Malignant tumors consist of cells that are capable of invading the surrounding tissues and establishing metastatic deposits at distant sites in the body. The major modalities for treating malignancies include surgery, radiation therapy, and chemotherapy. Surgery and radiation therapy are effective for treating localized disease, and chemotherapy is primarily effective for treating metastatic deposits of malignant cells as well as enhancing the effects of radiation therapy for localized malignancy. Metastatic deposits of malignant cells may be undetectable, either by physical exam, imaging techniques, or biomarkers, and the capacity to cure a patient

may be limited by the presence of these viable micrometastates outside of the local treatment field.

Clinical trials vary in their accrual size and scope. Dependent on the questions to be addressed the study population within the trial will range significantly. All of the NCI sponsored clinical trials are included within the comprehensive, computerized cancer information database found on the NCI Web site. Over 1,500 clinical trials are identified, many of which utilize combination therapies -radiation, surgery, and chemotherapy. About 30% of NCI-sponsored trials involve radiation therapy or radiosensitization.

There are a number of currently active major randomized clinical trials in malignancies in which both locoregional disease and distant metastases are major determinants of morbidity and mortality. These malignancies include those of the central nervous system, gastrointestinal tract, gynecological organs, head and neck, lung, and prostate. The objectives of some of these studies are to determine if combined modality therapy with both chemotherapy and radiotherapy gives superior outcome in terms of local and regional control, palliation of symptoms, and overall survival, compared to single modality therapy with either radiotherapy or chemotherapy. Objectives of other studies are to define the proper sequencing of these two modalities - e.g., given sequentially, or concurrently -, the role of altered fraction and dose schedules of the radiotherapy, and to identify whether radiosensitizers lead to enhanced tumor control and survival.

Active major trials in central nervous system malignancies include a pediatric trial comparing standard with dose-intensified chemotherapy with or without radiotherapy to the brain; a pediatric trial comparing radiotherapy to the brain and spinal cord with one of two sequential chemotherapy regimens; a trial comparing sequential chemotherapy + radiotherapy with concurrent chemotherapy + radiotherapy; a trial comparing radiotherapy + chemotherapy with and without a radiation sensitizing drug; and a trial comparing single or double agent chemotherapy with either standard or altered fraction radiotherapy.

An ongoing major trial in gastrointestinal malignancy is comparing chemotherapy with either high or conventional dose radiotherapy in cancer of the esophagus. There are trials in gynocological malignancies of the cervix, which include a trial comparing standard radiotherapy with 3 different regimens of chemotherapy; a trial comparing radiation therapy + surgery with or without chemotherapy; a trial comparing radiation therapy with or without concurrent chemotherapy; and a trial in vulvar cancer, a six-arm study of surgery followed by either observation or radiotherapy alone to those with negative lymph nodes, or to more extensive radiotherapy with or without chemotherapy to those with evidence of tumor in their lymph nodes.

Ongoing major trials in head and neck include a three-arm study comparing radiotherapy alone vs radiotherapy + chemotherapy vs altered fractionation radiotherapy + chemotherapy; a trial comparing 3 different methods of organ

preservation for cancer of the vocal cords, and a trial comparing radiotherapy with or without chemotherapy to patients after they have been surgically resected, but are at high risk for recurrent tumor.

Active major trials in lung include trials in locally advanced non-small cell lung cancer: a trial comparing chemotherapy with either standard or altered fractionation radiotherapy; a trial comparing chemotherapy and radiotherapy either given in sequence or given concurrently. One active trial in prostate cancer compares hormonal therapy with or without radiotherapy.

MOLECULAR CHARACTERISTICS OF CANCER

Mr. Stokes: What is there that is new to report with regard to the molecular characteristics of cancer?

Dr. Klausner: Technologic advances are making it possible to characterize the molecular alterations present in tumors more rapidly and more completely. For instance, refinements in the technique of Comparative Genomic Hybridization (CGH) have resulted in the ability to analyze archival tumor specimens so that studies requiring many years of patient follow-up can be performed on specimens collected 10-20 years ago. CGH is a technique that allows direct, simultaneous visualization of changes in the number of copies of DNA sequences across all chromosomes. Researchers have now applied this technique to identify regions of chromosomal amplification and deletion in prostate cancer that are associated with metastasis. These regions are being studied further by techniques that have greater resolution to identify the specific genes that are involved.

Genomic scanning technologies have recently identified mutations in a gene important in the induction of cell death in colon tumors with genomic instability. The initiation and progression of cancer in individuals with genomic instability syndromes, such as hereditary nonpolyposis colon cancer (HNPCC), results from secondary mutations in genes important in regulation of the cell cycle. Ongoing studies will determine whether inactivation of pathways leading to cell death plays a role in cancer initiation in these high risk patients.

The NCI recently launched the Cancer Genome Anatomy Project (CGAP) to identify all the genes expressed in tumors and to make nucleic acid sequence data and reagents available to the research community. Identification of molecular alterations in tumor cells will provide insight into the biological processes underlying cancer. As part of this project, the institute is making a major investment in the development of new technologies to speed the process of gene discovery and characterization. The long term goals of this project are to assure translation of the knowledge and technologies to improve the care of cancer patients.

Mr. Stokes: How does this knowledge help further advance cancer treatment, early detection, and prevention?

Dr. Klausner: Knowledge of specific alterations that play a role in cancer initiation and progression may identify markers that facilitate earlier detection of disease. Particular alterations may aid in the choice of specific therapies tailored to the individual patient. For example, patients with tumors that demonstrate genomic instability may benefit from therapies designed to induce cell death through an unaltered pathway. Other alterations may be used to determine, at the time of diagnosis, whether a tumor is likely to be aggressive or indolent and help the physician and patient decide on the management of the disease. This is of significant importance in early stage breast cancer and in organ-confined prostate cancer. Evaluation of the clinical importance of molecular alterations found through the CGAP will require considerable further research, but we are very confident that significant benefit will accrue from this initiative.

DIET AND CANCER

Mr. Stokes: With regard to the relationship between diet and cancer, what major research initiatives and/or research projects are underway to study the relationship between diet and cancer in African American women?

Dr. Klausner: Diet plays a significant role in cancer risk, and the NCI supports a number of studies aimed at clarifying the role of diet in cancer. Several of these studies have particular relevance to dietary factors and cancer incidence in minority populations. In a prospective study, an NCI grantee at Boston University has enrolled approximately 65,000 African American women to investigate the relation of obesity and other factors, including cigarette smoking, physical activity, alcohol use, diet, exogenous estrogen use and reproductive factors to the incidence of various cancers. In another study, an NCI grantee at the University of Hawaii has enrolled 35,000 African American men and women in a prospective multi-ethnic study to investigate cancer risk associated with dietary and other factors. Since dietary and nutritional factors are thought to be associated with a significant proportion of cancer, whenever feasible, NCI epidemiologic studies are designed to collect information to elucidate the etiologic role of these factors, especially as they may influence the ethnic and racial patterns of cancer incidence.

In addition, the NCI has two major initiatives that involve studies of dietary change among African Americans. The first initiative is the "Dietary Change Program for African Americans," which encourages investigator-initiated grant applications for research to develop and evaluate the effectiveness of culturally sensitive intervention strategies to assist African Americans in adopting eating patterns consistent with the NCI Dietary Guidelines. Twenty applications have been received in response to an ongoing Program Announcement; two studies were favorably reviewed and funded during FY 96 and an additional two studies are expected to be supported during FY 97. The second major NCI initiative aimed at cancer prevention through dietary change among African Americans is included as part of the 5 A Day for Better Health program. Two of the research projects supported through the 5 A Day program are targeting

dietary change among African Americans. Total support for these two studies is approximately $4 million.

CANCER IN MINORITY POPULATIONS

Mr. Stokes: What specifically is the institute doing to strengthen its research, research training, and outreach efforts which focus on breast, lung, and colorectal cancers particularly with regard to their impact on minority populations?

Dr. Klausner: The NCI remains committed to reducing the burden of cancer in all segments of the population. Toward this end an internal Special Action Committee was formed at my request to review NCI's activities and program mechanisms to ensure that the cancer problems of minorities, the underserved, and persons age 65 and over were being adequately addressed. The Special Action Committee issued its Report and Recommendations in May 1996. The report was intended to identify the specific efforts to deal with the cancer problems among these populations and to indicate opportunities for further action. Issues addressed by the Special Action Committee included the definition of minority and special population activities, monitoring of minority training, organization of NCI programmatic data on minority/special population activities, leadership and coordination of minority and special population activities, input of NCI staff into management of minority and special population activities, and identification of research opportunities.

As a tangible outcome of this analysis, I established in June, 1996 the Office of Special Populations within the Office of the Director. The Office of Special Populations will advise and guide the Director and serve as a focal point to provide leadership and coordination on research related to minorities and special populations. The office will coordinate NCI programs addressing scientific questions pertinent to these populations. Important elements of this office are the evaluation of current NCI programs and planning new initiatives. Through its evaluation function the office is determining what questions are important to special populations, what questions are being addressed through NCI's programs and portfolio of grants, and what research questions should be raised. Established epidemiologic data bases and current research findings will be used to define scientific questions pertinent to special populations. The office will develop concepts for new programs that need to be implemented by the scientific divisions of the NCI. An advisory committee of NCI staff will help define these questions. The expertise of individuals from the community will also be called upon.

NCI has expanded its surveillance efforts in tracking cancer rates for minorities. The institute has sponsored a number of patterns-of-care studies looking at the differences in cancer care among regions and among racial groups in the U.S. The NCI Black-White study reviewed differences in cancer biology, treatment, and outcomes in Blacks and Whites with bladder, uterus, breast, and colon cancer in several regions of the U.S. Several outreach initiatives have been established including the National Black Leadership Initiative on Cancer, the Hispanic Leadership Initiative on Cancer,

and the Appalachian Leadership Initiative on Cancer providing grants to non-government agencies to provide information concerning cancer prevention, early detection, and treatment to some special populations. For NCI treatment clinical trials, minority representation among the individuals enrolled in the trial reflects their representation among individuals with the disease under study. The NCI has also sponsored a national conference, the topic of which was the accrual and retention of minorities in clinical trials. Additional regional conferences on this topic will be held in the coming year utilizing NCI support.

The National Office of Samoan Affairs and the University of California at Irvine have entered a cooperative agreement with the NCI to conduct a phase I study to develop and validate needs assessment instruments to measure the effectiveness of cancer control methods among American Samoans. Findings from the review of cancer incidence data have provided valuable insights about the cancer control needs of this minority population. The most common cancers among American Samoans -- breast, lung, and cervix among women and lung in men-- are diseases for which primary or secondary preventative measures are available. Findings from the cancer incidence data also suggests that American Samoans receive diagnosis of cancer of all sites at later stages of the disease than does the general population.

A request for grant applications was issued in 1995 to improve the geographic, rural, and minority representation within the Breast Cancer Surveillance Consortium. An additional major NCI research effort evaluating community-based mammography screening is the Breast Cancer Screening Consortium. Two sites have significant percentages of black or Hispanic women in their study samples: Los Angeles -- 27% black and 37% Hispanic -- and North Carolina -- 15% black. In April, 1996, data on cancer incidence and mortality by specific racial/ethnic group were published in *Racial/Ethnic Patterns of Cancer in the United States, 1988-1992.* The groups represented are Alaska Natives, American Indians, Blacks, Chinese, Filipinos, Hawaiians, Japanese, Koreans, Vietnamese, Whites, Hispanics, White Hispanics, and White non-Hispanics. Efforts have been made to link routinely collected cancer incidence data to other data sources containing additional information on access to health care, health care costs, treatment and diagnosis. These data provide important clues in understanding differences in cancer rates and ultimately provide a blueprint for research and intervention. In response to the recent changes in prostate cancer incidence rates, the NCI has initiated a Surveillance, Epidemiology and End Results (SEER) special study involving 3,500 men in six SEER areas. An over sampling of African American and Hispanic men was built into this study.

ENVIRONMENTAL JUSTICE RESEARCH ACTIVITIES

Mr. Stokes: As you know, compared to the general population, African American and other minority populations have a disproportionately higher risk of developing cancer. Can you update the subcommittee with respect to the NCI's environmental justice research activities?

Dr. Klausner: NCI continues to conduct studies into environmental determinants of cancer in minority and low income communities. An example of one such initiative is the proposed Triana, Alabama study of DDT exposure and breast cancer risk among African American women. A DDT production plant was discovered to have discharged large quantities of the pesticide into tributaries of the Tennessee River for several decades, and local residents who consumed fish from the river accumulated body burdens of the chemical. Given this exposure and the availability of previously collected information and blood samples, NCI has proposed to investigate the relation between tissue levels of DDT and risk of breast cancer in this predominately African-American population.

As part of its efforts to identify and evaluate cancer hazards in the workplace, the NCI intramural research program has developed the Computerized Occupational Referent Population System (CORPS) database. This database now includes sufficient number of minority entries to permit cancer risks to be analyzed by racial and occupational group. Other efforts are attempting to identify environmental -- including lifestyle -- factors that may be related to the higher rates of multiple myeloma and cancers of prostate, esophagus and pancreas among African-American men. In addition, studies are underway to investigate racial disparities in rates of breast cancer among African American and Asian women, and cervical cancer among Hispanic women.

NCI's intramural program along with NIEHS and the Environmental Protection Agency (EPA) are collaborating on a large, comprehensive evaluation of the health risks associated with agricultural exposures. Special efforts are being made to enroll minority study participants so as to allow an assessment of risk factors that may be unique to this population. The collaboration of the three agencies will permit a comprehensive evaluation of a variety of environmental exposures -- for example, pesticides, solvents, dusts, and animal viruses — and their relation to health outcomes -- such as cancer, neurologic disease, and reproductive effects. In the extramural program, NCI is supporting a wide variety of epidemiologic studies aimed at clarifying the racial variation in cancer environmental risks among minority groups.

The NCI is continuing to collaborate with the National Institute of Aging on a series of research projects to investigate the effects of advanced age on the diagnosis and treatment of cancer in the elderly. A study is underway to assess the availability and quality of data in medical records regarding co-morbid conditions and functional limitations at initial diagnosis of cancer among the elderly. This study involves over 7,000 patients diagnosed with cancer of the colon, prostate, breast, ovary, cervix, bladder, and stomach in six SEER catchment areas.

The National Office of Samoan Affairs and the University of California at Irvine have entered a cooperative agreement with the NCI to conduct a phase I study to develop and validate needs assessment instruments to measure the effectiveness of cancer control methods among American Samoans. Findings from the review of cancer incidence data have provided valuable insights about the cancer control needs of this

minority population. The most common cancers among American Samoans -- breast, lung, and cervix among women and lung in men — are diseases for which primary or secondary preventative measures are available. Findings from the cancer incidence data also suggests that American Samoans receive diagnosis of cancer of all sites at later stages of the disease than does the general population.

Several grants from the NCI are investigating the role of environmental exposures in ethnic populations. These include a case-control study of women in the New York metropolitan area is evaluating the association of exposures to pesticides and polychlorinated biphenyls and breast cancer risk. The study population will consist of approximately 67% African-American or Hispanic women.

Another study is evaluating numerous potential biomarkers of lung cancer susceptibility in African-American, Mexican-American, and Caucasian men and women. Analysis will include ethnic comparisons by lung cancer cell-type, epidemiologic data, demographic characteristics, environmental exposures, and biomarker interactions.

There is a case-control study of American Indian women is assessing risk factors of cervical dysplasia including human papillomavirus (HPV) infections, dietary history, sexual behavior, lifestyle factors, and past sexually transmitted diseases. The data obtained will allow comparison with an ongoing, similar study in New Mexico Hispanic and non-Hispanic white women.

An epidemiologic study is investigating the synergistic relationship between HPV and diet, cigarette smoking and race in the development of cervical intraepithelial neoplasia (CIN). The study population is being recruited from a South Carolina health department family planning clinic and will be comprised of approximately 60% African-American.

ENVIRONMENTAL JUSTICE COLLABORATIVE ACTIVITIES

Mr. Stokes: With regard to environmental justice, what major progress do you have to report to the committee with respect to collaborative research efforts that are underway between NCI and NIEHS?

Dr. Klausner: The NCI spends over $350 million a year on environmental carcinogenesis research. As part of this effort, the NCI collaborates with the NIEHS on several environmental justice research activities.

The Northeast/Mid-Atlantic Breast Cancer Study made up of six ongoing projects is being supported by the NCI and the National Institute of Environmental Health Sciences (NIEHS) to investigate environmental exposures and breast cancer risk in the Northeast and mid-Atlantic regions of the United States. Women, including minority women, who are participating in this effort reside in New Hampshire, Connecticut, Delaware, Massachusetts, Maryland, New Jersey, New York, Rhode

Island, Vermont, and the District of Columbia. A major objective of the project is to assess the effects of organochlorine pesticides, polychlorinated biphenyls (PCBs), and electromagnetic field radiation, as well as known breast cancer risk factors such as reproductive and family history. The identification of breast cancer cases and controls, collection of questionnaire information, and laboratory analyses of biological specimens are nearing completion. Analyses of the data will be done for each study site, as well as to compare the different geographical regions.

In another effort, the NCI and NIEHS are coordinating a series of studies to investigate the contribution of environmental agents to the relatively high rate of breast cancer reported on Long Island. Among the agents that will be evaluated are DDT and chlordane pesticides, PCBs from electrical insulators, electromagnetic fields, and polycyclic aromatic hydrocarbons from car exhaust, cigarette smoke and other sources. Pioneering approaches are planned in assessing the impact of these environmental exposures on the risk of breast cancer.

Another major collaboration between NCI and NIEHS is the Agricultural Health Study, a large prospective cohort study of predominantly farm families. NCI is providing the majority of funding for this effort, and is the lead group for conducting the study and assessing cancer endpoints. NIEHS will evaluate a variety of non-neoplastic outcomes in relation to agricultural exposures.

Mr. Stokes: What initiatives are planned for FY 1998?

Dr. Klausner: The ongoing initiatives are slated to continue through FY1998. The outcome of these efforts will help to determine the future direction of new research.

Mr. Stokes: How much is included in the budget request for this activity, and how does it compare with the current funding level?

Dr. Klausner: NCI funding for these collaborative projects will be approximately $6.5 million in Fiscal Year 1997. The 1998 budget request for these projects would continue funding at about that same level.

Mr. Stokes: As the director of the National Cancer Institute, in your professional judgement, what specific activities and what level of funds are needed to effectively address environmental justice as it relates to activities under the purview of your institute?

Dr. Klausner: NCI will continue to support initiatives that address the Departmental strategy on environmental justice, particularly those with an emphasis on the goal of focusing attention on the human health and environmental conditions in minority and low-income communities. Epidemiologic studies will continue to be pursued to assess specific environmental and occupational hazards as they relate to undeserved populations.

Of particular concern is the finding that there is a 30% excess of certain cancers in the African-American population. These cancer sites include esophagus, multiple myeloma, stomach, larynx, pancreas and oral cavity for both sexes; lung and prostate in men; and uterine cervix in women. Some of these differences are related to higher exposure levels, such as higher tobacco use patterns in African-American men and greater rates of human papillomavirus infection in African-American women. Future research opportunities include increasing efforts to mitigate these risk factors through outreach activities, which should impact positively on racial differences in cancer rates. Additional studies include efforts to identify biologic markers of risk, such as for specific hazardous exposures, profiles of genetic susceptibilities, and gene-environment interactions. Expansion of research in these areas should culminate in a better understanding of the environmental and genetic determinants of cancer, resulting in applications to reduce the disproportionate burden of cancer in African-Americans and other minority groups.

CANCER MORTALITY BY RACE

Mr. Stokes: The Cancer mortality by race and gender chart indicates a significant decline in cancer among black men as compared to the rest of the population. Can you elaborate on this. Which cancers accounted for this decline?

Dr. Klausner: The overall cancer mortality rate declined for black males between 1990 and 1994. For black males, there were statistically significant declines in mortality for the following cancers: oral cavity and pharynx, lung and bronchus, and urinary bladder. There were also apparent declines for the following cancers: esophagus, stomach colon/rectum, melanomas, kidney, brain, thyroid, Hodgkin's disease, multiple myeloma and leukemia. For these cancers, the decline for African-American men have not reached statistical significance.

Mr. Stokes: What role did prevention, access to health care services, and early detection play? Please elaborate on your response to this question for the record?

Dr. Klausner: The decline in the overall mortality rate is probably due to a combination of factors, including behavioral changes, screening, advancements in therapy and possibly a decrease in risk factor exposures. It is therefore difficult to make a precise attribution to any one factor or set of factors.

The NCI recognizes that all of the issues that you include in your question are factors that have an impact on the course and outcome of cancer. The NCI has numerous programs that encompass one or more of these issues.

INSTITUTE OF MEDICINE CANCER STUDY

Mr. Stokes: Last year's Senate report that accompanied the FY 1997 appropriations bill included language calling for the Institute of Medicine to conduct a

review of the status of NIH research on cancer among minorities and the medically underserved. What is the status of that study and when is it expected to be completed?

Dr. Klausner: NIH recently received the Institute of Medicine's proposal to conduct the review of research on cancer among minorities and the medically underserved. We expect the study to be completed in early summer of 1998.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists' cloning of adult sheep. These articles expressed excitement with regard to opportunities for advances in medical treatments and concern with regard to misuse of the technology and the possibility of human cloning. This is another area where we must now be certain to assess and address the ethical, legal, and social issues of research on the front end. As a leading researcher and as the director of the National Cancer Institute, what is your professional opinion of this technology and what are your most serious concerns?

Dr. Klausner: The President has made clear the administration's position on human cloning. No federal funds may be used for such research, and the President has requested a voluntary ban on such research in the United States even if federal funding is not employed. The President has asked the National Bioethics Advisory Commission to examine the issues raised by the successful cloning of an adult mammal. I believe this to be the appropriate body to discuss the issues and to make recommendations.

I agree with Dr. Varmus in his testimony before the committee that there may be advantages that can come form research on cloning in non-human species. One concern is that the cloning of Dolly will result in a rush to regulate all cloning that might preclude the legitimate benefits of cloning research that does not involve humans.

Mr. Stokes: With regard to cancer, what are the most significant benefits that cloning would yield for your major areas of research?

Dr. Klausner: Perhaps the most significant benefit from non-human cloning research will be an increase in the understanding of how genes are turned on and turned off. All cells of an individual contains the same genetic material. The distinction between liver cells and brain cells lies in which of the genes that both contain are on or off. In the case of the cloning of Dolly, the nucleus from a differentiated adult tissue was reprogrammed to allow the expression of genes that were not on in the cell from which Dolly was derived. Just as the difference between liver cells and brain cells is in the genes that are on and off, so too the difference between a normal liver cell and a liver cancer cell is related to differential gene expression. Which genes are expressed in a given tumor that are not expressed in normal cells? How do these changes in gene expression come about during carcinogenesis or during normal development? These questions are the kinds of questions that CGAP is intended to address. While We know

something about their answers, there is certainly more to learn. Animal cloning experiments may help shed light on these processes.

Animal cloning may also be instrumental in the production of better animal models for human diseases including cancer. NCI has a Preclinical Models Working Group one of the aims of which is to address the inadequacies of current animal models for research in cancer. With models that more accurately reflect human cancer, we would be better able to test prevention, detection, and therapy innovations than is possible today.

It is also possible that animal cloning research would enable the more efficient production of therapeutic human proteins. It may be able to produce organs in animals that would be suitable for transplantation into humans. One procedure that is not uncommon in cancer treatment is bone marrow transplantation. Animal cloning could lead to the ability to produce bone marrow cells that would not be rejected by human recipients.

DISSEMINATION OF CANCER INFORMATION

Mr. Stokes: What steps have you taken to apply internet technology to the way NCI interfaces with the public in the dissemination of cancer information?

Dr. Klausner: NCI has made a tremendous effort to take advantage of network technology as a vehicle for providing information about NCI and NCI sponsored research, and NCI clinical trials to the public. The public can access a wealth of information about NCI through four primary vehicles; the NCI Homepage, CancerNet, and PDQ (Physicians Data Query), and the Cancer Information System (CIS).

Data ranging from basic information about NCI, to information about specific studies can be found using the NCI Homepage. It is organized topically to assist users. Sections for intramural and extramural research are included as well as technology transfer, administrative information, public information such as the NCI fact book, and the Frederick Cancer Research and Development Center. A hot link is provided to quickly connect users to the CancerNet. Most of the administrative branches within NCI have created home pages here as well.

The CancerNet is targeted to three separate audiences; Patients and the Public, Health Professionals, and Basic Researchers. The Patients and the Public section provides general information about cancer including treatment, detection, prevention, genetics, support and advocacy groups, clinical trials and provides a kid's homepage and information about the 1-800-4CANCER program. The Health Professionals section provides the latest treatment information, information about active clinical trials, cancer statistics, and provides a "hot news" digest. Finally, the Basic Research module includes information on the NCI Cooperative Breast Cancer Tissue Resource Database, the NCI AIDS Malignancy Bank Database, the NCI Cooperative Human

Tissue Network, the NCI Cooperative Family Registry for Breast Cancer Studies and the NCI-NAPBC Breast Cancer Specimen and Data System.

CancerNet provides information both in English and Spanish and is intended to provide a wide range of accurate, credible cancer information. All information located on CancerNet has been reviewed by oncology experts and is based on the results of current research.

PDQ was developed by the National Cancer Institute (NCI) with the help of cancer experts from across the Nation. It contains information statements on state-of-the-art cancer treatment, cancer screening and prevention, supportive care for cancer patients, and investigational and newly approved anticancer drugs. PDQ state-of-the-art treatment statements contain a description of prognosis (probable outcome), cellular classification, staging (extent of disease), and treatments for all major cancers and some related conditions. State-of-the-art treatments are the best therapies currently available for a specific type and stage (extent) of cancer. PDQ does not recommend one treatment over another, but lists treatment options so that the doctor can select the one that is best suited for a patient. Because advances in treatment are being made all the time, PDQ statements are reviewed monthly by doctors and other experts on PDQ Editorial Boards and are updated as needed.

The Cancer Information Service provides accurate, up-to-date information on cancer to patients and their families, health professionals, and the general public. The CIS has two main features: a telephone service that responds to more than 600,000 callers a year, and an outreach service that proactively takes cancer information to under served and minority populations that do not often use the telephone to gather information. CIS information is also available through the NCI's CancerFax and CancerNet services, and in the News Section of the PDQ database. Individuals who have access to the Internet may access the document on CancerNet, through an electronic mail (E-mail) service or via the National Institutes of Health gopher. To get the CancerNet contents list from the E-mail service, send an E-mail message that says "help" in the body of the message to cancernet@icicc.nci.nih.gov. To get the document from CancerNet via the NIH gopher, point your gopher client to gopher.nih.gov and look for CancerNet under "Health and Clinical Information." To get the document from NCI's PDQ database, access PDQ News on the National Library of Medicine's MEDLARS system or consult a medical librarian for assistance.

The CIS outreach service reached about 19 million people last year. Through both the telephone and outreach services, CIS provides information on the latest cancer treatments and how to manage their side effects, studies that test new treatments, tips on how to detect cancer early, tips on how to reduce cancer risk, and community services for patients and their families. The CIS operates regionally in 19 offices, but is reached with a single phone number, 1-800-4-CANCER. Its telephone counselors take calls in both English and Spanish. CIS also provides access to the hearing impaired. Hallmarks of the CIS are the rigorous and continuing training programs for its counselors, and its sophisticated quality control program.

We continuously try to identify useful new information to include in these systems, and new avenues of reaching the public using network technology as it continues to develop.

The addresses for the sites mentioned are:
NCI Homepage - www.nci.nih.gov
CancerNet - wwwicic.nci.nih.gov
PDQ -http://cancernet.nci.nih.gov
CIS - By Phone - 1-800-4CANCER

BEHAVIORAL RESEARCH

Mr. Stokes: Can you give us an update on what the NCI is doing in the area of behavioral research? I am particularly interested in the smoking and behavioral arena.

Dr. Klausner: A significant part of NCI's research in the area of smoking and behavior is the ASSIST (American Stop Smoking Intervention Study) program, begun October 1, 1991 with a two-year planning phase during which the states defined the structure, direction and course of action for the implementation period. During Phase II, (October 1, 1993 - September 30, 1999) the states will implement their comprehensive smoking control plans.

States have developed 220 tobacco control coalitions with about 3,000 members, comprising an unprecedented infrastructure to improve public health. It is estimated that more than 90 million Americans will be directly affected by ASSIST and nearly 1.2 million premature smoking-related deaths will be prevented. ASSIST is designed to prevent 2 million children from becoming addicted to tobacco products. ASSIST will reach vulnerable populations who are targeted by the tobacco industry, including ethnically diverse groups, blue collar workers and families, and the underprivileged.

In addition to ASSIST, the NCI is addressing behavioral issues in cancer prevention and control, and especially tobacco use, through a number of other initiatives. These include:

- Prevention and Cessation of Tobacco Use among Children and Youth in the U.S. - this Request for Applications, announced in January, 1997, represents the NCI's largest research commitment to reducing youth tobacco use in the U.S. Through this initiative, the Institute has committed $32 million over the next five years to support at least 16 studies to develop the most innovative, cost-effective, and durable methods of addressing the problem of tobacco use among children and youth in this country.

- Priorities in Behavioral Research in Cancer Prevention and Control - this Program Announcement, published in March 1997, articulates the NCI's goals for behavioral research in cancer prevention and control. This initiative calls for

research in such areas as tobacco use, risk communication, preventive services and health care delivery, outcomes of genetic testing, enhancement of quality of life among cancer patients, and promotion of healthy diets and physical activity.

- Skin Cancer Prevention Program - this initiative, begun in 1994, is supporting four intervention trials which are investigating the most effective approaches to educating both children and adults who are at high risk for skin cancer, especially through schools, day care programs, and primary care practices.

- 5 A Day for Better Health Community Intervention Research Program - this initiative, begun in 1994, is supporting nine intervention trials investigating how best to increase community-wide consumption of fruits and vegetables.

- Pharmaco-Behavioral Treatment of Nicotine Dependence - this initiative, begun in September, 1996, is supporting seven intervention trials to develop the most effective adjuvant behavioral therapies to support the pharmacological treatment of nicotine dependence.

- Investigator-Initiated Behavioral Research - the Investigator-Initiated Research Program remains the NCI's most visible and active initiative focusing on behavioral research in cancer prevention and control. More than one hundred studies are currently investigating a wide variety of approaches to such behavior-related issues as reducing tobacco use, changing diets, increasing adherence to screening advice, post-treatment rehabilitation, and amelioration of cancer pain.

SCIENCE INFORMATION SYSTEM

Mrs. Lowey: I understand that you are working to create a science information portfolio which when completed would allow scientists and interested lay persons to find out what type of cancer research grants are currently being funded. Can you say more about this project as it applies to breast cancer?

Dr. Klausner: The NCI supports scientific investigations into breast cancer as one of its highest priorities. During this year, 184,000 new cases of breast cancer will be diagnosed and 44,000 women are expected to die of the disease. Given the magnitude of this disease, NCI recognizes its obligation to supply or coordinate the dissemination of current information concerning NCI funded research grants and other NCI breast cancer related research and activities. Although there is a new Science Information System (SIS) in the developmental stage, other mechanisms to obtain information on grants and other activities funded by the NCI are currently operational.

The SIS is being designed as a Web-accessible, computer based virtual repository of information about the science that NCI supports, and its programs and activities. Many of the information sources -- reports of workshops, progress review groups, summaries of research activities -- will provide information on the state of the science for a particular area of cancer research. For example, concerning breast cancer research, SIS might be used to identify the major areas of breast cancer research currently being addressed, or what clinical trials NCI currently sponsors in breast cancer and the status of each. It could be used to identify what workshops related to breast cancer have taken place in the past three years, what recommendations came out of those workshops, and determine whether other workshops on breast cancer are planned for this year. It could help identify which NCI investigators and laboratories are involved in research relevant to breast cancer, what are they doing, and what their results have been to date.

Initially, the SIS will attempt to meet the needs of NCI scientific managers. However, over time it will be enhanced and expanded to provide useful interfaces for the larger community of cancer researchers, clinicians, and the general public.

SIS will not create many new information sources; rather, the SIS will link to and retrieve information from sources of data that already exist. Under SIS, the user will be able to access data from such diverse sources as grants and contract databases, reports from working groups and progress review groups, program analyses, and tools that enable the user to locate people, resources, and expertise--all through a single interface.

The NCI maintains a number of current information retrieval systems. The Computer Retrieval of Information on Scientific Projects (CRISP) system is an existing major biomedical database containing information on research ventures supported by the National Institutes of Health (NIH). Most of this research falls within the broad category of extramural projects: grants, contracts, and cooperative agreements

conducted primarily by investigators at universities, hospitals, and other research institutions. CRISP also contains information on NIH intramural research programs.

The CRISP database is updated weekly and is currently available on the Internet as a gopher-based system. To enhance search and retrieval capabilities of the database, there is also a plan to publish CRISP on the World Wide Web (WWW). Retrieval of scientific information for each project in CRISP is made available by the project title, principal investigator's abstract, and the term descriptors assigned by the Division of Research Grants, NIH.

In addition, NCI maintains internal databases indexed to provide information about special categories of research and specific anatomic sites. These databases include administrative information and principal investigator abstracts. There are plans to develop a subset of the data for access and limited searching over the World Wide Web.

Additionally, the NCI supports a comprehensive research program focused on breast cancer research. The portfolio includes research on risk factors, tumor biology, screening, diagnostics, therapeutics, novel clinical approaches, prevention and control, and quality-of-life issues. To better monitor and optimize all these efforts in breast cancer, NCI has established a Progress Review Group (PRG). The mission of the PRG is to identify research opportunities in breast cancer and assess the activities of the NCI in the context of these opportunities. It, along with a Prostate Cancer PRG, represents the first use of this mechanism. The Breast Cancer PRG will work with NCI staff to assess the current state of knowledge regarding this area and recommend how the Institute can optimally respond to and stimulate research opportunities in breast cancer. This approach will help set the NCI's research agenda in breast cancer by identifying and prioritizing those scientific opportunities that are most likely to expand our knowledge base and that will ultimately reduce the burden of this cancer. Information resulting from the PRG will be made accessible through the Scientific Information System.

IMPLEMENTATION OF THE SCIENCE INFORMATION SYSTEM

Mrs. Lowey: When would you hope to have it completed?

Dr. Klausner: The full development of the SIS will require several years. Feasibility testing for parts of the system is being conducted in the current year. Depending upon the success of the prototypes, one or more years of operational implementation may follow.

Mrs. Lowey: Is progress affected by cuts in your administrative budget?

Dr. Klausner: We are committed to improving our collection and categorizing of scientific information and sufficient funds will be available to implement this effort.

ESTROGEN AND BREAST CANCER

Mrs. Lowey: The major risk factors for breast cancer point to a potentially significant role of estrogen in the development of breast cancer. In fact, one researcher is experimenting with artificially lowering estrogen levels as a means of preventing breast cancer. What research are you funding in this area, particularly with regard to the prevention of the disease?

Dr. Klausner: NCI is currently supporting several projects, clinical trials as well as laboratory-based studies, which are assessing the effectiveness of strategies to reduce estrogen exposure in breast cancer prevention. The best known of these initiatives, the Breast Cancer Prevention Trial (BCPT) was implemented in 1992 by the National Surgical Adjuvant Breast and Bowel Project (NSABP). The study is testing the ability of tamoxifen, an agent with anti-estrogen properties used in post-surgical treatment of early-stage breast cancer, to prevent the first-time development of breast cancer in women at increased risk for developing the disease. Approximately 13,000 women at increased risk for breast cancer due to age, family history, and personal history, such as age at first birth, age at menarche, and previous breast biopsies, are being randomized to receive 20 mg of tamoxifen per day or a placebo for an initial period of five years. The study is being implemented in about 300 nucleus and sub-centers across the country and in Canada. As of Fall 1996, over 12,300 participants have been enrolled and randomized to either tamoxifen or placebo. The women who have volunteered for the BCPT typically have a 4 to 5 times higher chance of developing breast cancer than women in the general population.

While the study focuses on decreasing incidence of breast cancer as the major endpoint, cardiovascular effects, alterations in bone/mineral metabolism, occurrence of second primary cancers, and impact on quality of life will also be assessed. The effect of tamoxifen as it relates to the molecular genetics of breast cancer development as well as endometrial and ocular changes in women receiving tamoxifen are being studied. Information from these studies will guide the future routine care of women receiving tamoxifen in both treatment and prevention settings. The trial includes a program to defray costs for economically disadvantaged participants.

Several laboratory studies of the effect of modulators of estrogen production on breast and proliferation and breast cancer metastasis are also in progress. In one study, a naturally occurring component - indole-3-carbinol - of cruciferous vegetables such as broccoli and cauliflower is being evaluated for its ability to enhance the rate of estrogen metabolism and/or decrease the sensitivity of breast cells to estrogen. Another study is focused on exploiting the ability of the vitamin A metabolite, retinoic acid, to reduce the ability of estrogen or other substances to promote proliferation of breast cancer cells. Other studies involve the use of vitamin E-related chemicals and fatty acids to neutralize or reverse estrogen's effect on normal breast cells and breast tumor cells. It is anticipated that laboratory studies such as these will provide researchers with a new

generation of potential breast cancer preventive agents based on reducing or modulating estrogen effects.

OVARIAN CANCER

Ms. DeLauro: In FY 1997, NIH will spend only $41 million out of a $12.7 budget on ovarian cancer research. Over the past few years, increases in ovarian cancer research funding have been extremely incremental. How much does NCI plan to spend this year on ovarian cancer research?

Dr. Klausner: I have made a special effort to develop a Scientific Information System that will be responsive to the needs of the institute in at least two areas-- to identify areas and descriptions of what the NCI is supporting as well as areas that need to be addressed. It will take some time to complete this process which is, in fact, an experiment. Through that process, we hope to more clearly delineate funding. NCI represents the dominant share of the NIH ovarian cancer funding, currently projected to be $39 million in FY 1997 and $41 million for FY 1998.

Ms. DeLauro: What types of initiatives does this include?

Dr. Klausner: We have placed ovarian cancer as one of the first things to look for in the Cancer Genome Anatomy Project (CGAP). Libraries of genes from ovarian cancer cells have been started, so we can search for tags or molecules in systematic way. We are optimistic that this will provide us with better detection as well as better intervention. The National Cancer Institute has an active program in basic and applied ovarian cancer research including studies of the genetics of inherited ovarian cancer. The NCI has implemented or continued activities related to the recommendations of the NIH consensus conferences on ovarian and cervical cancer.

Major screening studies are underway for ovarian cancer as part of the PLCO (Prostate, Lung, Colorectal, and Ovarian) trial. The PLCO trial is designed to determine whether particular screening modalities will reduce the number of deaths through early detection and treatment. This trial is very large involving 148,000 participants. For ovarian cancer, women will have an annual ovarian palpation, transvaginal ultrasound, and blood test for the molecular tumor marker CA-125. Four geographically diverse clinical centers - Birmingham, Alabama; Pittsburgh, Pennsylvania; Oklahoma City, Oklahoma; and Seattle, Washington - will enroll a total of 7,200 women in this study.

NCI currently sponsors nine ongoing clinical trials for ovarian germ cell tumors and sixty ovarian epithelial cancers trials. Through the Gynecologic Oncology Group and NCI-designated cancer centers, the NCI continues to support critical research into the treatment of ovarian cancer. In addition, the NCI is working to strengthen gynecologic oncology services and research at the NIH Clinical Center.

Ms. DeLauro: Will the research be done primarily through the extramural or intramural program?

Dr. Klausner: NCI's effort in ovarian cancer is primarily through the extramural scientific community through investigator initiated research grants. Over 90% of our funding in this area is conducted by scientists located throughout the nation at universities and academic institutions. This proportion within the extramural program is similar to that of other areas and to the overall distribution of effort between the extramural and intramural research program.

GYNECOLOGIC CANCER RESEARCH

Ms. DeLauro: Dr. Klausner, I believe in the current clinical center there is one lab for gynecologic cancer research. Are you proposing that additional lab space in the new Mark O. Hatfield Clinical Canter be designated for gynecologic cancer research?

Dr. Klausner: There are actually four laboratories -- and one section -- performing active research in issues pertaining to gynecologic oncology. Work on growth factors in ovarian cancer growth as well as the development of vaccines against the human papilloma virus which is responsible for the majority of cervical cancer is one area of investigation. Another is the role of oncogenes in ovarian cancer growth, especially the role of nuclear proto oncogenes such as fos and jun. A number of clinical trials extending observations that DNA repair genes are associated with potential drug resistance in ovarian cancers are being conducted. Seminal work on alkylator therapy has led to the formulation of triple alkylator treatment in advanced ovarian cancer that is now standard in the field. A new chemotherapeutic agent CAI that appears to have efficacy in ovarian cancers has been developed.

Thus, the NCI work on gynecologic cancers is broad and intense. An NCI investigator has developed a new method of producing HPV vaccines that may revolutionize the field. Based on viral protein production in insect cells in culture, this effort has been able to reassemble the viral coat without the viral genetic material. This material acts as a superb vaccine in animal studies. Human trials are anticipated.

The NCI intends to continue to strengthen its program in gynecological cancers. These efforts will be accomplished within the clinical center space currently designated for the NCI.

WOMEN IN CLINICAL TRIALS

Ms. DeLauro: What kinds of strides has NCI made to include woman in clinical trials?

Dr. Klausner: The NCI has at any one time almost 3 million subjects enrolled in clinical studies concerning the detection, diagnosis, treatment, prevention or control of cancer. These subjects, which are predominately healthy individuals, are composed of 71% women and 45% minorities. NCI has vigorously pursued on its own and with its grantees recruitment of women and minorities in all studies, and conducts many trials specifically targeted at gender-specific cancers of high prevalence and impact. NCI has been extremely successful in ensuring representation in trials with therapeutic intent and with population-based data collections. For NCI treatment clinical trials, minority representation among the individuals enrolled in the trial reflects their representation among individuals with the disease under study. For treatment clinical trials approximately 183,000 individuals are participating, of which nearly 88,000 are women and about 95,000 are men. The NCI has also sponsored a national conference, the topic of which was the accrual and retention of minorities in clinical trials. Additional regional conferences on this topic will be held in the coming year utilizing NCI support.

Ms. DeLauro: How is the inclusion of women in clinical trials addressed in your FY 98 budget request?

Dr. Klausner: NCI's internal assessment of the fulfillment of meeting the inclusion requirement has assured compliance with the NIH Revitalization Act of 1993: Women and Minorities as Subjects in Clinical Research. A grant application that fails to meet the standard for inclusion receives an unacceptable gender or minority code, which results in an administrative bar-to-funding. This bar may be removed upon receipt of additional information. Program staff has some flexibility to work with an applicant and resolve problems the may prevent award of highly meritorious projects.

On February 26, 1997, based upon the review of the data presented to the National Cancer Advisory Board (NCAB), the NCAB concurred with the NCI's compliance in implementing the NIH Guidelines on the inclusion of women and minorities in clinical studies.

NCI PANELS AND ADVISORY BOARDS

Ms. DeLauro: I noticed that NCI convenes a variety of panels and advisory boards which aid the complex decision-making that goes into determining the next steps for biomedical research in the cancer field. Yet, given the recent controversy surrounding the panel on mammography, how effective are these panels in helping to assess NCI's priorities?

Dr. Klausner: I believe the NCI's advisory panels to be critical to the success and progress of the nation's cancer research investment. Our advisors represent the nation's leading experts in the varied disciplines of cancer research. The National Cancer Advisory Board, for example, has played a central role in the reformulation of the NCI Bypass Budget and in defining topics to be considered as priority opportunities for extraordinary investments. The NCI's Board of Scientific Advisors has initiated a

series of reviews of major extramural program areas such as Cancer Centers, Clinical Trials and Cancer Prevention and Control to ensure the structure of the NCI is poised to take advantage of priorities as they emerge in the future, as well as to ensure sound management of current resources.

I would note that the Development Conference on Mammography Consensus was convened by the NIH Office of Medical Applications of Research (OMAR) and that this panel is not one of our chartered advisory groups. The Consensus Conference process serves a useful purpose. The mammography conference led to the presentation of data that had not previously been presented. It brought together scientists in the field of mammography and led to a spirited discussion of the issues. The data presented at the conference and the panel's draft report is being used by our official advisory body— The National Cancer Advisory Board (NCAB) in their chartered role of advising and overseeing the NCI. The NCAB is in the process of developing its recommendation to the NCI regarding mammography.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

FY 1998 Budget — Page No.

Organization chart 2

Appropriation language 3

Language Analysis 4

Amounts available for obligation 5

Budget justification 6

Budget mechanism table 38

Budget authority by activity 39

Summary of changes 40

Budget authority by object 42

Administrative costs 43

Significant items in House and Senate Appropriation Committee Reports 44

Authorizing legislation 85

Appropriation history 86

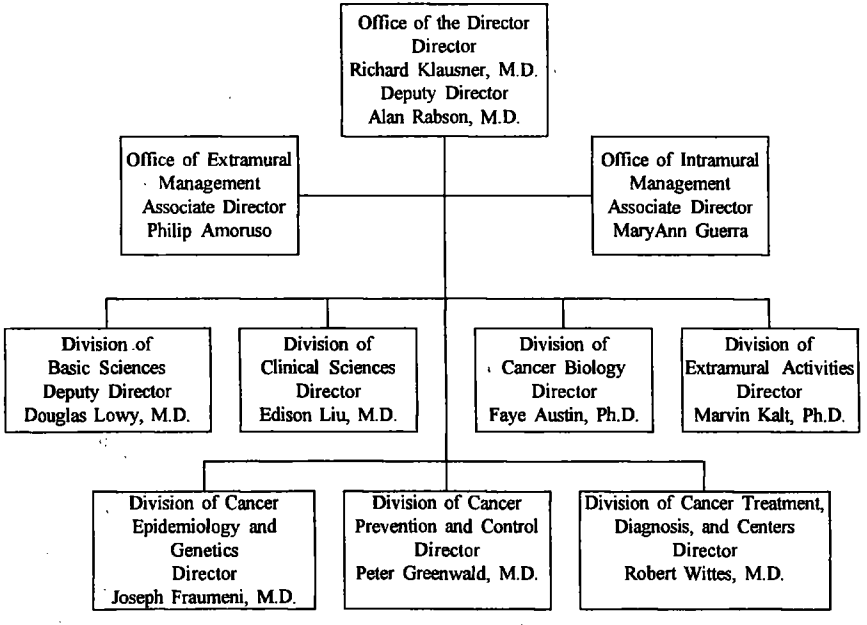
Detail of full time equivalent employment (FTE) 87

Detail of Positions 88

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Organization Chart



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Appropriation Language

For carrying out section 301 and title IV *(except section 417B(d))* of the Public Health Service Act with respect to cancer, [$2,382,532,000] *$2,217,482,000.*

(Department of Health and Human Services Appropriations Act, 1997).

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Language Analysis

Language Provision	Explanation
"...(except Section 417B(d))..."	This language has been added to remove the requirement that NCI spend ten percent of its total appropriation on cancer control activities. This will allow the NCI more flexibility when making funding decisions and allocating its resources to the numerous scientific opportunities that are available.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$2,251,084,000	$2,382,532,000	$2,217,482,000
Rescission in accordance with P.L. 104-134	(2,654,000)	---	---
Rescission in accordance with P.L. 104-208	---	(1,383,000)	---
Subtotal, Adjusted Appropriation	2,248,430,000	2,381,149,000	2,217,482,000
Real transfer from: Other NIH Institutes through the NIH Director's one percent transfer authority	6,951,000	---	---
Comparative transfer to Office of AIDS Research, NIH for HIV activities	(225,790,000)	(224,733,000)	---
Subtotal, adjusted budget authority	2,029,591,000	2,156,416,000	2,217,482,000
Unobligated balance, lapsing	(11,000)	---	---
Total obligations	2,029,580,000	2,156,416,000	2,217,482,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1996 - $14,213,000; FY 1997 - $20,000,000; FY 1998 - $20,000,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research:
FY 1998 - $224,256 ,000

Note: Excludes obligations of $7,151,000 in FY 1996 and $14,700,000 in FY 1997 of royalty funds.

Justification

National Cancer Institute

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
2180	$2,029,591,000	2180	$2.156,416,000	2180	$2,217,482.000	---	$61,066,000

This document provides justification for the FY 1998 non-AIDS activities of the National Cancer Institute (NCI). Justification of the NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

This FY 1998 budget request represents a progress report on the programs, initiatives and opportunities described within last year's budget document. It also provides significant resources for maintaining and expanding the research efforts promulgated within the NCI's Bypass Budget document *The Nation's Investment in Cancer Research, A Budget Proposal for Fiscal Years 1997/98.* These funds will permit the NCI to advance the investment opportunities, e.g. Cancer Genetics, Detection Technologies and Investigator-Initiated Research, identified within the Bypass Budget. Our knowledge and understanding of cancer are continually evolving. Our challenge is to present a budget document that effectively communicates to our many audiences the importance of continued investments in cancer research. It must offer an update of fundamental ongoing research programs that are the underpinning of our research efforts. In addition, new opportunities must be addressed. Treatments and techniques that revolutionized the field fifty, twenty-five, even five years ago are considered routine today. We fully expect the "extraordinary" opportunities of today to give way to new opportunities as the pace of scientific discovery accelerates. The opportunities are meant to be broad-based and multifaceted, requiring the Institute's strong commitment over an extended period of time. It is clear that implementation of the many new opportunities will take great effort and considerable time. Therefore, we do not envision a recasting of the annual budget submission, rather an evaluation of progress, accomplishments, and current opportunities, as well as the identification of opportunities based on new discoveries. We expect new opportunities, particularly in the areas of therapeutics, clinical trials, and cancer prevention and control, to come from many sources. The NCI is committed to continually solicit input. The scientific community, the NCI program staff, cancer research advocates and constituents as well as the review and progress groups (described later within this document) will play a significant role in identifying new opportunity areas and the future directions in cancer research.

Introduction

The National Cancer Institute is an Institute of science dedicated to the total eradication of cancer from our lives. Encouragingly, the nation's efforts in the areas of cancer prevention, early detection, basic research and treatment have begun to bear tangible fruit: The cancer death rate in the United States fell by nearly 3 percent between 1991 and 1995, the first sustained decline since national record-keeping was instituted in the 1930s. This translates into thousands of saved lives – this year alone, thanks to remarkable advances in cancer prevention, detection, and treatment, as many as 16,000 men, women, and children with cancer who may not have survived ten years ago now have a real chance at living long, full, and productive lives.

In 1971 Congress passed the National Cancer Act, increasing resources for cancer research and broadening the mandate of the National Cancer Institute, the principal Federal agency supporting and conducting cancer research. Since then, we have made significant progress against many cancers -- progress that has touched millions of Americans. New treatments for children's cancers, colon cancer, Hodgkin's disease, testicular cancer, and breast cancer, to name only a few, have given new hope to those stricken with these once nearly uniformly fatal diseases. Research has also led to a vastly improved quality of life for those who are battling cancer and for the growing number of people who, thanks to more effective treatments, have already won the fight.

But the most profound change has been in our understanding of the fundamental biology of this constellation of diseases. The genetic revolution in cancer and advances in biomedicine, generally along with the development of advanced computers and the biotechnology industry have created opportunities to learn about and help to fight cancer as well as other diseases-- for example, Alzheimer's disease and AIDS.

These advances have been heartening, and they herald great promise for the future. But there is still much to learn, much to do. Our understanding of cancer's complexities remains incomplete, frustrating our fervent desire to eradicate this scourge once and for all.

How do we continue to move forward? We must recognize and seize the extraordinary opportunities for further progress earned through our national investment and our diligence. We have built a successful discovery process, attracted some of the best scientific minds to the cancer problem, and initiated ground-breaking programs that already have yielded critical knowledge, improved patient care, and saved lives. We must continue to support these endeavors, ensuring that they remain vital and productive.

A rare disease at the turn of the century, cancer is all too commonplace today. This budget represents an investment in research, but more importantly an investment to improve the Nation's health. Most importantly, it is an investment in hope--the hope that springs from the discovery of the tools and knowledge that we must have to reduce the awful burden of cancer.

Over 45 percent of us will develop cancer; over 20 percent of us will die from cancer. Within five years cancer will be the leading cause of death in the United States, responsible for over 8 million years of life prematurely lost each year.

The National Cancer Institute (NCI) -- An Institution Dedicated to Discovery

Science is the way we understand the natural world and the NCI is an institution of science dedicated to discovery about all aspects of cancer. Its work is based on the premise that we must know what causes cancer in order to prevent it and we must know the nature of cancer in order to accurately detect, diagnose, and treat it.

Research is the process by which questions about cancer are asked and answered. These key questions include:

- Cancer Risk: Who is at risk for which cancers and why?
- Prevention: How can cancer be prevented?
- Detection: How do we screen for, detect, and diagnose cancer?
- Treatment: How do we best treat cancer?
- Rehabilitation: How do we improve quality of life for cancer patients and survivors?

While we have made progress in answering these questions, the burden of cancer continues, and so does the NCI's dedication to discovery.

Progress Against Cancer

We measure progress against cancer in terms of:

- The growth of knowledge about cancer; and
- Reductions in the cancer burden.

The Growth in Knowledge

Twenty-five years ago three theories of cancer (one based on viral causes, one based on heredity, and a third based on chemical causes) dominated cancer research, but there was little direct evidence for any of these theories for the vast majority of human cancer. All of that has changed with the discovery of two classes of genes, oncogenes and tumor suppressor genes. The first was discovered through the study of viral cancers in animals, the second through the study of hereditary cancers in humans. The present view of cancer has emerged from a fusion of all three hypotheses. Cancer is a disease of altered genes and altered gene function. These alterations can be inherited or acquired as the result of chemical or physical damage or the effects of viruses.

What is cancer? Today we know that cancer results from a series of changes in genes that control cell growth and behavior. These genetic changes transform a healthy cell, or one that has inherited a predisposition to these changes, into a cancer cell. One of the critical questions in cancer research is how and why these genetic errors occur, and just as important, why the errors are not corrected by the cell's normally efficient surveillance mechanisms. The relationship of these genetic

changes to the environment, and to behaviors such as diet and smoking, is especially important. Smoking is the cause of over 30 percent of cancer deaths and diet may be implicated in an even greater number of cancers. Cancer is a group of diseases whose origins lie in the interplay between the vulnerability of our genetic material, DNA, and the challenges and stresses that environment places on the cells in which DNA is housed.

These new developments in our understanding of cancer are extending to all forms of human cancer. At first, the genetic basis of cancer was observed in certain rare cancers, but now these insights are extending to the most common cancers. Genes whose dysfunction accounts for cancer are being rapidly identified. These genes ultimately determine the behavior and the relentless growth of cancer cells. Some of these genes, the oncogenes, can be activated inappropriately, similar to the uncontrolled accelerator of an automobile. Conversely, the tumor suppressor genes, or anti-oncogenes, can lose their function, like defective automobile brakes. Our knowledge about these genes is still incomplete, and many cancer genes remain to be found. Ideas abound on ways to use the new information for cancer prevention, diagnosis, prognosis, detection, and treatment. In short, the whole field of cancer research has been revolutionized and energized by this recent and continuing genetic revolution.

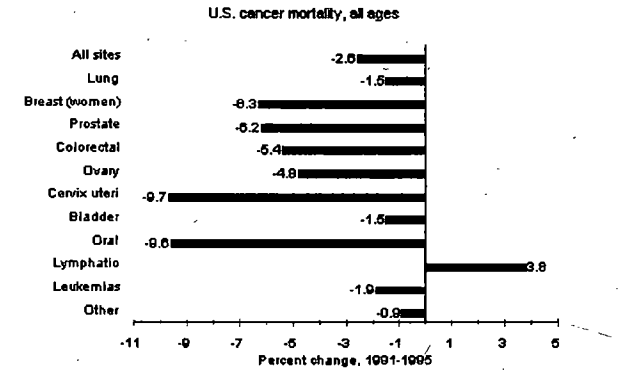
Reducing the Burden -- The NCI's Ultimate Goal

Reducing the burden of cancer can be measured in terms of fewer deaths, fewer new cases, increased length of survival, and increased quality of life of cancer survivors.

The 1990s may be remembered as the decade when we measurably turned the tide against certain cancers. After rising throughout the 1970s and 1980s, the overall cancer death rate fell nearly 3 percent between 1991 and 1995 – a real and promising trend that translates into thousands of lives saved. And for several cancers, decreasing death rates reflect cumulative research successes over the past 25 years: death rates from children's cancers have declined by over 40 percent, and with advances in chemotherapy, hormonal treatments, and in the access to and use of screening mammography, breast cancer mortality has finally begun to decline -- down over 6 percent between 1991 and 1995. After rising for years, mortality from prostate cancer has begun to decline -- 6 percent between 1991 and 1995. Deaths from colon and rectal cancers have dropped steadily, declining over 18 percent since 1973, and mortality rates have also decreased for Hodgkin's disease and testicular cancer, both due to dramatic advances in therapy.

Trends in Cancer Mortality, 1991-1995

The overall U.S. cancer mortality rate fell 2.6 percent between 1991 and 1995,* the first sustained decline since national record keeping was instituted ... in the 1930's. Most of the decline is attributable to decreases in mortality from lung, colorectal, and prostate cancers in men and breast, colorectal, and gynecologic cancers in women.



* 1995 Preliminary Data
Source: National Center for Health Statistics

In addition to improvements in mortality rates for many malignancies, we have achieved important improvements in the quality of life for cancer survivors through less disfiguring and less damaging surgical procedures, better pain control, and more effective medication for the side effects of cancer therapy.

After a formidable battle to reduce the prevalence of cigarette smoking, lung cancer rates for men have declined. As smoking rates among women have increased, however, their lung cancer mortality rates have risen alarmingly. For other cancers, including non-Hodgkin's lymphomas, multiple myeloma, melanoma of the skin, and brain and kidney cancers, mortality rates have not fallen or are increasing. Mortality for esophageal cancer increased 17 percent between 1973 and 1993; for liver and intrahepatic bile duct cancer, the mortality rate increased by 35 percent. And although the overall cancer mortality rate among African Americans is declining, it is still disturbingly higher than the overall mortality rate for other ethnic groups.
Even taking into account these advances in decreased mortality, overall cancer incidence continues to increase, emphasizing the formidable task ahead. The goal of a reduced cancer

burden can only be achieved by the successful translation of discoveries to the benefit of all people who are at risk for and who have cancer.

NCI's Research Program

Research Settings

The research programs of the NCI take place in three settings: the laboratory, the clinic, and the community. In the laboratory, research is pursued on the biology of cancer, the fundamental properties of cancer-causing agents and processes, and the body's defense against and response to cancer. In the clinic, patient-oriented research is carried out concerning prevention, detection, diagnosis, treatment, and rehabilitation. In the community, research is carried out on the causes, risks, predispositions, incidence, and behavioral aspects of cancer. The components of this research triad overlap. For example, population or community-based research on the effects of exposure to a potential cancer-causing agent links to the laboratory where an understanding of the agent's effect on the cell can be explored. Through these linkages, we have identified a sexually transmitted papilloma virus as the cause of cervical cancer and subsequently explained why only certain viral sub-types are cancer causing; and we have established the relationship between asbestos and mesotheliomas; between late menopause and breast cancer; and between diet and esophageal or stomach cancer.

Likewise, community-based research on family clusters of cancers can lead to the isolation of the specific genes responsible for inherited cancer syndromes. The identification of specific genetic pathways in cells studied in the laboratory then can be applied to patients in order to predict the course of their disease and their response to therapeutic interventions, or to find ways to detect these cancers very early in their development.

Research Areas

There are four fundamental cancer research areas – in effect four fundamental goals of cancer research: An understanding of cancer biology; identifying who is at risk for cancer and why; developing interventions to prevent, detect, diagnose, treat, and enhance survivorship from cancer; and bringing research discoveries to the public and to practice.

Cancer Biology - The Nature of Cancer. The most remarkable progress in the last 25 years has been in our knowledge of cancer biology. We are finally beginning to understand what is required to turn a normal cell into a cancer cell. Cancer arises when a single cell changes so that it divides continuously, released from the controls that constrain the replication of normal cells. In all cases this transformation is due to changes in the function and activity of genes, which are segments of DNA containing the information that directs a cell to make a particular protein product. Of the 100,000 genes found in the human genome, only the altered activities of a small number of genes are responsible for transforming a normal, well-behaved cell – be it in the breast, brain, blood, colon, prostate or other organ – into a cancer cell. Identifying these "cancer genes" defines the central scientific hunt in cancer biology. Their identification provides an unprecedented window into the nature of cancer. These genes normally function to instruct cells to produce accelerators that drive cells to proliferate, brakes that control proliferation, or mechanisms that underlie the repair of DNA damage or the sacrifice of damaged cells. Some

individuals inherit an altered form of a cancer gene. These individuals carry a very high lifetime risk of developing cancer because fewer subsequent changes in DNA are required to take place in one of the trillions of cells in our bodies to transform that cell to a cancer cell.

We now know that DNA changes are the core cause of all cancer. These changes can occur due to chemicals, viruses, radiation, and mistakes made each day in the course of duplicating the three billion units in our DNA when a cell divides. DNA, the molecule of life, is very vulnerable to damage, but each cell has the remarkable ability to recognize damage and correct it. The changes in DNA required to produce cancer result from the imbalance between damage and the cell's ability to repair the damage. When a normal cell recognizes damage to its DNA, it stops the process of growth and division called the cell cycle. A normal cell either repairs the damage or, if it fails, commits suicide. In the development of cancer these "checkpoint" controls are lost and the cell continues to divide, transmitting its damaged DNA to its descendants. It is for this reason that cancer is beginning to be seen as a problem of genetic instability.

No one genetic alteration, however, is enough to make a normal, healthy cell a cancer cell. Rather it is an accumulation of changes during the lifetime of a cell in a relatively small number of genes that is required. This understanding allows us to begin to define the development and evolution of cancer from predisposition to pre-cancer to cancer. Each cancer is ultimately defined by its particular pattern of altered and normal gene activity. This pattern determines the cancer's rate of growth, tendency to spread, responsiveness to hormones and therapies, and defines the ability of a person's immune system to recognize and respond to a cancer. It is these patterns that will define what each cancer is and how many different cancers there are.

By defining these molecular patterns we are beginning to be able to describe what distinguishes each cancer from its normal counterpart. Advances in our ability to detect, to diagnose, and to treat each cancer will most likely be found in these differences.

NCI's Cancer Genetics Network: A Tool for Information and Technology Transfer

The NCI has begun the creation of a Cancer Genetics Network. Currently in the initial planning stages, the Network will be a dynamic informatics and research infrastructure linking centers that test and counsel individuals for hereditary cancer susceptibility. The Network will provide an electronic information resource on genetic predisposition to cancer for both health care providers and consumers; it will establish a secure and confidential database of demographic, genetic, and outcome information on individuals who agree to participate; and it will serve as a vehicle to inform potentially eligible individuals included in the Network database of relevant IRB-approved research protocols through their Network physician.

Cancer Risk. Research on cancer risk quantifies the risk of developing cancer in various populations, and strives to identify the factors responsible for these risks. Research in this area is

critical to linking our knowledge of biological processes to the detection, management, and ultimately, prevention of cancer. Studying people who are at high risk of cancer is particularly important, since it may be possible to more readily identify the factors influencing risk and to assess means for prevention and risk reduction.

Epidemiology is the principal discipline used to study cancer patterns in the population and the determinants of cancer risk. Epidemiologists have uncovered distinct cancer patterns among various population groups. For example, African American men have the highest prostate cancer risk of any group in the world, while men in Asian countries have a relatively low risk. Similarly, women in Asian countries have the lowest rates of breast cancer, while those in the West have the highest. Interestingly, when Asian women migrate to the United States, their breast cancer risk rises over several generations until it matches that found in U.S. white women. These striking variations among populations have proven particularly useful in targeting further epidemiologic research into the causes of cancer. These studies underlie the commitment of the NCI to address the burden of cancer in all groups in our American community to assure that all groups receive the benefits of our research.

The epidemiologic approach has been successful in identifying many factors that increase cancer risk, some of which are environmental and lifestyle-related, while others are part of a person's genetic makeup. With the exception of a few genetic conditions, however, it is still not possible to predict with any degree of certainty that a person having one or more of these factors will develop cancer. This uncertainty is related to the very nature of cancer, and the need for a number of specific alterations to accumulate in the genetic material (DNA) of a single cell for that normal cell to be transformed to a malignant state.

The single most important exposure that increases cancer risk is the use of tobacco products, particularly cigarette smoking. Smoking is believed to contribute to more than 30 percent of all cancer deaths. In addition, certain aspects of the diet, particularly diets lacking in fruits and vegetables or high in fats, appear to be important contributors to cancer risk. An excess risk of cancer also has been linked to alcohol consumption, radiation (e.g., ultraviolet and x-rays), certain occupational exposures (e.g., asbestos), environmental pollution (e.g., arsenic), some pharmaceutical agents (e.g., estrogenic drugs), certain viral infections (e.g., human immunodeficiency virus and human papilloma virus), and hormonal factors. In addition, epidemiology plays a key role in revealing inherited cancer predisposition syndromes, as is seen in women who inherit alterations in the BRCA1 gene.

With recent major advances in molecular biology, a strategy called molecular epidemiology has emerged, combining the strengths of epidemiology with sensitive laboratory probes and providing new insights into genetic susceptibility and gene-environment interactions. This kind of interdisciplinary approach promises to elucidate the risk profiles and biologic mechanisms involved in cancer etiology, making it possible to predict cancer risk with greater certainty.

Cancer Interventions. Ultimately, the purpose of understanding tumor biology and cancer risk is to discover more effective ways of preventing, detecting, diagnosing, and treating cancer.

Although the full realization of this process lies ahead, important advances achieved over the past quarter century give ample reason for optimism.

The diagnosis of cancer depends on the microscopic appearance of tissue samples taken from growths or other suspicious lesions in the body. Advances in biological knowledge have improved our ability to subclassify cancers into accurate categories. For example, a better understanding of normal immune system development and biology has led directly to molecular techniques for classifying, for the first time, immune system tumors (lymphomas). More precise classification of cancers is important because it will lead to more precise prediction of clinical outcome for patients and to the discovery of more effective therapy. The experience with lymphoma serves as a model for what will very likely occur in a variety of malignancies. We expect that tumor diagnosis and classification will be revolutionized in the coming years by application of emerging knowledge in molecular genetics.

We have learned to see inside the body of living human beings with a precision that could not have been anticipated by a previous generation of physicians. Computed tomography, magnetic resonance imaging, and ultrasonography simply did not exist as useful clinical tools 25 years ago. Their development depended on first learning how the body interacts with x-rays, magnetic fields, and sound waves, and then figuring out how to create images from these interactions. These technologies permit us to locate internal tumors with unprecedented accuracy, and to biopsy internal organs without the need for major surgical procedures. There is every reason to believe that further improvement in their powers of resolution will enhance our ability to detect small tumors even earlier than is possible with currently available methods, such as x-ray mammography. Invasive procedures, such as colonoscopy and bronchoscopy, are on the verge of giving way to "virtual" procedures involving the imaging of these internal structures without any actual invasion of the body by tubes or scopes.

Our ability to prevent cancer depends on identifying and removing (or at least reversing the effects of) specific risk factors. Clearly, the most important of these is tobacco use. The NCI has strongly supported recent initiatives to avert the initiation of tobacco use among children and teenagers and continues to develop a variety of approaches to cessation among those already addicted. The effect of dietary modification and administration of preventive agents to forestall the occurrence of cancer in high-risk populations is currently under study. The testing of tamoxifen as a breast cancer preventive is one current approach. It should be quite clear, however, that major improvements in our approach to chemoprevention will depend on an improved understanding of the fundamental mechanisms of carcinogenesis -- the process by which normal cells are induced to become malignant.

The past quarter century has seen major progress in our ability to treat certain cancers. In addition to well-publicized improvements in the cure rates for many uncommon tumors, such as Hodgkin's disease, certain lymphomas, testicular cancer, and a variety of childhood cancers, adding chemotherapy to surgery and/or radiation has increased the cure rates for patients with breast and colorectal cancer. High-dose chemotherapy with stem-cell rescue is effective in the leukemias and is currently undergoing definitive testing in breast cancer. The application of molecular biology to the drug discovery process has ushered in the era of biological therapy by

permitting the large-scale production of so-called "recombinant" proteins. Following directly from this approach, the availability of interferon-alpha has markedly improved the outlook for patients with a rare form of leukemia. Both interferon and interleukin-2 provide improved palliation for some patients with kidney cancer. The availability of bone-marrow stimulatory factors have enhanced the quality of supportive care by mitigating the toxicity of chemotherapy to the blood elements. Over the past 15 years, the formidable problem of treatment-related nausea and vomiting has been markedly lessened by the development of truly effective drugs that block this side effect.

NCI is committed to research to improve the quality of life for those who develop cancer. As treatment becomes increasingly effective in the coming years we shall continue to see the emergence of certain problems associated with surviving cancer. These are of two general types. The first are the challenges to an optimal quality of life posed by the effects of cancer treatment itself. Although most acute side effects of treatment are rapidly reversible, some, such as the loss of a body part, have a lasting impact. The widespread use of techniques such as breast reconstruction, conservative surgery, and customized limb prostheses have greatly improved the emotional and functional outlook for survivors of breast and bone cancer. The knowledge, gained in a landmark clinical trial, that chemotherapy followed by radiation treatment is as effective as total removal of the voice box for cancer of the larynx has made preservation of natural speech possible for many patients with this condition. The recent FDA approval of effective drugs for protecting against the cardiac toxicity of the anthracycline antibiotics and the kidney toxicity of cisplatin can be expected to reduce the overall incidence of two particularly troublesome chronic effects of treatment.

The second general problem is the propensity of many cancer survivors to develop second cancers at the same or other body sites. In some cases, this too is a treatment effect, since many current therapies that effectively treat the patient's primary cancer unfortunately promote the development of second cancers in a small fraction of people who receive them. So, for example, women who have received radiation therapy to the chest for the treatment of Hodgkin's disease are at increased risk for developing breast cancer; and certain chemotherapy regimens are associated with the late appearance of acute leukemia in some patients who survive for years after the treatment. Sometimes, however, the development of a second cancer stems from influences having nothing to do with the therapy. Patients who survive a first cancer of the lung or oral cavity, for instance, have a high incidence of subsequent tumors at those sites, probably because of the continued carcinogenic influences of tobacco. Inherited risk may also play a role. Some breast, ovarian, and colorectal cancer patients have a genetic predisposition to those cancers and are likely to develop second primary cancers. The solution to these persistent problems is clearly to discover more targeted and less toxic treatments and to develop better surveillance and prevention strategies for people whose risk is elevated for reasons unrelated to treatment.

Psychosocial and behavioral research can make fundamental contributions to all aspects of cancer survivorship, improving the quality of life for both cancer patients and those at increased risk of developing cancer. Psychosocial research investigates how cancer affects quality of life and finds ways to address survivors' needs so they can meet the everyday demands of life and

return to a productive lifestyle. NCI is committed to such research to complement its cancer prevention, detection, and treatment research programs. We expect that this research will assume even greater importance as genetic advances pose difficult prevention and treatment choices.

Cancer Control. Cancer Control refers to the application of cancer research results and interventions to decrease the burden of cancer. Just as biology and epidemiology provide a foundation for intervention research, all three research areas provide a foundation for cancer control. The fact that significant smoking rate reductions have taken over 30 years to achieve since the first Surgeon General's Report which linked smoking causally with cancer demonstrates how difficult the widespread application of cancer research results can be.

Each year, over 500,000 Americans die of cancer, while over 1,000,000 are newly diagnosed. Clearly, knowledge gained in the biological and epidemiologic sciences as well as that gained in intervention research must be broadly applied to have an impact on the cancer problem in the United States. Effective applications rely upon rigorous, high quality science. Just as important, effective applications require an in-depth understanding of and sensitivity to the cultural, ethnic, and other social forces acting upon populations. Ultimately, cancer control will involve behavioral changes, both in the behavior of health professionals as they carry out their medical and public health practices and in the behavior of the American people in their everyday lives.

Recognizing that behavioral research can contribute importantly to understanding cancer risk and improving prevention and treatment strategies, NCI has added emphasis to this area. In 1996, an NCI-sponsored working group on behavioral research in cancer prevention and control identified research priorities for the coming years, including preventing tobacco use in children and teenagers, enhancing risk communication and comprehension, integrating prevention and early detection services into health delivery systems, and improving outcomes of genetic testing for cancer susceptibility. These and other research topics will be pursued to gain knowledge on how modifying behavior can influence the burden of cancer.

Effective cancer control requires attention to careful assessments of the nature of scientific evidence necessary for technology transfer from the laboratory to the clinic, public health department, and community. Effective cancer control also involves the highest standards of ethical conduct, not only in the conduct of science, but in terms of the social and ethnic mores of the uniquely diverse American society. Health professionals carry an important obligation to protect the public health through effective and appropriate interventions. The public, in turn, has a right to know about the nature of cancer research using human subjects and a right to know which treatments and preventive and early detection interventions are judged to be the best, given the scientific knowledge of the day.

A central effort in applying the knowledge gained in biology, epidemiology, and intervention research involves effective and widespread communication. The NCI maintains several important lines of communication. Information dissemination between scientists, physicians, and the public is facilitated through the NCI's nationwide Cancer Information Service (1-800-4-CANCER) and the PDQ computer-based cancer and clinical trials information system. The NCI

also maintains a public site on the World Wide Web containing information about the Institute and its operations, as well as the International Cancer Information Center's award-winning CancerNet site, which contains the very latest cancer treatment information available anywhere. These communication systems provide Americans -- physicians, patients and the public -- with the most current information possible on cancer treatments and on effective early detection, supportive care, and prevention technologies.

Cancer control is the final step in carrying out the basic mission of the NCI: to understand the nature of cancer and to apply that knowledge to reduce the burden of cancer -- the deaths and disabilities -- so that all Americans can lead healthier and longer lives.

How NCI Works: Planning, Review and Advisory Processes

The NCI employs a wide-ranging, multifaceted program of scientific research and other initiatives toward the goal of eliminating cancer from our lives. A variety of internal and external advisory and review groups ensure that these programs and initiatives operate comprehensively and efficiently to promote the overall goals of the National Cancer Program (NCP). In addition, several new offices have been formed to help the Institute understand and meet the needs of specific segments of the cancer community.

NCI's Advisory Groups

President's Cancer Panel

The continual appraisal and assessment of the National Cancer Program (NCP) is the responsibility of the President's Cancer Panel (PCP). The PCP consists of three individuals, appointed by the President, who monitor the development and execution of the activities of the NCP. They prepare an annual evaluation of the efficacy of the NCP, as well as periodic progress reports and other reports on areas of special interest to the President and the Congress.

National Cancer Advisory Board

The NCI's principal advisory body is the National Cancer Advisory Board (NCAB). This Presidentially-appointed group works more directly with the Institute than the PCP, advising the NCI Director on issues related to the entire NCP. The NCAB also provides a second level of review for grant applications referred to NCI and assesses the applications with regard to the NCP's priorities.

Board of Scientific Counselors

Other advisory groups provide guidance for specific components or functions of the NCI. A Board of Scientific Counselors (BSC) reviews and advises Institute leadership on intramural research activities.

Board of Scientific Advisors

Similarly, the Board of Scientific Advisors (BSA) appraises and makes recommendations for the extramural programs. It includes members of the lay community in addition to leading scientists.

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Intramural Advisory Board & Extramural Advisory Board
In order to solicit advice from the community of NCI intramural scientists and the scientific and administrative staff responsible for the review, award, and scientific management of the grant programs, the internal Intramural Advisory Board (IAB) and Extramural Advisory Board (EAB) meet regularly to advise on policy and process and serve as information conduits back to the staffs they represent.

NCI Executive Committee
The NCI Executive Committee meets weekly to make major policy and operating decisions for the Institute. The Executive Committee includes the chairs of the IAB, EAB, BSC, and BSA, as well as division directors and other key advisors to the Director. In this way, the extramural community and the internal working scientists and scientific administrators inform and influence NCI policies and actions.

New Working or Ad Hoc Groups and Planning Processes

A new family of planning groups and processes will allow the Institute to draw on expertise from outside NCI, involving the cancer community to a greater degree in setting and articulating priorities, and facilitating information exchange.

NCI Director's Working Groups
NCI Director's Working Groups are ad hoc "think tanks" appointed to address key issues in science. Their members include leaders in laboratory, clinical, and population-based research drawn from the extramural and intramural research community, staff of the NIH and other government agencies, members of professional organizations, and interested consumers and patient advocates. Recommendations will provide a framework for Institute strategic planning and for the development of operational plans by NCI divisions.

The initial quartet of Working Groups examines the four scientific areas identified as extraordinary opportunities for investment in the NCI's 1997/1998 Bypass Budget: cancer genetics, preclinical models of cancer, detection technologies, and developmental diagnostics. These four Working Groups have convened to identify strategies for transforming the broad goals articulated in the Bypass Budget into a realistic plan with short and long-term scientific aims and objectives, including implementation strategies and milestones for measuring progress. An additional working group in AIDS-related malignancies, established by the Division of Cancer Treatment, Diagnosis, and Centers, has a similar mission and charge.

Program Reviews
Program Reviews draw on the expertise of the external cancer community to provide in-depth, overarching reviews of broad organizational or trans-organizational programs. Composed of outside experts, the Program Review Groups focus on the effectiveness of a given program, soliciting testimony from NCI staff and representatives of the scientific community. Based on their findings, they issue recommendations on the future structure of the program under study. The Program Review Groups report to the BSA.

Progress Review Groups
NCI will establish another new scientific review mechanism to address high-priority, cross-cutting areas of cancer research. Progress Review Groups composed of physicians, scientists, and lay advocates will assess the state of knowledge in broad areas of research, such as breast cancer, and identify overarching scientific opportunities and needs. NCI will use the Groups' advice/recommendations to help set and sharpen scientific directions to move the science forward as rapidly as possible.

New Components

To help respond to the needs of, and forge productive partnerships with different segments of the cancer community, NCI has established several internal components.

Office of Special Populations
The Office of Special Populations advises and assists the NCI Director and provides leadership and coordination on research related to minorities and special populations.

Office of Liaison Activities
The Office of Liaison Activities was established to strengthen NCI relationships with cancer-related advocacy and voluntary organizations. The Office has two goals: 1) to create and maintain ongoing communications and information exchange between the national cancer advocacy organizations and NCI; and 2) to cooperate and collaborate with these groups in areas of mutual interest.

Office of Cancer Survivorship
It is estimated that over 10 million Americans alive today have had cancer, over two-thirds of these diagnosed 5 or more years ago. The Office of Cancer Survivorship addresses the unique physical, psychological, and economic issues faced by these individuals. Issues explored by this office include long-term medical and psychological effects of cancer treatment; factors that predispose cancer survivors to the development of second malignancies; reproductive and fertility problems following treatment; and genetic factors that may influence any of these occurrences.

How NCI Works: In Support of the Science

The most important component of the NCI's research program is investigator-initiated extramural research. It is the foundation of science and the cornerstone of the NCI. Almost half of the Institute's budget is devoted to such research, which is funded under a variety of peer-reviewed grant mechanisms designed to optimize the purpose of the research and the likelihood of project success. There are mechanisms focused on single projects undertaken by single investigators; on Program Projects that enable a team of investigators to develop a group of related projects, which by being carried out together will achieve more than if each was carried out singly; on FIRST awards for new investigators to enable them to develop a rapid foothold in science; and on small business and industry-academic collaborators.

Peer review is fundamental to investigator-initiated research. A grant proposal/application submitted to the NCI is reviewed by one of dozens of scientific review groups, which are panels of scientists in fields closely related to the applicant's research. The peer reviewers give each application a score reflecting the scientific importance of the topic proposed, the rigor of the study design, and the investigator's ability to achieve the aims of the research. With the assistance of its principal advisory body, the presidentially-appointed National Cancer Advisory Board, the NCI examines each of the grants submitted, weighs the evaluation of the peer review groups, then critically assesses cancer research priorities and its budget in order to make funding decisions.

To carry out research requires an extensive set of mechanisms, organizations, and networks linking researchers, facilities, and information. This infrastructure supports cancer research through diverse endeavors including developing central resources in tissue and data banking; conducting directed programs in drug discovery and large-scale screening for preventive agents, tracking changes in cancer incidence, mortality and morbidity; and fostering the critically needed training of cancer researchers.

Like investigator-initiated research, most components of the infrastructure are funded through grants and evaluated through peer-review, including a network of Cancer Centers, Community Clinical Oncology Programs, and Clinical Trials Cooperative Groups. Other components are funded under contract, such as the Surveillance, Epidemiology, and End Results Program, a network of cancer registries providing surveillance information on cancer incidence, mortality, and survival. The NCI's Frederick Cancer Research and Development Center is also funded under contract, and all contracts are evaluated through a peer-review mechanism.

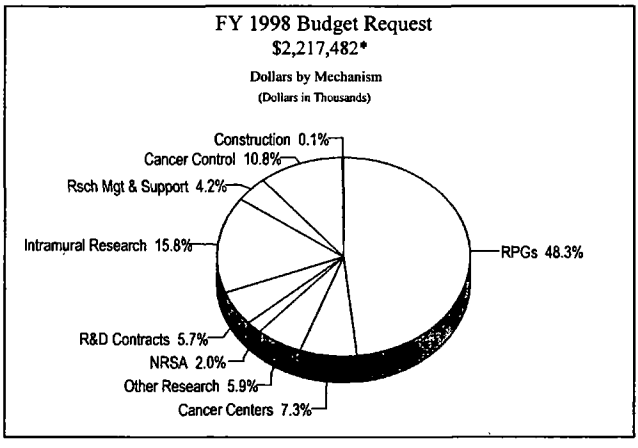
The purpose of research is to develop understanding. NCI's cancer research funding strategy is to assure that there is sufficient funding to enable scientists to pursue those research areas with the greatest scientific opportunity -- that is, the greatest opportunity to increase our knowledge of cancer. As we have noted, research on cancer involves the full spectrum of research, from the most fundamental laboratory research, to large-scale trials of cancer prevention and treatment methods. Funding decisions are based principally on the advice of scientists themselves as to those areas and projects that have the greatest potential to expand our knowledge of cancer. This expansion can occur in ways that at first may seem unlikely. For example, research on families who seem to have a propensity to develop breast cancer has shown they also have a higher risk of prostate cancer, linking both to the same gene. Similarly, research on the viral causes of cancer led to the identification of the gene p53, now understood to be a tumor suppressor gene that fights the development of almost all cancers.

A second critical factor that guides program direction, in addition to scientific opportunity, is the burden of specific cancers. For example, breast cancer, the leading cancer among women with over 184,000 new cases each year, is a major priority for NCI. Prostate cancer, the leading cancer among men, and in fact the single cancer with the greatest number of new cases each year -- over 300,000 -- is another NCI priority. Both of these cancers involve steroid-dependent epithelial cells, and the tools and insights required to make progress against both are difficult to separate. Research on the hormonal aspects of testicular cancer, a relatively rare cancer with

about 7,000 cases annually, may well provide clues to breast and prostate cancers as well. There is no research allocation schema that can account for these essential inter-relationships between cancers. Advances against one type of cancer may well affect every other type of cancer, and may occur in fundamental and applied research. These advances come from both targeted and, more often, non-targeted research that has the potential to apply to all cancers.

Resources for Cancer Research: FY1998 Budget Request

This FY1998 President's Budget of $2,217,482,000 represents an increase of $61,066,000 (2.8%) over the FY1997 estimate for non-AIDS activities. In addition, funds totaling $224,256,000 for NCI's AIDS research are included in the NIH Office of AIDS Research (OAR) request. This FY 1998 budget request will permit the NCI to continue the support of research directed toward the further identification of causes, improved detection and diagnosis approaches, improved clinical treatment studies, fundamental research and activities in the prevention and control of cancer.



Research Project Grants (RPGs).....	$1,070,241	Research & Development Contracts..	$125,353
Cancer Centers.....	161,647	Intramural Research.....	349,747
Other Research.....	131,063	Research Management & Support.....	92,091
National Research Service Awards..	44,419	Cancer Control.....	240,348
		Construction.....	2,573

* Funds for NCI AIDS research are requested through the NIH Office of AIDS Research

Infrastructure of Discovery

Supporting the achievement of the goals and objectives of the NCI is an infrastructure of researchers, research institutions, training, applications research, and cancer surveillance. In this section we briefly outline the components of this infrastructure of discovery and the funding being requested to continue making advances against cancer.

Creation of New Knowledge

The "gold standard" of scientific accomplishment is the creation of new knowledge through research. The Nation's researchers represent the single most valuable resource of the research program. To foster the creativity of this vital national resource and provide the freedom to pursue the best ideas that will yield progress against cancer, NCI offers researchers the opportunity to compete for research project grants. Recognizing the key role that individual investigators play in the cancer research enterprise, the NCI has shifted its funding priorities to support a significant number of new, investigator-initiated single project research grant applications, ensuring that more promising research projects have the support they need to come to fruition. The single-investigator grant pay line rose from the 15th to the 23rd percentile in FY 1996. We expect this pay line to continue in FY 1998. NCI has also instituted a quick appeals process for unfunded grant applications whose merit rating falls near the pay line, thereby permitting the independent investigator an expedited process to respond to the initial peer review comments. Through this Accelerated Executive Review (AER) over 50 grants were funded in FY 1996.

The main pool of funds expended by the NCI on extramural research is known as the Research Project Grant (RPG) pool. These dollars represent those funds competitively awarded through peer-review to support individual cancer investigators in hundreds of academic, medical, public, and private research institutions located in almost every state across the country.

Skin Cancer Genetics: An Example of Successful Investigator-Initiated Research

One of the most common human cancers is basal cell carcinoma (BCC) of the skin. BCC occurs in both a hereditary and a sporadic (nonhereditary) form; individuals with the inherited disease, known as Gorlin syndrome, are predisposed to skin cancer and to congenital skeletal defects. The gene for Gorlin syndrome, called PTCH, was recently identified by NCI-supported scientists. Defects in PTCH were found in members of several Gorlin syndrome families and in tumors from some patients with sporadic BCC as well. An unexpected but exciting finding was that PTCH is the human version of a gene studied extensively in the fruit fly and the mouse. This gene, known as *patched*, has been shown to be important in the early stages of fruit fly development and in the mouse for correct skeletal, limb, and nueral development. Extensive knowledge about the function of *patched* in the fruit fly and mouse has sped the study of the function of the PTCH gene product and has already given us a list of other genes that are now excellent candidates for other human cancer genes. The identification of PTCH in humans paves the way for additional studies to learn the pathology of BCC and for the design of effective new therapies targeted to the specific defects brought about by the mutation of the PTCH gene.

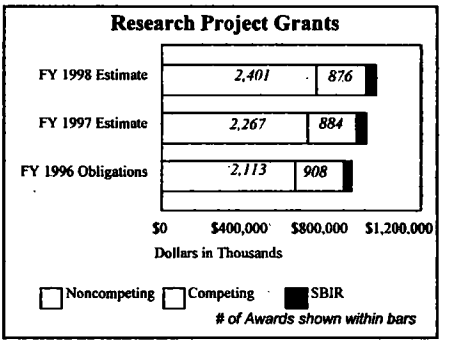
Collectively, these research project awards span the full range of basic, clinical, and population-based studies of cancer etiology, biology, prevention, detection, diagnosis, treatment, and control. These grant awards and the dedicated researchers behind them constitute the largest single categorical expenditure of resources that the NCI, through the extramural research community, commits annually to combat cancer. The scientific and medical advances that come from these investments represent the irreplaceable intellectual capital upon which rests the future of cancer research in this country and the world.

Research Project Grants: (in thousands)

FY1997 Estimate -- $1,020,743

FY1998 President's Budget -- $1,070,241

SBIR/STTR included in above:
FY 1997 Estimate -- $45,737
FY1998 President's Budget -- $45,855



Research Conducted Within Federal Laboratories

The NCI has a comprehensive research program targeted across many aspects of the cancer research spectrum. The Intramural Research Program (IRP) includes the Divisions of Basic Sciences, Clinical Sciences, and Epidemiology and Genetics and is one model of a comprehensive effort to understand and diminish cancer. With the FY 1998 budget for cancer of approximately $350 million, scientists, technical, and support staff, as well as research fellows and visiting scientists from around the world conduct basic, clinical, and population based research in all the cancer research areas. These include cancer biology, causes and predisposition, and clinical investigation in the areas of prevention, detection, diagnosis and treatment.

A large number of NCI intramural researchers are recognized leaders in their fields as reflected by citations of their work by other scientists, service on editorial boards of peer-reviewed scientific journals, and the prizes and honors they receive. Many NCI intramural scientists collaborate with investigators across the Nation and around the world and with the biotechnology and pharmaceutical industries to accelerate the application of new knowledge to development of products to benefit human health.

The Institute takes great care to ensure careful stewardship of resources and uniform standards of excellence in a stimulating environment where young people receive mentorship, training, and inspiration and where scientists at all stages of their careers are encouraged and stimulated to be

creative and strive for critically important knowledge. These efforts are detailed in the widely distributed manual *National Cancer Institute: Intramural Organization and Principles.* The IRP has long served as a training locus for cancer researchers in all fields, and many of the leading scientists across the country and in other nations have been trained in its clinics and laboratories. It continues to serve as an important resource to train the next generation of men and women who will carry forward the quest for knowledge that will lead us to successful strategies to prevent and cure cancer.

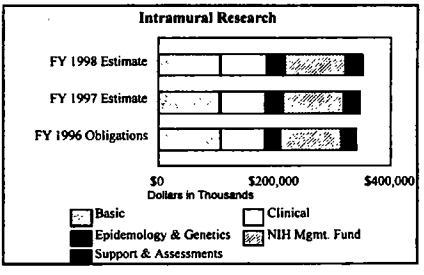
The intramural clinical research program is housed principally in the NIH Warren G. Magnuson Clinical Center where patients from across the country are treated only on research protocols. The Clinical Center is a unique resource for investigators to develop and test novel therapies derived from our growing body of knowledge. It provides a pivotal setting for the NIH community that facilitates the rapid transfer of new information from the laboratory to the patient and back to the laboratory in the search to understand the nature of cancer and how to tame it.

The existence of the IRP is central to the identity of the National Cancer Institute as a scientific, not a bureaucratic, organization. Many physicians who manage NCI extramural grants and programs spend part of each week doing research in the Clinical Center and would not stay in key administrative and managerial jobs without this opportunity. Interchange between active researchers, the scientists who manage the grant portfolios, and the scientist executives who direct the institute and set priorities and directions enriches the quality of decision making and continually reminds all of us of our mission: to learn how to reduce death and suffering from cancer.

Intramural Research: (in thousands)

FY1997 Estimate--$345,747

FY1998 President's Budget -- $349,747



Research Centers Located Across the Nation

NCI-supported Cancer Centers, including the Specialized Programs of Research Excellence (SPOREs), represent the strongest institutions in the nation dedicated to scientific innovation and excellence; to interdisciplinary research, training and education; and to coordinated recognition and pursuit of new research opportunities. Cancer centers are committed to transferring new knowledge to practical clinical and community applications that will reduce cancer incidence, morbidity, and mortality and increase the survival and quality of life of cancer patients. These institutions have the dynamic, flexible research infrastructures and organizational capabilities that consistently promote and sustain the kinds of collaboration between basic, clinical, and

population research scientists needed to address the complicated questions associated with cancer causation and progression.

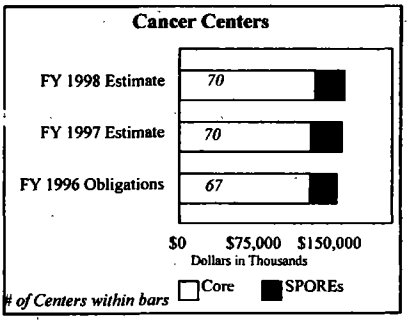
Research activities on the molecular and cellular dynamics of cancer cells, vaccine development, novel approaches to gene therapy, and prevention and control interventions all illustrate the need for such effective collaborative enterprises. Cancer centers achieve their objectives by providing a framework that stimulates the participation of a broad range of diverse, but complementary scientific interests. They provide ready access to the most advanced research technologies and services, assure a close association between state-of-the-art research and state-of-the-art care activities within the institution, develop key collaborations with industrial, community, and state health organizations, and link the research capabilities and expertise of scientists within the institution to problems of cancer incidence and mortality in their communities and regions. With their broad geographic distribution, cancer centers are key partners and, in many ways, a principal vanguard of the NCI in bringing the benefits of research more directly to local communities and regions of the country.

The NCI conducted an in-depth program review of the Cancer Centers program with a view toward enhancing and strengthening the ability of cancer centers to conduct research that will reduce the incidence and mortality of cancer. The Program Review Group identified the program's strengths, as well as opportunities for improved performance, and made several major recommendations regarding the designation, structure, function, and review of cancer centers and the distribution and use of cancer center funds. The Program Review Group also proposed an expanded role for cancer centers as key regional and national resources in the war against cancer.

Cancer Centers: (in thousands)

FY1997 Estimate--$158,647

FY1998 President's Budget -- $161,647



Clinical Trials

A strong clinical research structure including a comprehensive program of clinical trials in treatment, early detection, and prevention is a critical component of the NCI research program. The components of the program include the cancer centers described above and the Cooperative Groups described in the following section. The Community Clinical Oncology Program (CCOP) is also a crucial component, extending the opportunity for participation in clinical trials to communities across the country. Hundreds of clinical trials are supported through these and

other research mechanisms, such as individual research grants, program project grants, cooperative agreements, and contracts.

Increasing Access to Clinical Trials

Starting in 1996, through an innovative agreement between the NCI and the Department of Defense (DoD), thousands of DoD cancer patients have more options for care and greater access to state-of-the-art treatments. Under the agreement, patients who are beneficiaries of TRICARE/ CHAMPUS, the DoD's health program, are allowed to participate in NCI-sponsored Phase II and Phase III clinical treatment trials. In the past, DoD coverage was limited for medical care delivered as part of a clinical trial. NCI and DoD are refining a system that allows physicians and patients to determine quickly what current trials meet their needs and where they are taking place. By increasing enrollment in clinical trials, this partnership will foster clinical research as well as benefit patients.

An even wider-ranging agreement with the Veterans Administration (VA) will allow eligible veterans of the armed services to participate in NCI-sponsored prevention, diagnosis, and treatment studies. This agreement covers participation in phase I, phase II, and phase III clinical trials. About 2.9 million veterans receive care through the VA system each year.

Cooperative Group Clinical Trials Program. The nationwide Cooperative Group program promotes and supports clinical trials in cancer treatment, prevention, and early detection. More than 1,400 institutions and 8,500 investigators participate in these Cooperative Group studies.

The sheer number of different types of cancers and the biological complexity of individual cancers present extraordinary challenges to the efficient clinical investigation of new anti-cancer agents or new treatment strategies suggested by laboratory and animal experiments. To more rapidly test such potential treatment advances in patients, the NCI maintains a standing funded clinical trials program to conduct such investigations. In this way, new clinical trial organizations do not have to be created each time a potential new cancer treatment emerges. Nine NCI-sponsored Cooperative Groups place approximately 20,000 new patients onto cancer treatment protocols annually, principally large randomized Phase III clinical trials that have been responsible for establishing the current state-of-the-art for cancer treatment worldwide.

In addition, new anti-cancer agents being studied for the first time in patients are entered into Phase I and Phase II clinical trials; many of these early treatment clinical trials are conducted under NCI Investigational New Drug (IND) sponsorship in institutions funded by NCI cooperative agreement grants. Currently, close to 200 investigational agents or treatment strategies, ranging from new chemotherapy drugs and cancer vaccines to agents that prevent tumor blood vessel development, are being studied under NCI INDs. Many of these agents are being developed clinically as a result of active NCI cooperation with biotechnology and pharmaceutical companies, accelerating the clinical testing of scientific advances emerging from

these sources. Others come from the scientific laboratories and discovery programs of the NCI itself. Examples of important new anti-cancer agents that have recently come from NCI development include paclitaxel (Taxol®) for ovarian and breast cancers, interferon alpha for malignant melanoma and chronic myelocytic leukemia, fludarabine for chronic lymphocytic leukemia, and all-trans retinoic acid for acute promyelocytic leukemia.

Science is increasingly delineating the distinct biological bases for many tumors. As a result, many clinical trials of new treatments are linked to particular laboratory studies, and many NCI trials now include laboratory components in addition to the clinical evaluations. For example, clinical studies of new acute leukemia treatments now routinely include the analysis of genetic changes in the malignant leukemia cells of the individual patient. The NCI has funded small clinical trials groups especially to evaluate potential new treatments for patients with brain tumors, malignancies occurring in the setting of AIDS, and pediatric tumors, due to the very specialized nature of these cancers. A similar program has very recently been established to develop new therapies for breast cancer.

Furthermore, recognition of gender, age-related, and ethnic differences in individual responses to cancer therapy has led to initiatives to make such evaluations a routine part of the clinical development of new anti-cancer agents. A recent NCI evaluation shows that minority populations participate in treatment clinical trials in proportion to their cancer incidence. Minority participation in clinical research is a high priority for the Institute. Two new grant programs are supporting research on ways to increase participation of women and minority individuals in prevention and screening studies. Interventions are being tested on recruitment methods and steps to retain participants through the course of a trial.

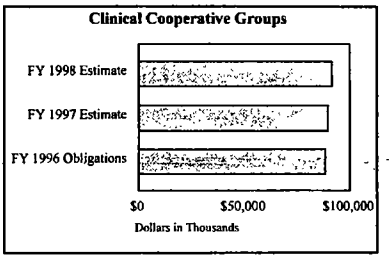
The NCI Role in the Development of Paclitaxel (Taxol®): Paclitaxel is a plant-derived drug originally identified through the NCI's natural products screening program and brought into clinical trial by the NCI in the mid 1980s. The drug has been found to have important anti-tumor activity in patients with ovarian and breast cancers; for example, one Cooperative Group-conducted protocol recently demonstrated a 50 percent increase in median survival time among women with advanced ovarian cancer who were treated with the combination of paclitaxel and cisplatin compared with the standard approach of cisplatin with cyclphosphamide. The NCI has collaborated with Bristol-Myers Squibb in the clinical development of paclitaxel under a Cooperative Research and Development Agreement.

Greater patient access to advanced therapeutic approaches has been a chief goal of the NCI clinical trials program. The field of childhood cancers is a success in this regard. About 70 percent of children who develop cancer in the United States annually are treated in NCI-sponsored Cooperative Group clinical trials. While the percentage of adults with tumors treated on protocols is much smaller (on the order of one percent), more than 8,500 oncologists participate in NCI trials, allowing patients to benefit from advanced treatment approaches whether they are seen at the most comprehensive cancer center or the smallest community hospital.

Clinical Cooperative Groups Clinical Trials:
(in thousands)

FY1997 Estimate--$89,328

FY1998 President's Budget -- $91,128



Community Clinical Oncology Program (CCOP). The Community Clinical Oncology Program (CCOP) is a mechanism that links community cancer specialists and primary care physicians with clinical Cooperative Groups and cancer centers to conduct cancer treatment, prevention, and control clinical trials. Currently, there are 51 CCOPs in 30 states, with 300 participating hospitals where approximately 2,000 physicians cooperate to enter patients and individuals at risk for cancer on NCI-approved clinical trials. An additional 8 minority-based CCOPs are funded to enhance the participation of minority populations in clinical trials research. These programs are located in nine states and Puerto Rico, bringing an additional 42 hospitals and 350 physicians into the clinical trials network. Through this network, individuals can access state-of-the-art clinical research trials while remaining in their home communities.

Each year the CCOPs enter over 4,000 patients into cancer treatment clinical trials (accounting for about one-third of all patients on NCI Phase III treatment efficacy trials). An additional 4,000 participants are entered onto cancer prevention and control clinical trials from the CCOP communities. Support is also provided for university members and affiliates to participate in prevention and control research.

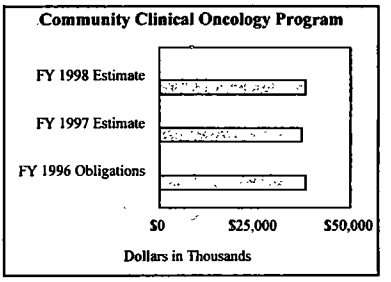
The CCOP covers the spectrum from testing new combinations of anti-tumor drugs in cancer patients to testing the ability of new agents to prevent first occurrences of cancer. Examples of the latter are the Breast Cancer Prevention Trial and the Prostate Cancer Prevention Trial. CCOPs have also demonstrated successful interventions for symptom management and continuing care of cancer patients, including treatment for mucositis and hot flashes, common side effects of chemotherapy. The program is rapidly evolving to include interventions for individuals with specific molecular alterations associated with genetic cancer susceptibilities.

Linking the community, university researchers, and the NCI, the CCOP has proved to be one of the critical paths for the dissemination of state-of-the-art cancer treatment information. The CCOP research network is well positioned to conduct the research of the future that will move oncologic practice from the treatment of established disease to the management of cancer risk.

Community Clinical Oncology Program:
(in thousands)

FY1997 Estimate --$37,073

FY1998 President's Budget -- $38,033
(Funds for CCOPs are included within the Cancer Control budget mechanism)



Training and Education

The Cancer Training Program is a critical resource to the NCI. It supports a broad range of training activities, individual fellowships and career awards, and education grants in the finest institutions in the country. Because those trained in research today will form the intellectual foundation in the basic, clinical, and population sciences ten years from now, training activities sponsored by the NCI must continually anticipate the human resource needs of cancer research in the future. The quality and progress of the Nation's cancer research effort tomorrow will depend directly on the quantity and quality of the individuals who are attracted to careers in cancer research today, and on the appropriateness of the strategies used to train these individuals. Rapid advances in our basic understanding of genetic and molecular changes contributing to the growth and spread of cancer cells provide increasing opportunities to move this knowledge into patient and population research settings and to have a direct impact on reducing cancer incidence and mortality through new screening, prevention, diagnostic, and therapeutic interventions.

To meet this challenge, the NCI is pursuing four interdependent training and education strategies. The first is to maintain the critical mass of independent basic scientists studying cancer at the most fundamental levels of genetics and molecular biology; basic discoveries will always generate the new knowledge critical for continued progress in eliminating cancer. The second strategy is to encourage a greater proportion of well-trained basic scientists to shift their interests in model systems to human biology and human disease; it is clear that the complex objectives of cancer research will depend more and more on effective collaborations between basic scientists and clinical and population scientists.

NCI's third training strategy focuses on attracting more young physicians and public health specialists into cancer research; of particular importance will be to develop and sustain training programs that will markedly improve the quality and quantity of physicians trained in the clinical sciences, as well as continue programs that will develop a larger contingent of physicians and public health specialists in the biostatistical, epidemiological, behavioral and other prevention and control sciences. The fourth strategy uses education grants to improve the curricula for medical and public health students and to improve community education and information dissemination programs.

NCI continues to support extensive training and career development programs for minority individuals in order to increase the number of biomedical scientists from under-represented population groups and to increase the number of research personnel leading us into the next century. This investment in intellectual resources is expected to pay off through the expansion of the nation's ability to identify and respond to cancer trends among all sectors of the population. NCI training programs support minority students in the pre-and post-doctoral phase of development, with awards made through the National Research Service Awards, career development awards, supplements to institutional awards, and cancer education grants. Additionally, the Comprehensive Minority Biomedical Program supports these activities through several mechanisms, including recently developed minority medical oncology awards intended to encourage newly trained clinicians to acquire clinical research experience in oncology. Of particular importance is the emphasis the program places on issues directly related to the health status of minority populations.

A new award mechanism used to "bridge the gap" between the mentored research environment to an independent research career is the Howard Temin Award. This special award originated last year is intended for scientists who have demonstrated unusually high potential during their initial stages of training and development. It is aimed at fostering the research careers of outstanding, junior, basic, clinical, and behavioral scientists who are committed to developing research programs highly relevant to the understanding of human biology and human disease as it relates to the etiology, pathogenesis, prevention, diagnosis, and treatment of cancer.

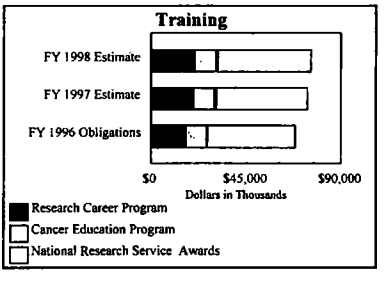
NCI is committed to supporting research training in the many disciplines that can contribute to understanding and ultimately solving cancer's mysteries. Strengthening the skills of basic, clinical, behavioral, and population scientists is an essential underpinning of our efforts to improve public health by reducing the burden of cancer.

This budget request provides a 3.5% stipend increase for post-doctoral fellows with 0 and 1 years of experience for the National Research Service Awards.

Training and Education:
(in thousands)

FY1997 Estimate--$73,747

FY1998 President's Budget --$75,097



An Infrastructure of Support

Research is a complex enterprise that only flourishes in the context of a strong, reliable support

infrastructure. Contracts are a primary mechanism that the Institute uses to provide support for research, information dissemination and management.

Contracts support a variety of research activities, such as components of drug development, cancer control, epidemiology, surveillance, cancer biology, and information dissemination activities. Contracts principally support program development activities in which the NCI defines the area of work, provides guidelines as to how the work will be accomplished, and establishes specific deliverables. The use of contracts is exemplified in the drug development program where a range of services are acquired to support drug screening, synthesis, acquisition, preclinical testing, pharmacology, toxicology, and drug formulation -- all sequential activities necessary to produce a new drug. The programs that employ contracts are broad and diverse, with a vital role in supporting laboratory, clinical, and population-based research, NCI's management infrastructure, and information dissemination to both the public and the scientific community.

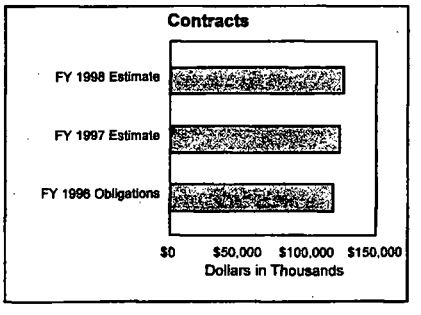
The contract mechanism is extremely useful for research support when the tasks can be identified at the outset of the program or project. When a specific end product is desired or a project needs to be conducted with the NCI's direct involvement, the contract mechanism is appropriate.

A good example of NCI's use of the contract mechanism is the operation of an in vitro cell-based drug screen to discover new agents with potential therapeutic value for cancer and HIV. The drug screen has helped to identify compounds with confirmed anti-cancer and/or anti-HIV activity from either synthetic chemical compounds or natural products. Contracts enable NCI to maintain a vigorous acquisition program for procuring both chemically defined synthetic compounds and crude natural products from all over the world for examination in this high-throughput screen. Since the inception of the present screening program in 1990, approximately 50,000 pure compounds have been screened. About 700 exhibited a unique pattern of activity and went on to further testing. Of these, NCI has selected five for full-scale development to clinical trials.

Research Support Contracts: (in thousands)

FY1997 Estimate--$122,953

FY1998 President's Budget -- $125,353



Cancer Control

Consensus among experts on the usefulness of new medical knowledge does not guarantee its widespread application. Cancer control, as supported by the NCI, addresses this challenge through research on the behavioral, psychosocial, health services, communication, and cancer surveillance aspects of translating proven technologies and tested methodologies into routine practice in the community. Among the requirements may be the removal of barriers to application often found in areas of information dissemination, access to health care services, or cultural conventions. These barriers may be present in the home, the community, the environment, or at the interface with the health care system.

NCI's cancer control activities include a special focus on population groups who bear excessive risks for cancer or who lack access to state-of-the-art cancer services. Research efforts have been undertaken with the collaboration of community and private sector organizations which can be mobilized to assist these population groups. Research networks of minority investigators and leadership groups of community representatives have been established to help accomplish NCI's cancer control objectives.

Important to the process of technology transfer, NCI's activities in information dissemination include programs for both the public and health care professionals. These programs are based upon population needs identified through epidemiologic studies and market research among specific population groups. This allows for the design of programs that are relevant and understandable to each group. Information can be disseminated nationally through the NCI's patient education program, the leadership initiatives for special populations, minority research networks and the Cancer Information Service.

Cancer surveillance is a critical component of cancer control and, in fact, underlies the entire NCI research portfolio. The tracking and analysis of trends in cancer incidence, mortality, and survival rates stimulate new activities and monitor the effects of ongoing programs. The cornerstone of this effort is the Surveillance, Epidemiology, and End Results (SEER) Program, which monitors the Nation's cancer burden and provides the basis for assessing individual, organizational and societal factors that can mediate cancer rates.

TRACKING PROGRESS: THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) PROGRAM

The SEER Program is the most authoritative source of information on cancer incidence, survival, and mortality in the United States. SEER is distinguished by its broad scope and rigorous quality standards which have made it the model for cancer registries throughout the world. Established in 1973, it now includes 10 state and regional registries (covering about 14 percent of the total U.S. population) that report data to NCI. More than 2 million cancer cases are in the database, and approximately 150,000 new cancers are registered annually. Data are collected on tumor site, morphology, stage at diagnosis, first course of treatment, patient demographics, and follow-up for vital status. To strengthen information about the cancer burden borne by defined populations including minorities, the underserved, the elderly, and

rural residents, the SEER sample was expanded in 1992 to improve representations of U.S. Hispanic, Asian/Pacific Islander, American Indian, and African American populations.

Updated annually and provided as a public service in print and electronic formats, SEER data are used by thousands of people each year. Users include researchers, people planning public health interventions, and legislators and health planners who want to assess progress and make policy and funding decisions. The public is exposed to SEER data virtually every day, though they may not know its source. Researchers use SEER to identify geographic and population differences in cancer patterns and to study possible links between cancer incidence and occupational, environmental, and lifestyle influences. SEER data increasingly are being used to answer questions about cancer causation, prevention, treatment, and control. For example, the database is now used to study patterns and outcomes of cancer care and to assess the extent to which state-of-the-art treatments are used across the country. An innovative linking of SEER and Medicare data now permits important research on patterns and sources of cancer care and the costs of cancer care among the elderly.

Information dissemination is a central component of NCI's mission and mandate. NCI reaches all segments of our diverse population with needed cancer information and speeds the assimilation of clinical advances in cancer into standard medical practice through vital programs including:

World Wide Web. Many NCI offices and laboratories already maintain their own Web sites. In order to fully realize the enormous information dissemination potential of the World Wide Web, the NCI is currently redesigning its web site to increase its usefulness as a communication tool. The new Web site, which will go on line in early 1997, will be organized so that clinicians, researchers, and the public at large can quickly and easily locate up-to-the-minute information that is relevant to their needs. In addition, an "NCI Only" area -- the NCI Intranet -- will facilitate information sharing among scientists at the Institute. The current version of the NCI web site can be found at **http://www.nci.nih.gov**.

The Cancer Information Service (CIS). The CIS provides accurate, up-to-date cancer information to patients and their families, the public, and health care professionals in all 50 states through 19 offices located at NCI-funded cancer centers and other health care institutions. By dialing 1-800-4-CANCER, callers are automatically connected, free of charge, to the office serving their region. Information on specific cancer types, state-of-the-art care, clinical trials, and resources such as support groups or screening and smoking cessation programs is provided in English or Spanish by specialists who respond to more than 600,000 inquiries annually. The CIS regional offices are also NCI's focal point for state and local level cancer education efforts which particularly target underserved, high-risk, and low literacy populations. The CIS offices also catalog local cancer-related services, catalyze community outreach efforts, and provide print materials and technical assistance to help local organizations sponsor cancer education programs, media campaigns, and other community programs.

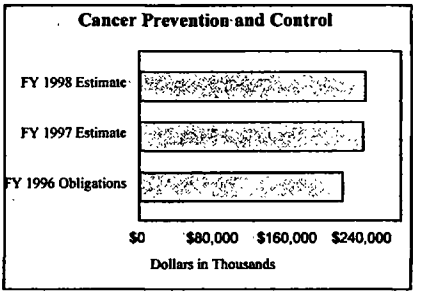
The International Cancer Information Center (ICIC). The ICIC provides an array of cancer information for scientists, health care professionals, and the public. They are responsible for developing and maintaining PDQ, the NCI's comprehensive cancer information database, as well as the bibliographic CANCERLIT database. ICIC also maintains the award-winning CancerNet web site (**http://cancernet.nci.nih.gov**), a repository of current cancer-related information, including selected PDQ information, NCI Fact Sheets for patients and the public, and news and information from the cancer community.

Selected PDQ information, NCI Fact Sheets, and other materials are available in Spanish and English 24 hours a day, seven days a week through NCI's CancerFax facsimile system, as well as via Internet electronic mail. All of the ICIC's scientific information services are available through its innovative Information Associates Program, a customer-oriented membership service launched in 1994.

Cancer Control: (in thousands)

FY1997 Estimate --$238,103

FY1998 President's Budget --$240,348



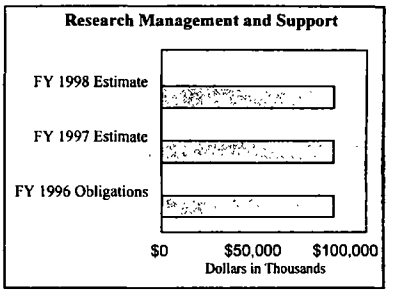
Management and Support

Activities essential to sustain, guide, and monitor both the extramural and intramural activities of the NCI are termed as the Research Management & Support function. These activities include overall scientific program direction and administration by the immediate Office of the Director, with assistance from grant and contract science managers and staff in finance, human resources, legislation, science policy and assessment, and technology transfer and development. The review and oversight activities of both the National Cancer Advisory Board and the President's Cancer Panel are also included. This segment of the budget also supports the NCI's share of central NIH facilities and operations, and extramural staff salaries (intramural salaries are included under the Intramural Research budget). A significant portion of the NCI's information dissemination and health education efforts are supported through this part of the budget, including materials prepared for the general public, health and medical professionals, and the scientific and research communities. It has been aligned in accordance with NCI's substantial reorganization and streamlining and reflect a level consistent with directives to the NIH for administrative reductions.

Research Management and Support:
(in thousands)

FY1997 Estimate -- $92,091

FY1998 President's Budget -- $92,091



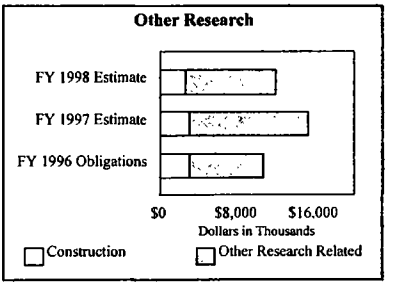
Other Research Support

There are several smaller grant activities such as Conference Grants, Scientific Evaluation, and Construction grants and contracts that contribute to the discovery function of the Institute. Conference awards support meetings, conferences and workshops relevant to promoting the goals of the NCI. Scientific Evaluation awards are the vehicle that supports the scientific review of grant and contract proposals. The grant reviews are conducted by either the NIH Division of Research Grants or the NCI, depending on the granting mechanism. Construction funds provide partial support for the modernization or development of cancer research facilities at institutions located throughout the Nation. Additionally, limited construction funds are provided for repair and improvement at the Frederick Cancer Research and Development Center.

Other Research: (in thousands)

FY1997 Estimate -- $15,057

FY1998 President's Budget -- $11,830



Budget Policy

The FY1998 President's Budget of $2,217,482,000 represents an increase of $61,066,000 over the level authorized within the FY 1997 Omnibus Appropriation adjusted for the rescission for administrative costs. This budget request permits the NCI to maintain the nation's commitment to cancer research and support the most highly meritorious research projects.

In the FY1998 President's Budget, the National Cancer Institute's support for research project grants (RPGs) would remain the highest priority of increase by 4.9 percent over FY1997. NIH policy links RPG average cost increases to total program budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for research project grants (RPGs). In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs will increase by up to two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP). These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 876 competing RPGs.

There are several trans-NIH special initiatives for FY1998 in which the NCI will participate significantly. Of the budget increase of $61,066,000, nearly 70% (or $42,500,000) is directed to these initiatives as indicated below. The independent investigator initiated grant (Research Project Grant) will be a primary funding vehicle to address new strategies and opportunities in these areas.

New Approaches to Pathogenesis
New Preventive Strategies Against Disease
Genetics of Medicine
Advanced Instrumentation & Computers in Medicine and Research
Therapeutics/Drug Development

An area of particular emphasis for exploration includes the Cancer Genome Anatomy Project. The growing understanding of the roles of specific genes in the development and behavior of cancer offers an unprecedented set of opportunities to fundamentally alter our approach to cancer. The NCI will initiate a new set of initiatives to produce a new generation of knowledge and technology to read the molecular fingerprint of cancer cells to aid in early detection, diagnosis, prevention and treatment of cancer. These programs will also provide us with the tools to unravel the critical interactions of genes with diet, hormones and the environment that have eluded us for so long.

Also, the recent discovery of specific genes that are predictive of predisposition to cancer will only benefit people if we rapidly move to provide interested individuals with an expanded opportunity to seek information, counseling and testing at centers of excellence and if we

establish the best surveillance and interventions to reduce the chances that individuals at risk will develop cancer. This will require additional clinical research. The Cancer Genetics Network will address these issues by establishing a network of centers of excellence in human cancer genetics to enhance our ability to answer the many pressing questions that these new discoveries raise.

In addition, in conjunction with the Department's youth tobacco prevention initiative, in FY 1998, the NCI will extend for one full year its support of its current American Stop Smoking Intervention Study (ASSIST) contracts. The ASSIST program, which NCI has supported since FY 1991, represents a collaborative effort among the NCI, the American Cancer Society, State and local health departments, and other voluntary organizations to develop comprehensive tobacco control programs in 17 States across the United States. Its purpose is to demonstrate that the wide-spread, coordinated application of the best available strategies to prevent and control tobacco use will significantly accelerate the current downward trend in smoking and tobacco use. More than 3,000 community organizations have joined ASSIST coalitions in the 17 States. The full-year extension in FY 1998 will carry the operations and infrastructure of these projects through to the end of FY 1999. Between now and then, NCI will be working with its Departmental and external partners to determine the most effective way to support and manage future tobacco prevention efforts as we expand beyond the research phase of ASSIST and transition to the essential task of supporting disseminated tobacco prevention and control programs in public health. Also in FY 1998, NCI will fund evaluation studies of the progress achieved by the ASSIST program sites to date.

Coordination of the many activities that comprise the National Cancer Program (NCP) calls for exchange of information, avoidance of overlap and duplication, support of the many areas of expertise needed to overcome cancer, and recognition and stimulation of research opportunities that lead to understanding the etiology and biology of cancer and thus provide the means to control and prevent it. The NCI acts as the facilitator of this concerted effort against cancer. These efforts often involve interactions with entities outside of the NCI including significant collaborative programs and projects with other NIH components as well as other sectors of the Federal government.

Funding for the NCI during the last five years has been as follows:

	Amount	FTE
1993	$1,805,391,000	2,601
1994	1,864,093,000	2,382
1995	1,913,167,000	2,231
1996	2,029,591,000	2,180
1997	2,156,416,000	2,180

Funds for AIDS research conducted by the NCI are included within the NIH Office of AIDS Research (OAR) request.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	2,113	$653,937,000	2,267	$715,470,000	2,401	$761,226,000
Administrative supplementals	(214)	14,615,000	(216)	15,000,000	(216)	15,000,000
Competing:						
Renewal	357	119,979,000	357	134,285,000	305	117,778,000
New	546	123,184,000	516	108,567,000	564	129,815,000
Supplemental	5	694,000	11	1,684,000	7	567,000
Subtotal, competing	908	243,857,000	884	244,536,000	876	248,160,000
SBIR/STTR	180	35,062,000	144	45,737,000	144	45,855,000
Subtotal, RPGs	3,201	947,471,000	3,295	1,020,743,000	3,421	1,070,241,000
Research Centers						
Specialized/comprehensive	67	153,857,000	70	158,647,000	70	161,647,000
Clinical reseach						
Biotechnology						
Comparative medicine						
Research centers in minority institutions						
Subtotal, Centers	67	153,857,000	70	158,647,000	70	161,647,000
Other Research						
Research careers	210	16,383,000	214	20,086,000	218	20,486,000
Cancer education	75	9,821,000	70	9,992,000	70	10,192,000
Cooperative clinical research	157	87,992,000	152	89,328,000	155	91,128,000
Biomedical research support						
Minority biomedical research support		1,874,000		2,588,000		2,788,000
Other	49	5,572,000	57	9,469,000	52	6,469,000
Subtotal, Other Research	491	121,642,000	493	131,463,000	495	131,063,000
Total, Research Grants	3,759	1,222,970,000	3,858	1,310,853,000	3,986	1,362,951,000
Training	FTTPs		FTTPs		FTTPs	
Individual	263	6,984,000	270	4,938,000	270	4,938,000
Institutional	1,280	34,186,000	1,285	38,731,000	1,285	39,481,000
Total, Training	1,543	41,170,000	1,555	43,669,000	1,555	44,419,000
Research & development contracts	145	117,896,000	167	122,953,000	167	125,353,000
(SBIR/STTR)	(4)	(1,165,000)	(5)	(1,000,000)	(5)	(1,187,000)
	FTEs		FTEs		FTEs	
Intramural research	1,336	338,328,000	1,336	345,747,000	1,336	349,747,000
Research management and support	656	90,040,000	656	92,091,000	656	92,091,000
Cancer prevention & control	188	216,187,000	188	238,103,000	188	240,348,000
Construction	0	3,000,000	0	3,000,000	0	2,573,000
Total, ICD	2,180	2,029,591,000	2,180	2,156,416,000	2,180	2,217,482,000
(Clinical Trials)		(353,887,000)		(364,189,000)		(372,607,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research:								
Cancer causation	564	$560,182	564	$588,715	564	$601,090	0	$12,375
Detection and diagnosis research	139	122,753	139	132,518	139	141,561	0	9,043
Treatment research	758	600,994	758	626,318	758	636,574	0	10,256
Cancer biology	425	289,153	425	319,007	425	342,091	0	23,084
Subtotal, research	1,886	1,573,082	1,886	1,666,558	1,888	1,721,316	0	54,758
Resource development:								
Cancer centers support	12	155,643	12	160,437	12	163,441	0	3,004
Research manpower development	24	71,083	24	77,491	24	78,874	0	1,383
Construction	2	3,223	2	3,215	2	2,782	0	(433)
Subtotal, resource development	38	229,949	38	241,143	38	245,097	0	3,954
Cancer prevention and control	256	226,549	256	248,715	256	251,069	0	2,354
Total obligations	2,180	2,029,580	2,180	2,156,416	2,180	2,217,482	0	61,066
Unobligated balance lapsing		11						
Total, Budget Authority	2,180	2,029,591	2,180	2,156,416	2,180	2,217,482	0	61,066

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes

1997 Estimated budget authority	$2,156,416,000
1998 Estimated budget authority	2,217,482,000
Net change	61,066,000

	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$103,328,000		$1,273,000
b. Annualization of January 1997 pay increase		103,328,000		860,000
c. January 1998 pay increase		103,328,000		2,243,000
d. Legislative proposal, 1.51% increase in the CSRS rate		103,328,000		467,000
e. Service and supply fund		17,941,000		391,000
f. Increased cost of laboratory supplies, materials, and other expenses		119,282,000		3,177,000
Subtotal				8,411,000
2. Research Management and Support:				
a. Within grade increase		44,201,000		760,000
b. Annualization of January 1997 pay increase		44,201,000		368,000
c. January 1998 pay increase		44,201,000		959,000
d. Legislative proposal, 1.51% increase in the CSRS rate		44,201,000		200,000
e. Service and supply fund		9,327,000		97,000
f. Increased cost of laboratory supplies, materials, and other expenses		24,687,000		787,000
Subtotal				3,171,000
3. Cancer Prevention and Control:				
a. Within grade increase		15,885,000		241,000
b. Annualization of January 1997 pay increase		15,885,000		132,000
c. January 1998 pay increase		15,885,000		345,000
d. Legislative proposal, 1.51% increase in the CSRS rate		15,885,000		72,000
e. Service and supply fund		3,123,000		81,000
f. Increased cost of laboratory supplies, materials, and other expenses		25,256,000		657,000
Subtotal				1,528,000
Subtotal, Built-in				13,110,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Summary of Changes--continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	2,267	$730,470,000	134	$45,756,000
b. Competing	884	244,536,000	(8)	3,624,000
c. SBIR/STTR		45,737,000		118,000
Total	3,151	1,020,743,000	126	49,498,000
2. Cancer Centers		158,647,000		3,000,000
3. Other research	493	131,463,000	2	(400,000)
4. Research training		43,669,000		750,000
5. Research and development contracts		122,953,000		2,400,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes		325,747,000		(7,411,000)
b. Special emphasis areas		20,000,000		3,000,000
Subtotal, intramural		345,747,000		(4,411,000)
7. Research management and support		92,091,000		(3,171,000)
8. Cancer Prevention and Control		238,103,000		717,000
9. Construction		3,000,000		(427,000)
Subtotal, program		2,156,416,000		47,956,000
Total changes				61,066,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Object

	FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	2,180	2,180	0
Full-time equivalent of overtime and holiday hours	17	17	0
Average ES salary	$118,232	$120,596	$2,364
Average GM/GS grade	10.7	10.7	0
Average GM/GS salary	$52,703	$54,284	$1,581
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$48,572	$50,029	$1,457
Average salary of ungraded positions	$57,072	$58,784	$1,712

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$88,024,000	$91,531,000	$3,507,000
11.3	Other than Full-Time Permanent	17,299,000	17,998,000	699,000
11.5	Other Personnel Compensation	5,184,000	5,320,000	136,000
11.8	Special Personnel Services Payments	23,865,000	25,216,000	1,351,000
11.9	**Total Personnel Compensation**	**134,372,000**	**140,065,000**	**5,693,000**
12.0	Personnel Benefits	28,932,000	30,231,000	1,299,000
13.0	Benefits for Former Personnel	110,000	112,000	2,000
	Subtotal, Pay Costs	**163,414,000**	**170,408,000**	**6,994,000**
21.0	Travel & Transportation of Persons	3,978,000	4,068,000	90,000
22.0	Transportation of Things	832,000	863,000	31,000
23.1	Rental Payments to GSA	71,000	75,000	4,000
23.2	Rental Payments to Others	646,000	665,000	19,000
23.3	Communications, Utilities & Miscellaneous Charges	11,196,000	11,215,000	19,000
24.0	Printing & Reproduction	3,838,000	3,985,000	147,000
25.1	Consulting Services	9,858,000	10,005,000	147,000
25.2	Other Services	82,655,000	73,470,000	(9,185,000)
25.3	Purchase of Goods & Services from Government Accounts	197,957,000	197,801,000	(156,000)
25.4	Operation & Maintenance of Facilities	45,368,000	45,454,000	86,000
25.5	Research & Development Contracts	167,376,000	168,460,000	1,084,000
25.6	Medical Care	250,000	250,000	0
25.7	Operation & Maintenance of Equipment	8,790,000	8,800,000	10,000
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**512,254,000**	**504,240,000**	**(8,014,000)**
26.0	Supplies & Materials	21,710,000	22,484,000	774,000
31.0	Equipment	13,001,000	13,466,000	465,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,424,826,000	1,485,358,000	60,532,000
42.0	Insurance Claims & Indemnities	630,000	635,000	5,000
43.0	Interest & Dividends	20,000	20,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**1,993,002,000**	**2,047,074,000**	**54,072,000**
	Total, Budget Authority by Object	**2,156,416,000**	**2,217,482,000**	**61,066,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$88,024,000	$91,531,000	$3,507,000
Other Than Full-Time Permanent (11.3)	17,299,000	17,998,000	699,000
Other Personnel Compensation (11.5)	5,184,000	5,320,000	136,000
Special Personnel Services Payments (11.8)	23,865,000	25,216,000	1,351,000
Total Personnel Compensation (11.9)	**134,372,000**	**140,065,000**	**5,693,000**
Civilian Personnel Benefits (12.0)	28,932,000	30,231,000	1,299,000
Benefits to Former Personnel (13.0)	110,000	112,000	2,000
Subtotal, Pay Costs	**163,414,000**	**170,408,000**	**6,994,000**
Travel (21.0)	3,978,000	4,068,000	90,000
Transportation of Things (22.0)	832,000	863,000	31,000
Rental Payments to Others (23.2)	646,000	665,000	19,000
Communications, Utilities and Miscellaneous Charges (23.3)	11,196,000	11,215,000	19,000
Printing and Reproduction (24.0)	3,838,000	3,985,000	147,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	9,858,000	10,005,000	147,000
Other Services (25.2)	82,655,000	73,470,000	(9,185,000)
Purchases from Govt. Accounts (25.3)	159,316,000	158,911,000	(405,000)
Operation & Maintenance of Facilities (25.4)	4,414,000	4,500,000	86,000
Operation & Maintenance of Equipment (25.7)	8,790,000	8,800,000	10,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**265,033,000**	**255,686,000**	**(9,347,000)**
Supplies and Materials (26.0)	21,310,000	21,984,000	674,000
Subtotal, Non-Pay Costs	306,833,000	298,466,000	(8,367,000)
Total, Administrative Costs	**470,247,000**	**468,874,000**	**(1,373,000)**

National Institutes of Health

National Cancer Institute

SIGNIFICANT ITEMS IN HOUSE and SENATE
APPROPRIATION COMMITTEE REPORTS

1997 House Appropriation Committee Report Language

Item

Grants management -- The Committee is encouraged by the Director's decision to increase the number of investigator-initiated grants in 1996. Investigator-initiated grants and other research project grants are at the core of basic research efforts and provide optimal opportunities for research breakthroughs. The Committee encourages the Institute to continue to make these grants a priority in 1997 to exploit research opportunities. p. 58

Action Taken or to be Taken

The NCI holds investigator-initiated grants as the highest priority for funding support. Last year, it redirected funds into this area and raised the percentile funding to the 23rd for competing RO1 investigator grants. For FY 1997 over $1.1 billion, or nearly 50% of the NCI budget will be directed into this mechanism of support, permitting continued support for the highest priority research project grants.

In addition to the higher payline for grants, the NCI has initiated Accelerated Executive Review (AER). The AER process enables investigators that fall just outside the payline to submit additional information for consideration by the NCI Executive Committee. Many of these grants would be funded upon resubmission, but AER allows this research to get underway more rapidly. For FY96, applications proposing non-patient oriented research that were within 4 percentile points of the payline were eligible for AER. Because of the importance that the NCI places on clinical research, applications proposing patient-oriented research that were within 10 percentile points of the payline were eligible for AER. Of the AER requests that were reviewed by the Executive Committee, 47% of all AER requests were funded with 41% of patient-oriented applications funded. The AER initiative has met with very enthusiastic support within the research community and will continue in FY97.

Item

Breast cancer -- The Committee recognizes that breast cancer continues to require a significant allocation of NCI resources in order to decipher the complex mysteries of this disease. The Committee agrees with NCI, which places breast cancer research as a high priority within the Institute, and understands that significant scientific opportunities exist which are not currently

being funded. Therefore, the Committee urges NCI to continue to strengthen its commitment to breast cancer research. p. 58

Action Taken or to be Taken

NCI holds scientific investigations into breast cancer as one of its highest priorities. In 1996, 184,000 new cases of breast cancer will be diagnosed and 44,000 women are expected to die of the disease. The NCI breast cancer research portfolio currently includes the full breadth of research on breast cancer including risk factors, screening, diagnostics, therapeutics, novel clinical approaches, prevention, and quality-of-life issues.

One aspect of the NCI's efforts in this area is the tracking of incidence and mortality data related to breast cancer. For the first time since such records have been compiled, the breast cancer death rate fell between 1991 and 1995. The decline in cancer mortality rates was 6.3% with a larger decline (9.3%) in women under the age of 65. The NCI is convinced that these gains reflect the success of both early detection via mammography screening and more effective therapeutic interventions such as adjuvant chemotherapy and hormone therapy. The newest statistics also reveal very significant and positive trends in the breast cancer mortality rates in African American women. In black women, the breast cancer death rate dropped 1.6% between 1991 and 1995 compared to an increase of 20.3% in the period from 1971 to 1990.

Screening and early detection are important components of reducing the burden of breast cancer. The NCI and the NIH Office of Medical Applications Research along with the National Institute of Aging, the Office of Research on Women's Health and the Center for Disease Control and Prevention sponsored an NIH Consensus Development Conference on Breast Cancer Screening in Women Ages 40-49 in January 1997. This conference brought together the investigators who have conducted clinical trials, epidemiologists, statisticians, radiologists, oncologists, and other experts, as well as representatives of the public to discuss the latest data on the topic and its analysis. Following 1½ days of presentations and discussions, an independent, non-Federal consensus panel weighed the scientific evidence and drafted a statement on mammography in women ages 40-49. The panel concluded that "at the present time, the available data do not warrant a single recommendation for mammography for all women in their forties. Each woman should decide for herself whether to undergo mammography," and that in making this decision, each woman and her health care provider should have access to the best information "in an understandable and usable form." The panel stated the costs should be reimbursed by third-party payors and health maintenance organizations. At the February 25 and 26 meeting of the National Cancer Advisory Board, the Board and the NCI will discuss the Consensus Conference and the data and make their own evaluation of the benefits and risks of screening women 40 to 49.

The NCI currently sponsors over 90 ongoing clinical trials aimed at aspects of breast cancer including 20 ongoing phase III studies. Phase III studies usually compare standard treatments (the treatment most accepted) with treatments that appeared to be good in the smaller phase II studies. Phase III studies look for longer life, better quality of life, fewer side effects, and fewer

cases of the cancer returning. Assuming satisfactory results, treatments being tested in phase III trials are closest to widespread use as new therapies. NCI has designated several breast cancer treatment clinical trials as "high priority trials". Some of these are aimed at women with advanced disease and are attempting to definitively evaluate the effectiveness of high doses of chemotherapeutic agents in conjunction with bone marrow and stem cell rescue. Trials are also underway that are intended to test agents for efficacy in prevention of breast cancer in high risk women.

To optimize our efforts in breast cancer, NCI has established a Progress Review Group, to assess research opportunities in breast cancer and the activities of the NCI in the context of these opportunities. It along with the Prostate Cancer Progress Review Group represent the first use of this mechanism. The Breast Cancer Progress Review Group will work with NCI staff in conducting an in-depth evaluation of the current state-of-knowledge regarding this area, survey the literature and related fields of science, and recommend to the NCI, through the National Cancer Advisory Board and the Board of Scientific Advisors, how the Institute can optimally respond to and stimulate research opportunities related to breast cancer. This exercise will help set the NCI's research agenda in breast cancer by identifying and prioritizing those scientific opportunities that are most likely to expand our knowledge base and that will ultimately reduce the burden of this cancer. An important feature of the Progress Review Group is its linking of planning at NCI with a comprehensive program analysis and with all of the institute's program implementation mechanisms.

The NCI has begun the Cancer Genome Anatomy Project (CGAP). The first two goals of CGAP are designed to build an infrastructure of resources, information, and technologies that will provide a platform for the establishment of an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. An early component of CGAP is the preparation of tumor samples for generation of cDNA libraries. During the first year of CGAP libraries will be produced from tissue derived from breast tumors (as well as from prostate, colon, lung, and ovarian tumors) and from corresponding non-tumor tissue samples. This project is aimed at accelerating our ability to develop new markers for breast cancer and to provide accurate and predictive diagnostic tests. Breast cancer is not one disease, and the CGAP is intended to identify the molecular characteristics that distinguish one breast cancer from another in ways that will guide future approaches to the design and choice of effective interventions.

Item

National Action Plan on Breast Cancer -- The Committee encourages the National Cancer Institute to maintain its support for the implementation of the National Action Plan on Breast Cancer (NAPBC). The implementation of the NAPBC should continue to be coordinated by the Office on Women's Health within the Office of the Secretary. This Plan, which unites the efforts of all DHHS and other Federal agencies and private sector groups, is an important element in the fight against breast cancer. The Committee also encourages NCI to support the clinical trials

related to the early detection of breast cancer initiated in 1996 through the Public Health and Social Services Emergency Fund. p. 58

Action Taken or to be Taken

National Action Plan on Breast Cancer (NAPBC)
The NCI is committed to continue its support of the goals and objectives of the NAPBC, (a unique public/private partnership described in more detail below). Implementation of the NAPBC is coordinated by the U.S. Public Health Service's Office on Women's Health (PHS OWH) with funds provided for the Plan in the NCI appropriation. In FY1996, as directed by Congressional legislation, the NCI provided over $14M to support the efforts of the NAPBC and will continue its active support of the plan in FY1997. The work of the NAPBC is guided by a Steering Committee and six Working Groups in which both PHS OWH and NCI staff are participants. The Deputy Assistant Secretary for Women's Health, and the President of the National Breast Cancer Coalition serve as co-chairs of the Steering Committee. Three senior NCI scientists serve on the NAPBC Steering Committee, and a number of NCI staff are active participants in the NAPBC working groups. Over the past year, the Steering Committee established a written operating plan, established and implemented a strategic planning process and budget monitoring system, and established a series of Ad Hoc Groups to address ongoing issues such as finance, operating procedures, evaluation, and establishment of public/private partnerships.

Working Groups comprised of government and nongovernment representatives have been active in six high-priority areas: hereditary susceptibility, clinical trials accessibility, national biological resource banks, etiology, , information dissemination, and consumer involvement. Each of the Working Groups has identified gaps in breast cancer knowledge, research, policy, and services, and are now developing products and sponsoring activities to fill these critical needs. Over the past year, each working group identified specific goals for the year and developed written action plans to focus and guide their work. Highlights of the activities of these six diverse working groups are described below; these activities and products reveal the unique perspective and approach of each working group to the fight against breast cancer.

Working Group on Hereditary Susceptibility. Staff of the PHS OWH, NCI and National Human Genome Research Institute (NHGRI) have played a critical role in facilitating the activities of this working group. The group has been evaluating the health needs and the ethical, legal, and policy issues affecting people who carry breast cancer susceptibility genes. During the past year the working group addressed a number of critical issues about genetic susceptibility. The group prepared several policy analyses and sponsored a series of workshops to address issues related to the potential for health insurance and workplace discrimination based on genetic information. The working group also presented testimony to the U.S. Senate on genetic testing and privacy issues during discussions on the Kennedy-Kassebaum health care bill, and produced a position paper that was published in the *Journal of Clinical Oncology*. A workshop was also conducted to review the current research on breast cancer heritability and resulted in identification of a series of research priorities. These priorities have been presented to the NCI

for follow up activities. Additionally, the Working Group has developed a curriculum outline for health care providers on genetic testing convened and a workshop that brought together consumer representatives from provider organizations, researchers and health educators to finalize the curriculum and initiate plans for adoption by health care provider organizations. Among the most noteworthy products from this Working Group was the production of an educational video for the public on the scientific and psychosocial issues related to testing for the presence of breast cancer susceptibility genes.

Clinical Trials Accessibility Working Group. This working group has addressed issues about the barriers to participating in clinical trials. They have examined issues such as who has access to clinical trials, the informed consent process, patient and physician misperceptions about clinical trials. the lack of information about the availability of trials, and the cost of individual participation in trials. They have reviewed and analyzed the research literature on clinical trials to identify the barriers women face and to develop ways to overcome those barriers and have created a marketing plan for a media campaign to educate women about clinical trials and stimulate increased participation in breast cancer clinical trials. Additionally, NCI staff have collaborated with the NAPBC Working Group to address issues about existing sources of information about clinical trials, convening meetings to share information about current clinical trials systems and initiating discussions about the development of a central registry of breast cancer clinical trials. NCI staff assisted the NAPBC in assembling a complete file of breast cancer clinical trials, and constructing of the Trial News Web site, that is CancerNet and consumer-friendly summaries of clinical trial protocols. NCI staff was also instrumental in providing technical support for an NAPBC grant to the FDA for getting breast cancer clinical trial protocols into NCI's Physician's Data Query (PDQ) and are participating in the design of a survey of private sector pharmaceutical companies to identify impediments for these companies in submission of their breast cancer clinical trial protocols to PDQ.

National Biological Resources Banks Working Group. The development of a national mechanism and standard for obtaining and storing tissue for breast cancer research is an important goal that will have far reaching impact on future research. To meet this goal, the Working Group convened a workshop to discuss the ethical issues related to collecting and using biological tissues and creating a national network of tissue databases. This workshop produced a model informed consent form for use with research participants, and focus groups were conducted to test the model consent form. The NAPBC's findings were presented by the PHS OWH staff and incorporated into a report to the President's National Bioethics Advisory Commission. The NCI worked with the NAPBC to develop a publicly accessible database listing available breast specimen resources for research. The NCI will continue to maintain and update the database upon conclusion of the current contract (Sept. 1997). At the NAPBC meeting of September 1996, recommendations emerged to the effect that methods be developed to assure that existing specimen resources be better utilized and that such resources be created or modified to meet changing research needs. In response to these recommendations, NCI will be developing a pilot project to assure that researchers who need breast tissue specimens are linked to the available resources will monitor requests and determine which new resources need to be developed. A NAPBC meeting is planned for June 1997 at which time issues related to

development, field testing, and dissemination of a model for informed consent in specimen collection for research will be tested.

Etiology Working Group. This working group strives to expand the biomedical, epidemiological, and behavioral research being conducted on breast cancer. During the past year, a workshop on "Hormones, Hormone Metabolism, and Breast Cancer" was held in September 1995 cosponsored by the NAPBC NCI, and Tulane University. This workshop brought together scientists to assess the state-of-the-art science in measurement and metabolism of hormones, the effects of hormones in the development of breast cancer, and major research gaps and data needs. A special monograph edition of will publish many of the papers presented at this workshop. Additional NAPBC workshops entitled "Ionizing Radiation and Breast Cancer: What We Know and What We Only Suspect--Implications for Prevention Research", "Electric and Magnetic Fields, Light-at-Night and Breast Cancer" and "Viruses and Human Breast Cancer" are being planned for 1997. The PHS OWH staff and NCI scientists are involved in organizing the workshops and will participate and prepare the workshops' summary reports. To identify research gaps and needs in breast cancer etiology, the NAPBC is compilating an inventory of research projects on breast cancer etiology. Additionally, a breast cancer core questionnaire is being developed that will greatly facilitate evaluation by researchers of a broad range of potential and proven breast cancer risk factors.

Information Action Council. This working group has the essential task of improving public access to information about breast cancer via the Internet and other information technologies. Working with and the National Women's Health Information Center, this group launched the NAPBC World Wide Web site, which links together federal and private sector breast cancer resources. The Website was announced by President Clinton on October 27, 1996.

Additionally, the Working Group conducted a series of regional meetings and focus groups across the United States to determine the interest of underserved women and community-based organizations and potential private sector partners in an initiative to help women in underserved communities gain access to breast cancer information via the Internet. As a result of these meetings, the initiative will be implemented in 1997 and will recruit community-based organizations to carry out a pilot project in communities where women have little access to breast cancer information.

Consumer Involvement Working Group. As its name suggests, this working group seeks to ensure that consumers are involved at all levels in the development of research, education, and service delivery programs related to breast cancer. The Working Group has collected information and reviewed and discussed methods of increasing and institutionalizing consumer involvement in decisions made that affect consumers–those with breast cancer and their families and friends. A study will be initiated in 1997 to assess the level and nature of consumer involvement in cancer centers and related-health organizations.

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Clinical Trials on Early Detection of Breast Cancer
Screening and early detection are important components of reducing the burden of breast cancer. The NCI funds numerous research projects to improve conventional mammography and develop alternative imaging technologies to detect and characterize breast tumors. Efforts to improve conventional mammography center on refinements of the technology and quality assurance in the administration and interpretation of the x-ray films. To advance the technology, NCI is funding research to reduce the already low radiation dosage; enhance image quality; develop digital mammography as an improvement over the conventional, film-based technique; develop statistical techniques for computer-assisted interpretation of digitized images; and enable long-distance image transmission technology for clinical consultations.

Item

Environmental factors in breast cancer -- Data from the International Agency for Research from 1947 through 1992 found that women in the San Francisco Bay area had the highest rate of breast cancer in the world. The Committee is concerned that none of the scientists testifying before the Committee has been able to explain whether environmental factors contribute to this finding. The Committee urges the NCI in cooperation with the National Institute of Environmental Health Sciences to work with local researchers and breast cancer groups to find answers to these disturbing questions. p. 58-59

Action Taken or to be Taken

Researchers have known for decades that a number of factors are associated with increased risk of developing breast cancer. The well-established breast cancer risk factors include: older age; first birth at an older age; having no children; early age of menarche; late age of menopause; family history of the disease; high levels of alcohol intake; obesity; and a history of biopsy-proven benign breast disease. Most of these risk factors are associated with a moderate (1.5 to 3 times) increased risk suggesting that multiple factors may play a role in each woman's disease, and that as yet unrecognized factors may exist. Genetic, lifestyle, and environmental factors and their interactions are believed to play a role in the development of breast cancer.

NCI investigators recently determined that the breast cancer mortality rates are much more uniform throughout the United States when regional differences in the percentages of women with established breast cancer risk factors are taken into account. However, not all of the geographic variation is accounted for by this consideration. Similar research is underway at Stanford University to try to determine how San Francisco rates in particular compare when controlled for the prevalence of known risk factors in the population.

One of the most difficult research problems has been the evaluation of the role of dietary and environmental exposures (e.g., to pesticides) in breast cancer risk. It has been especially difficult to determine how such risk accumulates over a lifetime of exposure, or how factors in combination may affect a person's level of risk. The Long Island Breast Cancer Study Project,

funded by the NCI and the National Institute on Environmental Health Sciences, is supporting research on developing measurement tools that will be useful in investigating environmental determinants of breast cancer in other geographic areas.
NCI's breast cancer research portfolio currently includes the full breadth of research on breast cancer, including risk factors, screening, diagnostics, therapeutics, novel clinical approaches, prevention, and quality of life. Significant portions of this work is being conducted in the San Francisco Bay Area. For example:
• NCI is supporting a breast cancer translational research program (SPORE) which includes strong programs in basic research that can be translated quickly to patient care settings.
• Researchers are studying methods for establishing accessible, more affordable screening and access to treatment for breast and cervical cancer in an underserved, multi-ethnic population.
• Scientists are investigating the roles of breast cancer susceptibility genes (e.g., BRCA-1) and environmental factors in the etiology of breast cancer.
• Investigators are establishing a computerized link to mammography facilities to analyze utilization, proportion of abnormal exams, predictive value, and tests and costs associated with follow-up.
• Women are participating in a study looking at women's choice of breast cancer treatments and the possible influence of ethnicity on these choices.
• Researchers are testing effectiveness of an education support group targeted for women with breast cancer under age 50.
• Scientists are studying immune markers for breast cancer risk following pregnancy.

An NCI request for grant applications entitled "Cooperative Family Registries for Epidemiologic Studies of Breast Cancer" was published in November 1994. Its purpose was to collect pedigree information, epidemiological and clinical data, and biological specimens from individuals and families with a history of breast cancer to provide a resource for basic, clinical, epidemiological, and behavioral breast cancer research. In addition, this initiative sought to identify a population that is at high risk for breast cancer and could benefit from new preventive and therapeutic strategies. The Northern California Cancer Center, Memorial Sloan-Kettering Cancer Institute, Fox Chase Cancer Center, Ontario Cancer Treatment and Research Center, and the University of Melbourne are now participating in this collaborative venture. The project at the Northern California Cooperative Family Registry has as its catchment area the Greater San Francisco Bay area. Northern California is a SEER (Surveillance Epidemiology and End Results) program area with a population-based tumor registry that will allow selection of breast cancer cases and controls representative of the total population. It will assist in the development of research methods for population-based studies of familial and nonfamilial breast cancer which can be rapidly applied to other SEER areas nationwide.

NCI, in conjunction with the National Institute of Environmental Health Sciences (NIEHS), is continuing to support two Congressionally-mandated studies of breast cancer risk and the role of environmental factors on Long Island and Mid-Atlantic states, regions with reported high rates of breast cancer. The Long Island Breast Cancer Study Project (LIBCSP) consists of several studies investigating risks associated with exposures to pesticides, contaminated drinking water, air pollution, electromagnetic fields, and hazardous waste, as well as occupational exposures,

diet, and various host factors. As part of the LIBCSP, a large, population-based, case-control study is being carried out by grantees at Columbia University and a consortium of academic, medical, and research institutions in the New York area, including the State University of New York (SUNY) at Stony Brook, American Health Foundation, Memorial Sloan-Kettering Cancer Center, Yale University, SUNY Buffalo, Long Island Jewish Medical Center, Strang-Cornell Cancer Prevention Center and Cold Spring Harbor Laboratory. The Columbia-led study entered the field in August 1996, and has thus far identified over 800 eligible breast cancer cases and a similar number of population-based controls.

The Northeast/Mid-Atlantic Breast Cancer Study (NE/MA), involves the states of Connecticut, Delaware, Massachusetts, Maryland, New Hampshire, New Jersey, New York, Rhode Island, Vermont and the District of Columbia. Grantees at six collaborating institutions (i.e., Brigham and Women's Hospital, Johns Hopkins School of Hygiene and Public Health, Mount Sinai School of Medicine, SUNY Buffalo, SUNY Stony Brook and Yale University School of Medicine) are quantifying effects of environmental exposures (e.g., pesticides, PCBs, electromagnetic fields, dietary components and smoking) in association with other suspected breast cancer risk factors. Data collection is nearing completion and laboratory analyses of blood and adipose tissue is beginning. One investigative team has preliminary observations suggesting that cigarette smoking may modify breast cancer risk in a genetically defined subgroup of postmenopausal women. This finding requires confirmation and is presently being evaluated by other NE/MA investigators.

The growing understanding of the roles of specific genes in the development and behavior of cancer offers unprecedented opportunities to alter quite fundamentally our approach to cancer epidemiology. Among the avenues that will be opened by more complete knowledge of the genetic basis of cancer predisposition is the ability to dissect gene effects from environmental effects and to see more clearly what has been termed gene-environment interactions. By gene-environment interactions is meant the influence of an individual's genetic make-up on the impact of exposure to environmental carcinogens. Unrecognized but relevant genetic heterogeneity within a population complicates the analysis of epidemiologic data. NCI has initiated several programs that are intended to provide us with the tools to unravel the critical interactions of genes with diet, hormones and the environment that have eluded us for so long. For example, efforts are underway to formulate long-range plans that address issues associated with the discovery of a BRCA1 mutation linked to the Ashkenazi Jewish population. It should be noted that it is estimated that there are about 220,000 Jewish people in the San Francisco Bay area (3.6% of the population), of which 55,000 are in San Francisco.

The Geographic Information System (GIS), a computer mapping and analysis technology that allows information to be viewed and analyzed within a geographic context, is now available. It is capable of linking information with map features to display data, produce maps and perform spatial analysis. GIS has the ability to overlay several themes, or map layers. When geographic data are stored in a common coordinate system, many map layers can be viewed simultaneously, providing the user with a better understanding of the spatial relationships (such as distance, proximity and adjacency) among features from each one. For example, a GIS could allow the

user to view breast cancer cases, residential areas, power line grids, hazardous waste sites, and air traffic patterns simultaneously and over time. The usefulness of GIS for cancer epidemiology has been addressed in a recent workshop held at the NCI. Experts noted the need for significant additional methodological work before the full potential for GIS in studying cancer will be clear. A report of this group is expected.

The NCI is also establishing a Cancer Genetics Network, which will serve as a dynamic informatics and research infrastructure linking institutions that test individuals for hereditary cancer susceptibility as well as provide counseling and interventions to prevent cancer in these individuals.

Item

Cancer and minority population -- While research progress has been made, the Committee remains seriously concerned about this critical public health problem. African Americans and other minorities have a disproportionately higher risk for cancer. The Institute is encouraged to strengthen its research, research training, and outreach efforts which focus on breast, lung, and colorectal cancers, particularly in their impact on minority populations. The NCI is also encouraged to continue its initiatives to study the relationship between diet and cancer in African American women. p. 59

Action Taken or to be Taken

The NCI remains committed to reducing the burden of cancer in all segments of the population. Toward this end an internal Special Action Committee was formed at the request of the NCI Director to review NCI's activities and program mechanisms to ensure that the cancer problems of minorities, the underserved, and persons age 65 and over were being adequately addressed. The Special Action Committee issued its Report and Recommendations in May 1996. The report was intended to identify the specific efforts to deal with the cancer problems among these populations and to indicate opportunities for further action. Issues addressed by the Special Action Committee included the definition of minority and special population activities, monitoring of minority training, organization of NCI programmatic data on minority/special population activities, leadership and coordination of minority and special population activities, input of NCI staff into management of minority and special population activities, and identification of research opportunities.

As a tangible outcome of this analysis, the NCI Director established in June 1996 the Office of Special Populations within the Office of the Director. The Office of Special Populations will advise and guide the Director and serve as a focal point to provide leadership and coordination on research related to minorities and special populations. The office will coordinate NCI programs addressing scientific questions pertinent to these populations. Important elements of this office are the evaluation of current NCI programs and planning new initiatives. Through its evaluation function the office is determining what questions are important to special populations, what questions are being addressed through NCI's programs and portfolio of grants, and what

research questions should be raised. Established epidemiologic data bases and current research findings will be used to define scientific questions pertinent to special populations. The office will develop concepts for new programs that need to be implemented by the scientific divisions of the NCI. An advisory committee of NCI staff will help define these questions. The expertise of individuals from the community will also be called upon.

NCI has expanded its surveillance efforts in tracking cancer rates for minorities. The institute has sponsored a number of patterns-of-care studies looking at the differences in cancer care among regions and among racial groups in the U.S. The NCI Black-White study reviewed differences in cancer biology, treatment, and outcomes in Blacks and Whites with bladder, uterus, breast, and colon cancer in several regions of the U.S. Several outreach initiatives have been established including the National Black Leadership Initiative on Cancer, the Hispanic Leadership Initiative on Cancer, and the Appalachian Leadership Initiative on Cancer providing grants to non-government agencies to provide information concerning cancer prevention, early detection, and treatment to some special populations. For NCI treatment clinical trials, minority representation among the individuals enrolled in the trial reflects their representation among individuals with the disease under study. The NCI has also sponsored a national conference, the topic of which was the accrual and retention of minorities in clinical trials. Additional regional conferences on this topic will be held in the coming year utilizing NCI support.

The National Office of Samoan Affairs and the University of California at Irvine have entered a cooperative agreement with the NCI to conduct a phase I study to develop and validate needs assessment instruments to measure the effectiveness of cancer control methods among American Samoans. Findings from the review of cancer incidence data have provided valuable insights about the cancer control needs of this minority population. The most common cancers among American Samoans (breast, lung, and cervix among women and lung in men) are diseases for which primary or secondary preventative measures are available. Findings from the cancer incidence data also suggests that American Samoans receive diagnosis of cancer of all sites at later stages of the disease than does the general population.

Diet plays a significant role in cancer risk, and the NCI supports a number of studies aimed at clarifying the role of diet in cancer. Several of these studies have particular relevance to dietary factors and cancer incidence in minority populations. In a prospective study, an NCI grantee at Boston University has enrolled approximately 65,000 African American women to investigate the relation of obesity and other factors, including cigarette smoking, physical activity, alcohol use, diet, exogenous estrogen use and reproductive factors to the incidence of various cancers. In another study, an NCI grantee at the University of Hawaii has enrolled 35,000 African American men and women in a prospective multi-ethnic study to investigate cancer risk associated with dietary and other factors. Since dietary and nutritional factors are thought to be associated with a significant proportion of cancer, whenever feasible, NCI epidemiologic studies are designed to collect information to elucidate the etiologic role of these factors, especially as they may influence the ethnic and racial patterns of cancer incidence.

A request for grant applications was issued in 1995 to improve the geographic, rural, and minority representation within the Breast Cancer Surveillance Consortium. A second major NCI research effort evaluating community-based mammography screening is the Breast Cancer Screening Consortium. Two sites have significant percentages of black or Hispanic women in their study samples: Los Angeles (27% black and 37% Hispanic) and North Carolina (15% black). In April, 1996, data on cancer incidence and mortality by specific racial/ethnic group were published in *Racial/Ethnic Patterns of Cancer in the United States, 1988-1992*. The groups represented are Alaska Natives, American Indians, Blacks, Chinese, Filipinos, Hawaiians, Japanese, Koreans, Vietnamese, Whites, Hispanics, White Hispanics, and White non-Hispanics. Efforts have been made to link routinely collected cancer incidence data to other data sources containing additional information on access to health care, health care costs, treatment and diagnosis. These data provide important clues in understanding differences in cancer rates and ultimately provide a blueprint for research and intervention. In response to the recent changes in prostate cancer incidence rates, the NCI has initiated a Surveillance, Epidemiology and End Results (SEER) special study involving 3,500 men in six SEER areas. An oversampling of African American and Hispanic men was built into this study.

The NCI has two major initiatives that involve studies of dietary change among African Americans. The first initiative is the "Dietary Change Program for African Americans," which encourages investigator-initiated grant applications for research to develop and evaluate the effectiveness of culturally sensitive intervention strategies to assist African Americans in adopting eating patterns consistent with the NCI Dietary Guidelines. Twenty applications have been received in response to an ongoing Program Announcement (PA); two studies were favorably reviewed and funded during FY 96 (total funding $7.1M) and an additional two studies are expected to be supported during FY 97. The second major NCI initiative aimed at cancer prevention through dietary change among African Americans is included as part of the 5 A Day for Better Health program. Two of the research projects supported through the 5 A Day program are targeting dietary change among African Americans. Total support for these two studies is approximately $4 million.

Item

Prostate cancer -- More than 314,000 new cases of prostate cancer are expected to be diagnosed in 1996, making it the most commonly diagnosed cancer. Over 41,000 men will die from prostate cancer this year. In particular, the Committee is concerned about prostate cancer among African American males. The Committee urges the NCI to intensify its efforts in this area. A vigorous research effort should be pursued to ascertain why this group is more prone to this type of cancer, and why they have an exceedingly high mortality rate from the disease. Further, since community-based programs focusing on prevention, detection, diagnosis, and treatment have been used successfully to decrease incidence and mortality rates for other cancers, the Committee encourages the NCI to employ this approach in an effort to gain a better understanding of this devastating disease and its effect on this segment of the population. p. 59

Action Taken or to be Taken

NCI research efforts concerning prostate cancer, and this specific population, are and have been vigorous and varied encompassing development of new treatments, epidemiology and prevention research, the study of practice patterns, and basic science studies to understand the disease at a molecular level. A Prostate Cancer Progress Review Group is being established. It along with the Breast Cancer Progress Review Group represent the first use of this mechanism. The Prostate Cancer Progress Review Group will assess research opportunities in prostate cancer and the activities of the NCI in the context of these opportunities. The Prostate Cancer Progress Review Group will work with NCI staff in conducting an in-depth evaluation of the current state-of-knowledge regarding this area, survey the literature and related fields of science, and recommend to the NCI, through the National Cancer Advisory Board and the Board of Scientific Advisors, how the Institute can optimally respond to and stimulate research opportunities related to prostate cancer. This exercise will help set the NCI's research agenda in prostate cancer by identifying and prioritizing those scientific opportunities that are most likely to expand our knowledge base and that will ultimately reduce the burden of this cancer. An important feature of the Progress Review Group is its linking of planning at NCI with a comprehensive program analysis and with all of the institute's program implementation mechanisms.

NCI has recently established the Urologic Oncology Branch within the Division of Clinical Sciences. One of the major areas of emphasis of this branch will be prostate cancer. In addition, NCI has established a new fellowship program in urologic oncology that will also have as a major focus NCI's commitment to reduce the burden of prostate cancer in all segments of our society.

The NCI recently conducted a large interview-based study of prostate cancer in African Americans and whites. Analysis of the results have not thus far revealed any specific factor that could explain the racial differences in risk. However, further studies are underway, including an extensive evaluation of the role of different components of the diet. In addition, since a number of molecular alterations have been reported recently in prostate tumors, stored tumor specimens from the study subjects are being obtained to look for tumor-stage and race differences in these markers, and the potential relation of the markers to possible risk factors. The molecular events associated with the initiation and progression of prostate cancer are poorly understood, and NCI researchers continue to initiate research aimed at learning more about these changes.

NCI is also making a major investment in the prostate component within the Prostate, Lung, Colon and Ovary (PLCO) screening trial. This is an important resource to investigate reasons for the excess risk of prostate cancer among African Americans. The NCI has issued a Request for Applications which was co-funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Institute of Environmental Health Sciences (NIEHS) in order to stimulate innovative molecular epidemiologic research into the origins of prostate cancer. Eleven epidemiologic studies were funded or co-funded by NCI in September 1995 for a durations of 3-5 years. Eight of the 11 studies include an assessment of risk factors among African American men.

A consortium of investigators is being formed to collaborate on interdisciplinary studies following the recent discovery of a prostate cancer susceptibility gene on chromosome 1. Leads from this effort may help to clarify genetic and gene-environment interactions responsible for black-white differences in risk. NCI plans to support physical mapping of a region of chromosome 8 thought to contain a gene involved in prostate cancer, and to isolate and screen candidate tumor suppressor genes on this chromosome.

Researchers continue to evaluate anti-cancer agents that appear to inhibit tumor growth through novel mechanisms. One agent which has shown clinical promise is suramin. In the mid-1980's, suramin was tested as an antiviral agent in patients with AIDS because of its ability to inhibit reverse transcriptase in vitro. During this trial, it was noted that some AIDS-associated malignancies, e.g., Kaposi's sarcoma and high-grade B-cell lymphomas, regressed under suramin therapy. Suramin has since been tested as a treatment for a variety of human solid tumors. The greatest potential benefit appears in the treatment of patients with advanced prostate cancer. Other agents currently being evaluated clinically are high-dose tamoxifen, thalidomide, and CAI in patients with hormone-refractory prostate cancer.

NCI clinical studies in prostate cancer have significant African-American participation. One NCI study shows that 14.7% of men enrolled onto NCI sponsored prostate cancer treatment trials are Black while 10.3% of Americans diagnosed with prostate cancer are Black. Serum and tissue samples from NCI sponsored treatment, prevention and screening trials are being used to study racial differences. To date NCI sponsored studies have shown that increased length of the trinucleotide CAG repeat on the androgen receptor gene seem to correlate with decreased prostate cancer risk. NCI sponsored studies have also shown that blacks have shorter CAG repeats than whites. This may be a biologic reason explaining why blacks have a higher incidence and mortality from prostate cancer. NCI is planning to study CAG repeat differences among black and white men in the Prostate Cancer Prevention Trial. The major goal of the trial is to determine if a drug finasteride can prevent prostate cancer. By following these men over the next decade the hypothesis that shortened CAG repeat length confers greater risk of prostate cancer may be validated. These studies, though preliminary, are the first to link a specific germline genomic polymorphism and prostate cancer risk. The ability to stratify men according to prostate cancer risk by a relatively simple genomic test could potentially alter current approaches to prostate cancer screening and/or prevention efforts.

An NCI researcher is studying the enzyme 5 alpha reductase in a special population in the Dominican Republic. There is a suggestion that individuals with lower 5 alpha reductase activity have a lower risk of prostate cancer. It is known that individuals who genetically lack 5 alpha reductase do not develop prostate cancer. There is also some evidence of a racial variation in 5 alpha reductase activity. Some studies suggest that blacks have a higher average 5-alpha reductase activity than whites. Working in collaboration with Howard University, NCI scientists will analyze a large number of stored prostate samples from African American patients with prostate cancer. This will compare those results to tissue available at the NCI from non-African American patients, looking at a series of molecular endpoints. Samples from patients currently

being treated at Howard University and NCI will also be obtained for analysis. These studies may give us insights into the increase measured in African Americans.

Staff from the NCI and the Department of Defense have collaborated in a study of treatment data from an equal access system and shown that equal treatment yields equal outcome within stage. This finding suggests that all NCI efforts to improve prevention, diagnosis and treatment of this disease benefit all patients equally. However, NCI staff analyzing SEER Program data have shown that there are tremendously differing patterns of care among black and white men with prostate cancer.

The NCI has begun the Cancer Genome Anatomy Project (CAP.). The first two goals of CAP. are designed to build an infrastructure of resources, information, and technologies that will provide a platform for the establishment of an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. An early component of CAP. is the preparation of tumor samples for generation of Cana libraries. During the first year of CAP. libraries will be produced from tissue derived from prostate tumors (as well as from breast, colon, lung, and ovarian tumors) and from corresponding non-tumor tissue samples. This project is aimed at accelerating our ability to develop new markers for prostate cancer and to provide accurate and predictive diagnostic tests. Prostate cancer is not one disease, and the CAP. is intended to identify the molecular characteristics that distinguish one prostate cancer from another in ways that will guide future approaches to the design and choice of effective interventions.

Item

Gynecologic cancers -- The Committee encourages NCI to continue to enhance its efforts in basic and applied gynecologic cancer research specifically the implementation of the recommendations from the NIH consensus conference on ovarian and cervical cancer. The Committee hopes that the NCI will, if the Director believes that the mechanism is appropriate, choose to provide funding for gynecologic cancers, specifically ovarian, under SPORE, Specialized Projects of Research Excellence. p. 59

Action Taken or to be Taken

The National Cancer Institute has an active program in basic and applied gynecologic cancer research. Important areas of research include the genetics of inherited ovarian and breast cancer, the hormonal carcinogenesis of endometrial cancer, and the biology of the human papillomavirus and its role in cervical cancer. The NCI has implemented or continued activities related to the recommendations of the NIH consensus conferences on ovarian and cervical cancer. Of particular note is a major new initiative on the part of NCI to develop vaccines effective against human papilloma virus (HPV), the causative agent for about 90% of cervical neoplasia worldwide. Given that cervical cancer is the second most common cancer in women, an effective vaccine for HPV has enormous potential to cut cancer mortality. While Pap smear screening has led to a sizable reduction in the incidence of cervical cancer, incidence in women

under age 50 is actually rising. Moreover, a disproportionate number of the 5,000 cervical cancer deaths per year in the United States occur in women from minority groups (African Americans, Hispanics, and Native Americans). Work performed by NCI intramural researchers has demonstrated that viral-like particles that include the viral capsid protein L1 from HPV can protect animals from the corresponding animal papilloma virus. A team has been assembled by the NCI to plan the development of HPV vaccine. Several companies are engaged in licensing discussions involving patents that would underlie such a vaccine, and it is likely that a pharmaceutical company would be involved in a collaboration with the NCI in developing the HPV vaccine.

Major screening studies are underway for ovarian cancer, as part of the PLCO trial, and precancerous cervical lesions, as part of a study to compare management of positive Pap smears. The PLCO trial (Prostate, Lung, Colorectal, and Ovarian) is designed to determine whether particular screening modalities for these cancers will reduce the number of deaths through early detection and treatment. This trial is very large involving 148,000 participants. For ovarian cancer the women will have an annual ovarian palpation, transvaginal ultrasound, and blood test for the molecular tumor marker CA-125. The latter trial is designed to determine the optimal management of minor and low grade cervical cytological abnormalities. Two to three million of the 50 million Pap smears performed in the United States each year are reported as abnormal. Four geographically-diverse clinical centers (Birmingham, AL; Pittsburgh, PA; Oklahoma City, OK; and Seattle, WA) will enroll a total of 7,200 women in this study. Through the Gynecologic Oncology Group and NCI-designated cancer centers, the NCI continues to support critical research into the treatment of gynecologic cancers. In addition, the NCI is working to strengthen gynecologic oncology services and research at the NIH Clinical Center.

NCI sponsors a significant number of ongoing clinical trials for gynecologic cancers. These include uterine sarcomas (13 trials), uterine endometrial cancers (13 trials); ovarian germ cell tumors (9 trials), ovarian epithelial cancers (60 trials), cervical cancers (29 trials), fallopian tube cancers (14 trials), vaginal cancers (5 trials), and vulvar cancers (5 trials).

The SPORE program was developed initially as an experiment to see if this special grant mechanism, which brings laboratory and clinical scientists together, could quicken the pace of translational research in cancer. SPORE sites currently funded by the NCI focus on cancers of the breast, prostate, lung and the gastrointestinal tract. These diseases are major cancer killers which together are responsible for over 65% of cancer deaths in this country. The SPORE program is still an experiment, however. Until an evaluation of the program has been made, it is premature to consider other cancer sites for this mechanism. We hope to perform this evaluation of the SPORE program sometime in the next two to three years. If the SPORE program is determined to be successful, then we will consider other cancer sites, including gynecologic cancers, for SPORE implementation.

Item

Leukemia -- Future development of new pharmaceutical, gene therapy, immunotherapy, and new approaches to stem cell replacement could further advance the remission and cure rate. In order to make further advances in the treatment and cure of these diseases, the Committee urges the National Cancer Institute to consider all special opportunities and creative partnerships with industry, academic institutions and other private health research agencies. p. 59-60

Action Taken or to be Taken

Leukemia is a general term for a diverse group of diseases. These include chronic lymphocytic leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, acute promyelocytic leukemia, acute myeloid leukemia, and hairy cell leukemia. NCI is currently sponsoring over 200 clinical trials aimed at new therapies for these diseases in both adults and children. NCI-sponsored adult cooperative groups and NCI-sponsored Cancer Centers have been extremely active in conducting high quality clinical and translational research in the field of leukemia. NCI has also supported clinical trials by pediatric Cooperative Groups across the nation. NCI has been a leader in the coordination of leukemia research with standards for diagnostic and response criteria for acute myelogenous leukemia and chronic lymphocytic leukemia (the most common form of adult leukemia) developed through the NCI having been adopted around the world. These standards have greatly facilitated comparison of clinical trial findings among studies.

The treatment of certain childhood leukemias is one of the striking success stories in the battle to reduce the nation's burden of cancer. The vast majority of children in the United States are entered onto clinical trials. Such trials have led to a continuing improvement in the outcome of acute lymphoblastic leukemia, the most common form of any cancer in children. The current 4-year survival rates are exceeded 80% in the 1990's—up from only 20% in the late 1960's. Improvements in survival of children with less common leukemias have also improved, but the overall survival remains below that of children with acute lymphoblastic leukemia. NCI has a number of partnerships with institutions that are part of the consortia of institutions associated with either the Pediatric Oncology Group or the Children's Cancer Group. In addition, NCI-sponsored clinical trials are being conducted on the NCI campus in Bethesda, and by large single institutions receiving NCI support (e.g., St. Jude's Children's Research Hospital). One especially promising new drug is being tested in multiply relapsed T-cell acute lymphocytic leukemia, a condition that is notoriously difficult to treat. This study underscores NCI participation in highly cooperative efforts to continue improving the prognosis of children with leukemia. The study involves a collaboration with the Pediatric Oncology Group, the Children's Cancer Group, the pharmaceutical industry (Glaxo-Wellcome).

NCI intramural researchers have made impressive strides in the detection and treatment of leukemia and related disorders. Several collaborative pilot clinical trials have been established including the evaluation of chemotherapy combined with growth factor (G-CSF) in children with lymphoblastic leukemia. Another trial was established to evaluate the role of intravenous and oral thioguanine in the treatment of children with lymphoblastic leukemia. An integrated

preclinical/clinical program to develop new chemotherapeutic treatments and preventive strategies for the meningeal spread of leukemia has been launched. Phase I and II trials of a series of retinoids which have proven highly effective for the treatment of acute promyelocytic leukemia is underway. A promising method for reducing relapse rates of those with chronic myelogenous leukemia is being studied in which anti-sense oligonucleotides are directed against the bcr-abl breakpoint and are able to disrupt the expression of the oncogenic protein. This procedure may ultimately be used to help clear the bone marrow of residual cancerous cells when coupled with bone marrow transplantation.

The structure and expression of folates and antifolates are being analyzed to provide insight into the development of novel antifolate drugs and other therapies. Promising new pharmacological agents, such as allogeldanamycin, and new modalities such as electroporation of anti-sense oligonucleotides are being evaluated for use in selectively removing leukemia cells from normal bone marrow. Both of these approaches have shown promise in early studies, and will be incorporated into new approaches. Gene insertion into bone marrow cells has been used as a tool for evaluating leukemia treatment approaches, and may lead to improved treatment strategies.

Many of these advances lay the foundation for further development and application by industry, academic institutions and private health research agencies. Every effort will be made to transfer this research to industry and the private sector as these and all new discoveries made at NCI are developed.

Item

Clinical research -- The Committee continues to be concerned about the status of clinical research coverage in this country. The ability of physician-researchers to conduct clinical investigations and of patients to have access to treatment in the context of clinical trials is threatened by the refusal of third-party payers to cover the costs of routine patient care in such trials. In this regard, the Director of the National Cancer Institute should be commended for negotiating an agreement with the Department of Defense (DoD) that provides appropriate reimbursement for the care provided to patients enrolled in clinical trials. . . . The Committee would like to be kept informed of the negotiations between NCI and other agencies of the Federal government regarding clinical trials coverage and to receive notification of any agreement finalized by NCI. p. 60

Action Taken or to be Taken

The NCI continues to actively pursue coverage for all phases of cancer clinical trials with health care payer organizations. The recently signed NCI-VA agreement includes access to the full range of studies, including phase I, for cancer treatment, prevention, and diagnosis. Along with other national groups concerned about the future of clinical trials in cancer, NCI has been engaged in discussions with HCFA in an effort to develop a broad demonstration project to provide Medicare beneficiaries access to cancer clinical trials. A dedicated gateway to these NCI information systems for military physicians has been established by NCI staff who will also

supply technical support for these services. Information on quality clinical trials that are not sponsored by the NCI are accessible via PDQ. As the agreement with the Department of Defense completes its first year, the NCI has requested that the DoD consider expansion of the agreement to include phase I trials and prevention studies.

The NCI and the Department of Veterans Affairs have recently signed an interagency agreement for a partnership in clinical trials for cancer. This agreement was effective January 1, 1997 and begins a three-year demonstration project focused on expanding the already productive relationship between the VA and the NCI into a more formal and extensive partnership. Under the terms of the agreement, eligible veterans gain access to the complete range of NCI-sponsored studies in diagnosis, treatment, and prevention. The agreement covers all three phases of treatment trials. This agreement should pave the way for more NCI-sponsored clinical trials to be carried out at VA medical facilities.

To realize the full benefits of this NCI-VA partnership, enhanced linkages will be developed between the VA system and the NCI cooperative groups and between VA hospitals and academic medical centers, providing more extensive participation in the NCI's early clinical trials program. Additional clinical trials efforts to be conducted under this agreement include the internet listing of all studies included in the demonstration through the NCI information systems (PDQ and Cancer Net) and the development of joint health services research projects to evaluate cost effectiveness.

In addition to an overall higher payline for grants (23rd percentile for FY96), the NCI has initiated Accelerated Executive Review (AER). The AER process enables investigators that fall just outside the payline to submit additional information for consideration by the NCI Executive Committee. Many of these grants would be funded upon resubmission, but AER allows this research to get underway more rapidly. For FY96, applications proposing non-patient oriented research that were within 4 percentile points of the payline were eligible for AER. Because of the importance that the NCI places on clinical research, applications proposing patient-oriented research that were within 10 percentile points of the payline were eligible for AER. Of the AER requests that were reviewed by the Executive Committee, 47% of all AER requests were funded with 41% of patient-oriented applications funded. The AER initiative has met with very enthusiastic support within the research community and will continue in FY97.

Item

Neurofibromatosis -- Enormous advances in research on neurofibromatosis have recently occurred, including discovery of the NF1 and NF2 genes, developing animal models and a diagnostic blood test and prenatal testing for NF. NF also offers the potential for significant advances in broader areas, like tumor suppressor genes, and for other disorders such as many of the most common cancers, brain tumors, and learning disabilities. Accordingly, the Committee encourages the National Cancer Institute (NCI) to continue to pursue an aggressive program in basic and clinical research in NF and urges the NCI to employ novel approaches in the clinical development of NF research, including the use of: requests for applications, as appropriate; the

national cooperative drug discovery group program; and small business innovation research grants. The Committee requests that the NCI be prepared to report on the status of its NF research program, including progress in implementing the recommendations in this and last year's Committee reports, at its hearings on the fiscal 1998 budget. p. 74

Action Taken or to be Taken

NCI supports several clinical trials that specifically include children with cancers associated with neurofibromatosis. One is a phase II clinical trial of cyclophosphamide, vincristine, and carboplatin for children with progressive astrocytoma: The primary objective of this study is to evaluate the response rate of cyclophosphamide (1.2 gm/m^2 for 4 courses every 3-4 weeks) in children < 10 years with astrocytoma. The study will evaluate the response rate as well as estimate the two-year progression-free survival of a new therapeutic regimen in children under 10 years of age with astrocytoma. Children with neurofibromatosis who have low grade astrocytomas and evidence of progressive disease are eligible for the study.

A second NCI-sponsored phase II clinical trial of neoadjuvant vincristine, ifosfamide, doxorubicin, and G-CSF in children with advanced non-rhabdomyosarcoma soft tissue sarcomas also involves children with neurofibromatosis. The primary objective of this study is to evaluate the response rate to the combination of vincristine, ifosfamide, and doxorubicin (VID) in children with newly diagnosed inoperable or metastatic non-rhabdomyosarcoma soft tissue sarcomas. The study will additionally provide an estimate of the 2-year survival and event-free survival of children treated with VID in combination with radiotherapy and/or surgery and will additionally establish a bank of frozen tissue (tumor and peripheral blood) for use in further molecular studies of these tumors. Children with neurofibromatosis are predisposed to develop malignant peripheral nerve sheath tumors (neurofibrosarcomas) and are eligible for this study.

Children with neurofibromatosis, type 1 are at increased risk of developing malignant myeloid disorders and their bone marrows frequently show loss of the normal allele of the NF1 tumor-suppressor gene. While often these cases present as juvenile myelomonocytic leukemia (JMML), myeloproliferative syndrome with monosomy 7 also occurs at a significant frequency. The latter group of patients with neurofibromatosis are eligible for the an NCI-sponsored study, that seeks to identify the chromosomal location of the gene on chromosome 7 that is important in the development of leukemia.

Another NCI-sponsored clinical trial has as its primary objective of the study is to compare event-free-survival (EFS) in children who are treated either with a regimen of carboplatin and vincristine (CV) or with a regimen of 6-thioguanine (6TG), procarbazine, CCNU, and vincristine (TPCV). Accrual is limited to children with disease that is progressive after surgery or those whose risk of neurologic impairment with progression is high enough to require immediate treatment. Children with neurofibromatosis who have radiographic diagnosis of chiasmatic-hypothalamic tumor are eligible for the study after tumor progression is documented radiographically.

Since 1987, NCI intramural scientists have conducted clinical studies of patients and families with NF2. This work, which involved collaborators from the National Eye Institute (NEI), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Deafness and Other Communication Disorders (NIDCD)and the NIH Clinical Center (CC), has provided a valuable resource for expanding NF2 research. In particular, specimens from these families have been used to confirm the location of the NF2 gene on the long arm of chromosome 22 and to identify and clone it. Evaluation of the NF2 patients in these families indicated that clinical manifestations of NF2 are similar among affected members of a family but differ between families, leading to the delineation of mild and severe subtypes of NF2. After the NF2 gene was cloned it became possible to identify mutations in individual families and assess if either the type or site of mutation differed between subtypes.

Comparisons between the underlying germline mutations in NF2 families and the clinical features of affected family members have shown that, in general, patients with severe NF2 (characterized by the presence of many central nervous system tumors in addition to the characteristic vestibular schwannomas) have mutations that prematurely terminated the NF2 protein. In contrast, patients with few central nervous system tumors usually have mutations that alter individual amino acids in the protein or remove some amino acids but leave the beginning and end of the protein intact. This correlation between severity of disease and protein truncating mutations has been observed in other syndromes resulting from mutations in tumor suppressor genes. Studies linking the types of NF2 mutations with specific clinical findings should lead to a better understanding of the function of different components of the NF2 protein. Ophthalmologic examinations of patients by NEI investigators showed that certain types of cataracts are a major features of NF2. Less frequent was the presence of abnormalities of the retina. Both ocular manifestations may be present at birth or shortly thereafter, and may be useful in the early identification of affected individuals in NF2 families. NCI continues to follow NF2 patients from high-risk families and, when the mutation in a family has been identified, offers DNA testing of asymptomatic family members. Future clinical studies include defining the natural history of tumors that develop within the spinal cord of some patients with NF2 and evaluating patients with unusual clinical features. In collaboration with investigators from the Massachusetts General Hospital, both studies will attempt to determine underlying germline mutations.

It has long been know that radiation can induce tumors, especially among individuals exposed to radiation during childhood. NCI investigators are contacting individuals treated with radiation in childhood who subsequently developed schwannomas within the irradiated area. DNA will be obtained from paraffin blocks of the radiation-induced tumors, and examined for the pattern of mutations in the NF2 gene as compared wit', that seen in sporadic schwannomas.

NCI scientists are also striving to understand the genetic and molecular basis of neurofibromatosis. Significant progress has been made in the development of animal models. By generating mice whose hematopoietic system is reconstituted with neurofibromatosis type 1 (NF1)-deficient hematopoietic stem cells, NCI intramural scientists showed that Nf1 gene loss produces a myeloproliferative disease similar to human juvenile chronic myelogenous leukemia,

which is observed at increased frequency in juvenile human NF1 patients. They also identified three homeobox genes (Hoxa7, Hoxa9, and a Pbx1-related gene, Meis1) that appear to cooperate with NF1 gene loss in the progression to acute murine myeloid disease. They showed that Meis1 is part of a multigene family with at least two other family members, defining a new family of Pbx-related homeobox genes and two new potential disease genes. The NCI will avidly pursue this exciting line of research using the appropriate mechanisms to translate these discoveries into practical clinical applications.

Item

Environmental justice -- NCI is encouraged to work with NIEHS in a collaborative effort in the area of environmental hazards and their disproportionate impact on minority populations. P. 61

Action Taken or to be Taken

As part of its efforts to identify and evaluate cancer hazards in the workplace, the NCI intramural research program has developed the Computerized Occupational Referent Population System (CORPS) database. This database now includes sufficient number of minority entries to permit cancer risks to be analyzed by racial and occupational group. Other efforts are attempting to identify environmental (including lifestyle) factors that may be related to the higher rates of multiple myeloma and cancers of prostate, esophagus and pancreas among African-American men. In addition, studies are underway to investigate racial disparities in rates of breast cancer among African American and Asian women, and cervical cancer among Hispanic women.

NCI's intramural program along with NIEHS and the Environmental Protection Agency (EPA) are collaborating on a large, comprehensive evaluation of the health risks associated with agricultural exposures. Special efforts are being made to enroll minority study participants so as to allow an assessment of risk factors that may be unique to this population. The collaboration of the three agencies will permit a comprehensive evaluation of a variety of environmental exposures (e.g., pesticides, solvents, dusts, and animal viruses) and their relation to health outcomes (e.g., cancer, neurologic disease, and reproductive effects). In the extramural program, NCI is supporting a wide variety of epidemiologic studies aimed at clarifying the racial variation in cancer environmental risks among minority groups.

The NCI is continuing to collaborate with the National Institute of Aging on a series of research projects to investigate the effects of advanced age on the diagnosis and treatment of cancer in the elderly. A study is underway to assess the availability and quality of data in medical records regarding co-morbid conditions and functional limitations at initial diagnosis of cancer among the elderly. This study involves over 7,000 patients diagnosed with cancer of the colon, prostate, breast, ovary, cervix, bladder, and stomach in six SEER catchment areas.

The National Office of Samoan Affairs and the University of California at Irvine have entered a cooperative agreement with the NCI to conduct a phase I study to develop and validate needs

assessment instruments to measure the effectiveness of cancer control methods among American Samoans. Findings from the review of cancer incidence data have provided valuable insights about the cancer control needs of this minority population. The most common cancers among American Samoans (breast, lung, and cervix among women and lung in men) are diseases for which primary or secondary preventative measures are available. Findings from the cancer incidence data also suggests that American Samoans receive diagnosis of cancer of all sites at later stages of the disease than does the general population.

Several grants from the NCI are investigating the role of environmental exposures in ethnic populations. These include:

- A case-control study of women in the New York metropolitan area is evaluating the association of exposures to pesticides and polychlorinated biphenyls and breast cancer risk. The study population will consist of approximately 67% African-American or Hispanic women.
- A study is evaluating numerous potential biomarkers of lung cancer susceptibility in African-American, Mexican-American, and Caucasian men and women. Analyses will include ethnic comparisons by lung cancer cell-type, epidemiologic data, demographic characteristics, environmental exposures, and biomarker interactions.
- A case-control study of American Indian women is assessing risk factors of cervical dysplasia including human papillomavirus (HPV) infections, dietary history, sexual behavior, lifestyle factors, and past sexually transmitted diseases. The data obtained will allow comparison with an ongoing, similar study in New Mexico Hispanic and non-Hispanic white women.
- An epidemiologic study is investigating the synergistic relationship between human papilloma viruses (HPV) and diet, cigarette smoking and race in the development of cervical intraepithelial neoplasia (CIN). The study population is being recruited from a South Carolina health department family planning clinic and will be comprised of approximately 60% African-American.

1997 Senate Report Language

Item

Cancer genetics and molecular biology -- The Committee has reviewed the report of the NCI Director, "The Nation's Investment in Cancer Research, and is very pleased to provide additional funds to undertake some of the new and exciting approaches described in this document. The Committee agrees that new technologies will be needed to allow researchers, physicians, and patients to benefit from the vast amounts of information that are certain to be available in the near future as a result of our expanding knowledge of cancer genetics and molecular biology. The Committee encourages the NCI to develop and implement the strategies necessary to achieve investment opportunities and looks forward to hearing about progress in these areas at next year's hearing. p. 71

Action Taken or to be Taken

Recent discoveries have enhanced our understanding of how tumors develop. We now know that cancer is a disease caused by mutations in key target genes that give selective advantage to the growth of a tumor cell. The accumulated mutation allows the cells to grow out of control. The most direct and ultimately the most effective approach to preventing, detecting, diagnosing, and treating cancer is to learn the properties of responsible genes. Several new and highly interesting projects have been identified by NCI as principle targets for expansion in this area..

The NCI has begun its ambitious Cancer Genome Anatomy Project (CGAP) to convert emerging biological knowledge into clinical tools. The growing understanding of the roles of specific genes in the development and behavior of cancer offers an unprecedented set of opportunities to fundamentally alter our approach to cancer. NCI has identified a new set of initiatives to produce a new generation of knowledge and technology to read the molecular fingerprint of cancer cells to aid in early detection, diagnosis, prevention and treatment of cancer. These programs are intended to provide us with the tools to unravel the critical interactions of genes with diet, hormones and the environment that have eluded us for so long.

The first two goals of CGAP are designed to build an infrastructure of resources, information, and technologies that will provide a platform for the establishment of an index of all genes that are expressed in tumors and support development of new technologies that will allow high throughput analysis of gene and protein expression as well as mutation detection. An early component of CGAP is the preparation of tumor samples for generation of cDNA libraries. During the first year of CGAP, libraries will be produced from tissue derived from tumors (breast, colon, lung, ovarian, and prostate tumors) and from corresponding non-tumor tissue samples. This project is aimed at accelerating our ability to develop new markers for cancer and to provide accurate and predictive diagnostic tests. Cancer is not one disease—even cancers that share site and appearance differ from one another at the molecular level. The CGAP is intended to identify the molecular characteristics that distinguish one cancer from another in ways that will guide future approaches to the design and choice of effective interventions.

The growing understanding of the roles of specific genes in the development and behavior of cancer offers an unprecedented set of opportunities to fundamentally alter our approach to cancer. NCI has identified a new set of initiatives to produce a new generation of knowledge and technology to read the molecular fingerprint of cancer cells to aid in early detection, diagnosis, prevention and treatment of cancer. These programs are intended to provide us with the tools to unravel the critical interactions of genes with diet, hormones and the environment that have eluded us for so long.

Another major new initiative of the NCI is the Cancer Genetics Network. The recent discovery of specific genes that are predictive of predisposition to cancer will only benefit people if we rapidly move to provide interested individuals with an expanded opportunity to seek information, counseling and testing at centers of excellence. In addition, we must establish the best surveillance and interventions to reduce the chances that individuals at risk will develop cancer.

This will require additional clinical research. The Cancer Genetics Network will address these issues by establishing a network of centers of excellence in human cancer genetics to enhance our ability to answer the many pressing questions that these new discoveries raise.

While recent advances in the understanding of the genetic basis of tumor development represents an extraordinary opportunity for investment in cancer research, the need is critical for an integration of basic, clinical, and epidemiologic research in this area. The aim must be not only to identify and characterize genes which modify inherited predisposition to cancer, but also to assess the efficacy of risk-reduction strategies. The NCI intends to facilitate the construction of the Cancer Genetics Network as a dynamic informatics and research infrastucture linking institutions that test individuals for hereditary cancer susceptibility and provide counseling and intervention to these individuals.

Item

Regional variations in cancer rates -- The Committee understands that the San Francisco Bay, CA, area has one of the highest rates of breast cancer incidence in the world and mortality rates significantly higher than State and national levels. Regional variations in cancer rates can provide important information about environmental contributions to breast cancer. Epidemiologic investigations are needed to identify novel risk factors, including environmental exposures, which may be contributing to the high incidence and mortality rates of breast cancer in these areas. The Committee encourages the Institute, in collaboration with the National Institute of Environmental Health Sciences, to support research on the risk factors for the high breast cancer incidence and mortality rates in the San Francisco Bay area, and explore the feasibility of mapping disease rates along with environmental exposure information.

In addition to the San Francisco Bay area, the Committee also recognizes that the incidence of breast cancer is significantly higher than the national average in the Northeastern States of Rhode Island, Pennsylvania, New Hampshire, and Maine. The mortality rate is approximately 12 percent higher for women with breast cancer living in these States than for women residing in the Midwestern and Western United States. For example, according to the Centers for Disease Control [CDC], New Hampshire has the ninth highest per capita mortality rate at 39.7 deaths per 100,000. This rate is disproportionately even higher in Coos County, NH; concern has been expressed that there may be an environmental cause related to this tragic problem. The Committee hopes that NCI will work with other agencies in a coordinated manner toward the goal of eliminating all causes of breast cancer.

In addition to the importance of studies of regional variations in cancer rates, the Committee appreciates that future advances in our knowledge about breast cancer will also result from a more complete understanding of the breast cancer genome. The Committee is supportive of the NCI's initiative to gather more complete information regarding genetic damage, cell signal pathways, and a number of other factors, and how these factors can lead to a greater understanding of environmental factors and their relationship to breast cancer.

The Committee requests that the NCI be prepared to provide an update of progress on research on the risk factors for high breast cancer incidence and mortality rates in the San Francisco Bay area, as well as the Institute's cancer genome anatomy project during the fiscal year 1998 budget hearings. p. 71-72

Action Taken or to be Taken

Researchers have known for decades that a number of factors are associated with increased risk of developing breast cancer. The well-established breast cancer risk factors include: older age; first birth at an older age; having no children; early age of menarche; late age of menopause; family history of the disease; high levels of alcohol intake; obesity; and a history of biopsy-proven benign breast disease. Most of these risk factors are associated with a moderate (1.5 to 3 times) increased risk suggesting that multiple factors may play a role in each woman's disease, and that as yet unrecognized factors may exist. Genetic, lifestyle, and environmental factors and their interactions are believed to play a role in the development of breast cancer.

NCI investigators recently determined that the breast cancer mortality rates are much more uniform throughout the United States when regional differences in the percentages of women with established breast cancer risk factors are taken into account. However, not all of the geographic variation is accounted for by this consideration. Similar research is underway at Stanford University to try to determine how San Francisco rates in particular compare when controlled for the prevalence of known risk factors in the population.

One of the most difficult research problems has been the evaluation of the role of dietary and environmental exposures (e.g., to pesticides) in breast cancer risk. It has been especially difficult to determine how such risk accumulates over a lifetime of exposure, or how factors in combination may affect a person's level of risk. The Long Island Breast Cancer Study Project, funded by the NCI and the National Institute on Environmental Health Sciences, is supporting research on developing measurement tools that will be useful in investigating environmental determinants of breast cancer in other geographic areas.

NCI's breast cancer research portfolio currently includes the full breadth of research on breast cancer, including risk factors, screening, diagnostics, therapeutics, novel clinical approaches, prevention, and quality of life. Significant portions of this work is being conducted in the San Francisco Bay Area. For example:

- NCI is supporting a breast cancer translational research program (SPORE) which includes strong programs in basic research that can be translated quickly to patient care settings.
- Researchers are studying methods for establishing accessible, more affordable screening and access to treatment for breast and cervical cancer in an underserved, multi-ethnic population.
- Scientists are investigating the roles of breast cancer susceptibility genes (e.g., BRCA-1) and environmental factors in the etiology of breast cancer.
- Investigators are establishing a computerized link to mammography facilities to analyze utilization, proportion of abnormal exams, predictive value, and tests and costs associated with follow-up.

• Women are participating in a study looking at women's choice of breast cancer treatments and the possible influence of ethnicity on these choices.
• Researchers are testing effectiveness of an education support group targeted for women with breast cancer under age 50.
• Scientists are studying immune markers for breast cancer risk following pregnancy.

An NCI request for grant applications entitled "Cooperative Family Registries for Epidemiologic studies of Breast Cancer" was published in November 1994. Its purpose was to collect pedigree information, epidemiological and clinical data, and biological specimens from individuals and families with a history of breast cancer to provide a resource for basic, clinical, epidemiological, and behavioral breast cancer research. In addition, this initiative sought to identify a population that is at high risk for breast cancer and could benefit from new preventive and therapeutic strategies. The Northern California Cancer Center, Memorial Sloan-Kettering Cancer Institute, Fox Chase Cancer Center, Ontario Cancer Treatment and Research Center, and the University of Melbourne are now participating in this collaborative venture. The project at the Northern California Cooperative Family Registry has as its catchment area the Greater San Francisco Bay area. Northern California is a SEER (Surveillance Epidemiology and End Results) program area with a population-based tumor registry that will allow selection of breast cancer cases and controls representative of the total population. It will assist in the development of research methods for population-based studies of familial and nonfamilial breast cancer which can be rapidly applied to other SEER areas nationwide.

NCI, in conjunction with the National Institute of Environmental Health Sciences (NIEHS), is continuing to support two Congressionally-mandated studies of breast cancer risk and the role of environmental factors on Long Island and Mid-Atlantic states, regions with reported high rates of breast cancer. The Long Island Breast Cancer Study Project (LIBCSP) consists of several studies investigating risks associated with exposures to pesticides, contaminated drinking water, air pollution, electromagnetic fields, and hazardous waste, as well as occupational exposures, diet, and various host factors. As part of the LIBCSP, a large, population-based, case-control study is being carried out by grantees at Columbia University and a consortium of academic, medical, and research institutions in the New York area, including the State University of New York (SUNY) at Stony Brook, American Health Foundation, Memorial Sloan-Kettering Cancer Center, Yale University, SUNY Buffalo, Long Island Jewish Medical Center, Strang-Cornell Cancer Prevention Center and Cold Spring Harbor Laboratory. The Columbia-led study entered the field in August 1996, and has thus far identified over 800 eligible breast cancer cases and a similar number of population-based controls.

The Northeast/Mid-Atlantic Breast Cancer Study (NE/MA), involves the states of Connecticut, Delaware, Massachusetts, Maryland, New Hampshire, New Jersey, New York, Rhode Island, Vermont and the District of Columbia. Grantees at six collaborating institutions (i.e., Brigham and Women's Hospital, Johns Hopkins School of Hygiene and Public Health, Mount Sinai School of Medicine, SUNY Buffalo, SUNY Stony Brook and Yale University School of Medicine) are quantifying effects of environmental exposures (e.g., pesticides, PCBs, electromagnetic fields, dietary components and smoking) in association with other suspected

breast cancer risk factors. Data collection is nearing completion and laboratory analyses of blood and adipose tissue is beginning. One investigative team has preliminary observations suggesting that cigarette smoking may modify breast cancer risk in a genetically defined subgroup of postmenopausal women. This finding requires confirmation and is presently being evaluated by other NE/MA investigators.

The growing understanding of the roles of specific genes in the development and behavior of cancer offers unprecedented opportunities to alter quite fundamentally our approach to cancer epidemiology. Among the avenues that will be opened by more complete knowledge of the genetic basis of cancer predisposition is the ability to dissect gene effects from environmental effects and to see more clearly what has been termed gene-environment interactions. By gene-environment interactions is meant the influence of an individual's genetic make-up on the impact of exposure to environmental carcinogens. Unrecognized but relevant genetic heterogeneity within a population complicates the analysis of epidemiologic data. NCI has initiated several programs that are intended to provide us with the tools to unravel the critical interactions of genes with diet, hormones and the environment that have eluded us for so long. For example, efforts are underway to formulate long-range plans that address issues associated with the discovery of a BRCA1 mutation linked to the Ashkenazi Jewish population. It should be noted that it is estimated that there are about 220,000 Jewish people in the San Francisco Bay area (3.6% of the population), of which 55,000 are in San Francisco.

The Geographic Information System (GIS), a computer mapping and analysis technology that allows information to be viewed and analyzed within a geographic context, is now available. It is capable of linking information with map features to display data, produce maps and perform spatial analysis. GIS has the ability to overlay several themes, or map layers. When geographic data are stored in a common coordinate system, many map layers can be viewed simultaneously, providing the user with a better understanding of the spatial relationships (such as distance, proximity and adjacency) among features from each one. For example, a GIS could allow the user to view breast cancer cases, residential areas, power line grids, hazardous waste sites, and air traffic patterns simultaneously and over time. The usefulness of GIS for cancer epidemiology has been addressed in a recent workshop held at the NCI. Experts noted the need for significant additional methodological work before the full potential for GIS in studying cancer will be clear. A report of this group is expected.

The NCI is also establishing a Cancer Genetics Network, which will serve as a dynamic informatics and research infrastructure linking institutions that test individuals for hereditary cancer susceptibility as well as provide counseling and interventions to prevent cancer in these individuals.

Item

Consumer involvement related to breast cancer research -- Over the past 3 years, breast cancer research has benefitted from the increased involvement of lay breast cancer advocates who represent, are accountable to, and report to organizations representing the affected community.

The involvement of these consumers at all levels of decision making that affects their lives has helped foster new and innovative breast cancer research funding designs and research projects. While maintaining the highest quality assurance through peer review, consumer involvement has helped to ensure that all breast cancer research reflects the experiences and wisdom of individuals from the scientific and lay communities. The Committee encourages NCI to continue to give consideration to increasing the involvement of consumers in decision making related to breast cancer research, and to be prepared to report to the Committee on progress that the Institute is making toward that goal at the fiscal year 1998 hearings. p.72

Action Taken or to be Taken

Breast cancer advocates play a key role in the development of NCI's research agenda. They serve as members of the President's Cancer Panel, the National Cancer Advisory Board, and the Board of Scientific Advisors playing an important role in advancing NCI's research mission.

The creation of two new entities within the NCI during the past year underscores the commitment on the part of the NCI to continued participation of breast cancer advocates (as well as other cancer advocates) in helping to shape the research agenda of the Institute. The first of these new entities is the Director's Consumer Liaison Group (DCLG), and the second is the Office of Cancer Survivorship. The DCLG, consisting of 15 consumer-advocates who are involved in cancer advocacy and/or volunteer organizations, will meet several times each year with the Director of the NCI. The DCLG will help develop and establish mechanisms for identifying appropriate consumer-advocates to serve on key advisory bodies to the NCI. The DCLG will also participate in discussion of the broad development of NCI programmatic and research priorities e.g., the development of the annual Bypass Budget. The DCLG will also serve as a conduit for communication and facilitate the maintenance of a strong partnership between the NCI and the consumer-advocate community.

The Office of Cancer Survivorship was established by the Director, NCI to address the research questions associated with surviving cancer. Currently, there are over 10 million cancer survivors with over 7 million long-term survivors, having had cancer diagnosed more than five years ago. America's women with breast cancer have significantly benefitted from the increase in cancer survivorship with the majority of breast cancers now diagnosed while the cancer is in an early stage and the five-year survival rate for all breast cancer has risen from 74% twenty years ago to 84% today. Efforts to increase survivorship must continue and increase, but it must also be recognized that living as a cancer survivor is in itself challenging. The Office of Cancer Survivorship will explore the physical, psychological, and economic well-being of individuals who are cancer survivors. The office will support research covering the spectrum of issues facing cancer survivors including long-term medical and psycho social effects of cancer treatment, factors that predispose survivors to second malignancies, reproductive problems following cancer treatments, and insurance/employment issues unique to cancer survivors. In November 1996, NCI invited experts from the scientific community, as well as advocacy groups (including breast

cancer survivors) to a meeting to help set the research agenda for the new Office of Cancer Survivorship.

A Breast Cancer Progress Review Group is currently being established by the NCI, and this group will, of course, include breast cancer advocates. This Progress Review Group will assess the opportunities for research in breast cancer along with the current activities of the NCI in this area. Breast cancer advocates have also been highly involved through the NCI's Cancer Genetics Working Group in the complex issues surrounding discovery of the breast cancer genes and potential genetic testing of individuals.

Breast cancer advocates are playing an important role in the implementation of clinical research, serving as advisors to clinical researchers and educators. This year, for example, they participated as advisors on the Breast Cancer Prevention Trial and cooperated with NCI to encourage interest in several bone marrow transplant trials for breast cancer. They also joined NCI in a meeting with other advocacy groups to begin to address the extremely important issue of managed care coverage of clinical trials. Recently, they have formed a new partnership with NCI to highlight and translate all breast cancer clinical trials in the NCI PDQ database into patient friendly language. Summaries written using lay terms are now available for the first time on the World Wide Web, making this critical research information more accessible to consumers.

Breast cancer advocates are participating in the NIH Consensus Development Conference on Breast Cancer Screening in Women Ages 40-49, January 21-23, 1997, and notification of the meeting was widely disseminated to breast cancer organizations. The Office of Liaison Activities within the Office of the Director, NCI actively keeps the breast cancer advocacy community informed of up-to-date information on breast cancer research through regular communications including mailings and faxing of time-sensitive materials. Planned for spring of 1997 is a special tour and meeting with key researchers at NCI for the National Breast Cancer Coalition. Finally, a number of NCI staff work with breast cancer advocates as members of the National Action Plan on Breast Cancer Working Groups.

Finally, breast cancer advocates have participated in special discussions with the NCI to help with the design and implementation of urgent, high priority studies. These include studies aimed at determining the prevalence of breast cancer susceptibility gene mutations in specific populations and the potential roles of prophylactic surgery in high-risk women.

Item

Cancer prevention and control --The Committee recognizes the important role of behavior in preventing cancer and reducing its effects. New scientific data indicates that psycho social and complementary medicine interventions improve the quality of life and increase treatment compliance for cancer patients. The Committee urges the NCI conduct an inter-Institute initiative of basic and applied research on the psycho social factors involved in treating cancer, AIDS, diabetes, heart disease, and other diseases with a behavioral component. The Committee intends that grants for such research be made to cancer centers which have personnel and

facilities to conduct psycho social and complementary medicine research projects on diverse ethnic and racial populations. p. 73

Action Taken or to be Taken

In early 1997, the NCI will issue a Program Announcement (PA) entitled "Priorities in Behavioral Research in Cancer Prevention and Control". It will remain active for three years, after which the NCI and its Working Group on Behavioral Research will assess the results of the PA and modify it accordingly.

The NCI has been actively collaborating with the NIH Office of Behavioral and Social Science Research (OBSSR). Two notable outcomes of this collaboration include a trans-NIH RFA aimed at disease prevention through behavioral research which is in the final planning stages, and a symposia at the August, 1997 annual meeting of the American Psychological Association in which NCI is taking a leading role. NIH and NCI behavioral and prevention research will be featured.

Behavioral and psycho social factors are crucial aspects of interventions to reduce the incidence and mortality from cancer, and are inseparable from the interventions themselves if they are to translate into benefit at the population level. Much remains to be learned about the role of these factors and how they can be more effectively used to prevent and control cancer. Over the next decade NCI's investment in behavioral research will rise to meet the needs of cancer prevention and control. From prevention to treatment to rehabilitation, NCI's research emphasis will be on the role of these factors in the cause of cancer, on access to care, public and provider behavioral change and on assuring that the successful results of this important research reach the public and health professionals in an efficient, timely, and usable manner.

Item

Clinical trials -- the Committee commends the NCI for taking an important first step toward correcting the problem of appropriate reimbursement for the care provided to patients enrolled in peer-reviewed clinical trials by negotiating an agreement with the Department of Defense [DOD]... The Committee understands that NCI is also in the process of negotiating similar arrangements with other Federal agencies involved in the support of health care services. In negotiating these agreements, the Committee urges the NCI to be mindful of other quality mechanisms outside NCI. For example, a number of trials involving leukemia have been approved by the National Heart, Lung, and Blood Institute. In addition, the review processes of the Food and Drug Administration, in granting investigational new exemptions, are second to none in their rigor. Finally, the committee encourages the NCI to consider including phase I studies under the current, and future agreements with third-party payers. p. 73

Action Taken or to be Taken

The NCI continues to actively pursue coverage for all phases of cancer clinical trials with health care payer organizations. The recently signed NCI-VA agreement includes access to the full range of studies, including phase I, for cancer treatment, prevention, and diagnosis. Along with other national groups concerned about the future of clinical trials in cancer, NCI has been engaged in discussions with HCFA in an effort to develop a broad demonstration project to provide Medicare beneficiaries access to cancer clinical trials. A dedicated gateway to these NCI information systems for military physicians has been established by NCI staff who will also supply technical support for these services. Information on quality clinical trials that are not sponsored by the NCI are accessible via PDQ. As the agreement with the Department of Defense completes its first year, the NCI has requested that the DoD consider expansion of the agreement to include phase I trials and prevention studies.

The NCI and the Department of Veterans Affairs have recently signed an interagency agreement for a partnership in clinical trials for cancer. This agreement is effective January 1, 1997 and begins a three-year demonstration project focused on expanding the already productive relationship between the VA and the NCI into a more formal and extensive partnership. Under the terms of the agreement, eligible veterans gain access to the complete range of NCI-sponsored studies in diagnosis, treatment, and prevention. The agreement covers all three phases of treatment trials. This agreement should pave the way for more NCI-sponsored clinical trials to be carried out at VA medical facilities.

To realize the full benefits of this NCI-VA partnership, enhanced linkages will be developed between the VA system and the NCI cooperative groups and between VA hospitals and academic medical centers, providing more extensive participation in the NCI's early clinical trials program. Additional clinical trials efforts to be conducted under this agreement include the internet listing of all studies included in the demonstration through the NCI information systems (PDQ and Cancer Net) and the development of joint health services research projects to evaluate cost effectiveness.

In addition to an overall higher payline for grants (23rd percentile for FY96), the NCI has initiated Accelerated Executive Review (AER). The AER process enables investigators that fall just outside the payline to submit additional information for consideration by the NCI Executive Committee. Many of these grants would be funded upon resubmission, but AER allows this research to get underway more rapidly. For FY96, applications proposing non-patient oriented research that were within 4 percentile points of the payline were eligible for AER. Because of the importance that the NCI places on clinical research, applications proposing patient-oriented research that were within 10 percentile points of the payline were eligible for AER. Of the AER requests that were reviewed by the Executive Committee, 47% of all AER requests were funded with 41% of patient-oriented applications funded. The AER initiative has met with very enthusiastic support within the research community and will continue in FY97.

Item

Ataxia-telangiectasia — The Committee continues to view research on this rare genetic disorder as a high priority, not only because of the severe impact of the disease on children, but also because of the relevance of A-T research to many fields, including breast cancer. The Committee is pleased with the intramural and extramural projects the Institute has supported, and the sharing of reagents and resources by the scientific community. The Committee encourages the NCI to support additional studies on A-T heterozygotes with increased emphasis on the development of A-T therapies. p. 74

Action Taken or to be Taken

NCI continues to pursue several avenues of research with respect to ataxia-telangiectasia (A-T). The Institute is coordinating a large collaborative record-linkage study in several European countries (participants include the Danish Cancer Registry, Finnish Cancer Registry, Norwegian Cancer Registry and Swedish Cancer Registry) to evaluate the risk of cancer among carriers of the A-T gene. In addition, biologic samples from young breast cancer patients from populations exposed to ionizing radiation (e.g., radiologic technicians) are being obtained and will be examined for mutations in the A-T gene to clarify the possible role of this gene in radiogenic breast cancer.

NCI considers research on Ataxia-telangiectasia related cancers to be an area of high programmatic and scientific priority. Accordingly, interactions with major investigators in this field and the solicitation of grant proposals have led to the formulation of several research projects, including:

- A grant to the New York Medical College for a prospective follow up of over 265 A-T families to characterize their gene-carrier status, investigate susceptibility to cancer and other diseases among A-T heterozygous carriers, and study the effects of environmental factor on cancer risk.
- A grant to Mount Sinai Medical Center will undertake a study to address the issue of breast cancer susceptibility in A-T heterozygous carriers through an examination of a large cohort of women with breast cancer who received radiation therapy in the contralateral breast.
- A grant application is expected to be submitted for a large, cooperative, national and international effort to characterize genetically more than 400 A-T families and to refine the analyses of gene-environment interactions and cancer susceptibility among individuals carrying A-T gene mutations.

NCI continues to interact with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Human Genome Research Institute (NHGRI) to coordinate research activities related to A-T. The NCI continues to support research to define the role of the gene whose mutation is associated with the development of ataxia-telangiectasia, ATM. The spectrum of mutations of ATM associated with the development of this syndrome are being delineated. In addition, over the past year it has become clear that the protein product encoded by this gene is similar to other previously identified proteins that function in recognition and repair of DNA damage and the preservation of chromosomal integrity. The elucidation of the function of this

gene is the first step in devising a strategy to counteract or correct the cellular defect that causes A-T. Furthermore, a murine model for A-T was established in 1996 that will provide an experimental model in which to study the pathophysiology of this pleiotropic disorder.

The correlation between A-T heterozygote status and increased risk of breast cancer is being actively investigated by the NCI through its support of both intramural and extramural activities. As of the close of 1996 the issue still remains controversial, with disparate results emerging from disparate studies. It is not yet definitively established that A-T heterozygotes carry an increased risk for the development of breast cancer or that the ATM gene is a frequent target for malignant transformation in sporadic breast cancers. A genetic epidemiological analysis is now being spearheaded by a group of NCI investigators in order to establish a larger linkage analysis of what may be a complex, multigenic trait that ultimately will shed light on this issue.

A-T patients manifest a level of genetic instability that places them at increased risk for the development of lymphoid malignancy. Within the intramural program of the NCI, a test of lymphocyte-specific genetic instability has been developed that scores significantly positive in A-T homozygotes. The test has not yet been applied to a sufficient number of obligate heterozygotes to determine whether it will prove useful in these cases. The same laboratory that developed this assay has identified one of the genes, MTCP, whose disruption by chromosomal translocation contributes to the development of leukemia in A-T patients. A related gene, TCL1, has been identified and characterized by an extramural NCI-funded laboratory. Dysregulation of TCL1 by chromosomal translocation is an even more commonly seen occurrence associated with leukemogenesis in A-T patients.

In addition to the involvement of the A-T gene in cancer development, intramural researchers have found evidence that individuals with defects in DNA repair may be more susceptible to neurodegenerative disorders such as Alzheimer's Disease. These deficiencies in DNA repair are very similar to those found in affected individuals with A-T. Thus, our current studies are centered on determining whether A-T heterozygotes may be more likely to develop Alzheimer's than non A-T carriers. If confirmed, then interventions based on blocking DNA damage may be used to prevent this serious degenerative disorder.

Item

Gynecologic cancers -- The Committee encourages NCI to continue to expand its efforts in basic and applied gynecologic cancer research, specifically the implementation of the recommendations from the NIH consensus conferences on ovarian and cervical cancer. The Committee also encourages the NCI to give consideration to utilizing the SPORE mechanism to support research on gynecologic cancers. p. 74

Action Taken or to be Taken

The National Cancer Institute has an active program in basic and applied gynecologic cancer research. Important areas of research include the genetics of inherited ovarian and breast cancer, the hormonal carcinogenesis of endometrial cancer, and the biology of the human papillomavirus

and its role in cervical cancer. The NCI has implemented or continued activities related to the recommendations of the NIH consensus conferences on ovarian and cervical cancer. Of particular note is a major new initiative on the part of NCI to develop vaccines effective against human papilloma virus (HPV), the causative agent for about 90% of cervical neoplasia worldwide. Given that cervical cancer is the second most common cancer in women, an effective vaccine for HPV has enormous potential to cut cancer mortality. While Pap smear screening has led to a sizable reduction in the incidence of cervical cancer, incidence in women under age 50 is actually rising. Moreover, a disproportionate number of the 5,000 cervical cancer deaths per year in the United States occur in women from minority groups (African Americans, Hispanics, and Native Americans). Work performed by NCI intramural researchers has demonstrated that viral-like particles that include the viral capsid protein L1 from HPV can protect animals from the corresponding animal papilloma virus. A team has been assembled by the NCI to plan the development of HPV vaccine. Several companies are engaged in licensing discussions involving patents that would underlie such a vaccine, and it is likely that a pharmaceutical company would be involved in a collaboration with the NCI in developing the HPV vaccine.

Major screening studies are underway for ovarian cancer, as part of the PLCO trial, and precancerous cervical lesions, as part of the ALTS trial. The PLCO trial (Prostate, Lung, Colorectal, and Ovarian) is designed to determine whether particular screening modalities for these cancers will reduce the number of deaths through early detection and treatment. This trial is very large involving 148,000 participants. For ovarian cancer the women will have an annual ovarian palpation, transvaginal ultrasound, and blood test for the molecular tumor marker CA-125.The latter trial is designed to determine the optimal management of minor and low grade cervical cytological abnormalities. Two to three million of the 50 million Pap smears performed in the United States each year are reported as abnormal. Four geographically-diverse clinical centers (Birmingham, AL; Pittsburgh, PA; Oklahoma City, OK; and Seattle, WA) will enroll a total of 7,200 women in this study. Through the Gynecologic Oncology Group and NCI-designated cancer centers, the NCI continues to support critical research into the treatment of gynecologic cancers. In addition, the NCI is working to strengthen gynecologic oncology services and research at the NIH Clinical Center.

NCI sponsors a significant number of ongoing clinical trials for gynecologic cancers. These include uterine sarcomas (13 trials), uterine endometrial cancers (13 trials); ovarian germ cell tumors (9 trials), ovarian epithelial cancers (60 trials), cervical cancers (29 trials), fallopian tube cancers (14 trials), vaginal cancers (5 trials), and vulvar cancers (5 trials).

The SPORE program was developed initially as an experiment to see if this special grant mechanism, which brings laboratory and clinical scientists together, could quicken the pace of translational research in cancer. SPORE sites currently funded by the NCI focus on cancers of the breast, prostate, lung and the gastrointestinal tract. These diseases are major cancer killers which together are responsible for over 65% of cancer deaths in this country. The SPORE program is still an experiment, however. Until an evaluation of the program has been made, it is premature to consider other cancer sites for this mechanism. We hope to perform this evaluation of the SPORE program sometime in the next two to three years. If the SPORE program is

determined to be successful, then we will consider other cancer sites, including gynecologic cancers, for SPORE implementation.

Item

Neurofibromatosis – Enormous advances in research on neurofibromatosis (NF) have recently occurred, including discovery of the NF1 and NF2 genes, developing animal models and a diagnostic blood test and pre-natal testing for NF.... Accordingly, the Committee encourages the National Cancer Institute to continue to pursue an aggressive program in basic and clinical development of NF research, including the use of Requests for Applications, the National Cooperative Drug Discovery Group program, and Small Business Innovation Research grants, as the Institute deems appropriate. The Committee requests that the NCI be prepared to report on the status of its NF research program at its hearings on the fiscal year 1998 budget. p. 60

Action Taken or to be Taken

NCI supports several clinical trials that specifically include children with cancers associated with neurofibromatosis. One is a phase II clinical trial of cyclophosphamide, vincristine, and carboplatin for children with progressive astrocytoma: The primary objective of this study is to evaluate the response rate of cyclophosphamide (1.2 gm/m^2 for 4 courses every 3-4 weeks) in children < 10 years with astrocytoma. The study will evaluate the response rate as well as estimate the two-year progression-free survival of a new therapeutic regimen in children under 10 years of age with astrocytoma. Children with neurofibromatosis who have low grade astrocytomas and evidence of progressive disease are eligible for the study.

A second NCI-sponsored phase II clinical trial of neoadjuvant vincristine, ifosfamide, doxorubicin, and G-CSF in children with advanced non-rhabdomyosarcoma soft tissue sarcomas also involves children with neurofibromatosis. The primary objective of this study is to evaluate the response rate to the combination of vincristine, ifosfamide, and doxorubicin (VID) in children with newly diagnosed inoperable or metastatic non-rhabdomyosarcoma soft tissue sarcomas. The study will additionally provide an estimate of the 2-year survival and event-free survival of children treated with VID in combination with radiotherapy and/or surgery and will additionally establish a bank of frozen tissue (tumor and peripheral blood) for use in further molecular studies of these tumors. Children with neurofibromatosis are predisposed to develop malignant peripheral nerve sheath tumors (neurofibrosarcomas) and are eligible for this study.

Children with neurofibromatosis, type 1 are at increased risk of developing malignant myeloid disorders and their bone marrows frequently show loss of the normal allele of the NF1 tumor-suppressor gene. While often these cases present as juvenile myelomonocytic leukemia (JMML), myeloproliferative syndrome with monosomy 7 also occurs at a significant frequency. The latter group of patients with neurofibromatosis are eligible for the an NCI-sponsored study, that seeks to identify the chromosomal location of the gene on chromosome 7 that is important in the development of leukemia.

Another NCI-sponsored clinical trial has as its primary objective of the study is to compare event-free-survival (EFS) in children who are treated either with a regimen of carboplatin and vincristine (CV) or with a regimen of 6-thioguanine (6TG), procarbazine, CCNU, and vincristine (TPCV). Accrual is limited to children with disease that is progressive after surgery or those whose risk of neurologic impairment with progression is high enough to require immediate treatment. Children with neurofibromatosis who have radiographic diagnosis of chiasmatic-hypothalamic tumor are eligible for the study after tumor progression is documented radiographically.

Since 1987, NCI intramural scientists have conducted clinical studies of patients and families with NF2. This work, which involved collaborators from the National Eye Institute (NEI), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Deafness and Other Communication Disorders (NIDCD)and the NIH Clinical Center (CC), has provided a valuable resource for expanding NF2 research. In particular, specimens from these families have been used to confirm the location of the NF2 gene on the long arm of chromosome 22 and to identify and clone it. Evaluation of the NF2 patients in these families indicated that clinical manifestations of NF2 are similar among affected members of a family but differ between families, leading to the delineation of mild and severe subtypes of NF2. After the NF2 gene was cloned it became possible to identify mutations in individual families and assess if either the type or site of mutation differed between subtypes.

Comparisons between the underlying germline mutations in NF2 families and the clinical features of affected family members have shown that, in general, patients with severe NF2 (characterized by the presence of many central nervous system tumors in addition to the characteristic vestibular schwannomas) have mutations that prematurely terminated the NF2 protein. In contrast, patients with few central nervous system tumors usually have mutations that alter individual amino acids in the protein or remove some amino acids but leave the beginning and end of the protein intact. This correlation between severity of disease and protein truncating mutations has been observed in other syndromes resulting from mutations in tumor suppressor genes. Studies linking the types of NF2 mutations with specific clinical findings should lead to a better understanding of the function of different components of the NF2 protein. Ophthalmologic examinations of patients by NEI investigators showed that certain types of cataracts are a major features of NF2. Less frequent was the presence of abnormalities of the retina. Both ocular manifestations may be present at birth or shortly thereafter, and may be useful in the early identification of affected individuals in NF2 families. NCI continues to follow NF2 patients from high-risk families and, when the mutation in a family has been identified, offers DNA testing of asymptomatic family members. Future clinical studies include defining the natural history of tumors that develop within the spinal cord of some patients with NF2 and evaluating patients with unusual clinical features. In collaboration with investigators from the Massachusetts General Hospital, both studies will attempt to determine underlying germline mutations.

It has long been know that radiation can induce tumors, especially among individuals exposed to radiation during childhood. NCI investigators are contacting individuals treated with radiation in

childhood who subsequently developed schwannomas within the irradiated area. DNA will be obtained from paraffin blocks of the radiation-induced tumors, and examined for the pattern of mutations in the NF2 gene as compared with that seen in sporadic schwannomas.

NCI scientists are also striving to understand the genetic and molecular basis of neurofibromatosis. Significant progress has been made in the development of animal models. By generating mice whose hematopoietic system is reconstituted with neurofibromatosis type 1 (NF1)-deficient hematopoietic stem cells, NCI intramural scientists showed that Nf1 gene loss produces a myeloproliferative disease similar to human juvenile chronic myelogenous leukemia, which is observed at increased frequency in juvenile human NF1 patients. They also identified three homeobox genes (Hoxa7, Hoxa9, and a Pbx1-related gene, Meis1) that appear to cooperate with NF1 gene loss in the progression to acute murine myeloid disease. They showed that Meis1 is part of a multigene family with at least two other family members, defining a new family of Pbx-related homeobox genes and two new potential disease genes. The NCI will avidly pursue this exciting line of research using the appropriate mechanisms to translate these discoveries into practical clinical applications.

Item

Developing cancer centers -- The Committee urges the Institute with a portion of its increased funds to promote improved instrumentation and equipment at developing cancer centers in regions without existing comprehensive cancer centers, including giving consideration to issuing an RFP for equipment and instrumentation which is needed to measure levels of cancer causing chemicals in humans, and equipment needed to measure the activities of cancer genes in human breast tumors. It is critical that the physical as well as the grant resources be made available to complement developing cancer centers. The NCI, in coordination with the NCRR should do everything feasible to encourage the continued development of cancer centers that serve rural and minority populations with a high incidence of cancer. The Committee expects that such programs will be discussed during the fiscal year 1998 hearings. p. 75

Action Taken or to be Taken

The NCI-designated cancer centers are the centerpiece of the nation's effort to reduce morbidity and mortality from malignant disease. Cancer centers are collectively the major source of new knowledge relating to the biological nature of cancer and its causes, the development of new and more effective diagnostic, therapeutic, and preventive approaches, the delivery of these more effective interventions to the patients and families needing them, and the education of health-care professionals and the public. An excellent cancer center is a local, regional, and national treasure, having an impact that goes well beyond its own walls into the communities it serves directly and, by the generalizable knowledge it creates, into the world at large. To defeat cancer, it is not sufficient to perform excellent research, or to turn research results into therapies or preventives, or to prove that these work in the clinic, or to educate health-care professionals about the latest advances, or to reach out to underserved populations. It is necessary to do all these things together. This is what cancer centers do.

NCI's recognition of the complex requirements for cancer's conquest has been clearly exemplified in its Cancer Centers Program. Because discoveries and their real-world applications are made by people working in institutions, the NCI has long sought to enhance the potential of institutions for discovery and for the effective application of discovery to patients and people at risk for cancer. For years the major sources of advances in cancer biology and therapy, NCI centers have more recently devoted increasing resources to newly emerging areas of opportunity, such as cancer prevention. To broaden the geographical distribution of centers in the United States, the NCI has awarded planning grants to promising institutions developing new programs. NCI has asked its centers to develop outreach activities, so that the benefits of state-of-the-art approaches to diagnosis, treatment, and prevention can be realized broadly throughout the population. Linkages between the centers and NCI's Cancer Information Service have expedited the flow of reliable information on cancer to patients, their families, and the general population.

To further strengthen NCI's Cancer Centers Program, in 1996 the Director of NCI convened a blue-ribbon panel to assess the Program and make recommendations to NCI. The report of the Cancer Centers Program Review Group (CCPRG), entitled "Renewing the Cancer Centers Program of the National Cancer Institute" (1996), contained a great many constructive suggestions for how NCI might better support institutions engaged in cancer research.

Among its major recommendations, the CCPRG asked the NCI to do the following:
•...foster excellence in science relating to cancer, promote multidisciplinary approaches, and facilitate the translation of new findings back and forth among laboratory, clinic, and populations;
•...promote diversity in the scientific agendas of centers and permit diverse organizational solutions to serve scientific activities;
•...provide increased flexibility to excellent research institutions, while demanding at the same time strict accountability through a highly competitive peer-review process;
•...promote opportunities for the creation of new centers in institutions that successfully develop strong scientific bases.

The Report emphasized the overwhelming importance of excellence in research across a broad spectrum of scientific and medical concerns relevant to cancer. Indeed, the core of NCI's support to its cancer centers has long been for the promotion of research. To assist discovery and its translation into direct benefit to patients and the general public, the NCI has awarded cancer-center support grants (CCSG) to institutions that have a critical mass of excellent cancer-relevant scientific research. The CCSG has provided developmental and infrastructure support that, in turn, increases flexibility and responsiveness. This is particularly important now at a time of unparalleled scientific opportunity. The CCSG's focus on research has stemmed from NCI's long-held conviction that a culture of discovery, scientific excellence, and multidisciplinary emphasis generates a cascade of beneficial effects extending far beyond the gaining of new knowledge itself. An NCI center's research components - the main objects of direct CCSG support - constitute a core around which are a much larger penumbra of activities - clinical care, teaching, outreach, and education. These activities extend the benefits of research directly to patients, their families, and the general public. An institution with a strong research emphasis is ideally positioned to educate professional and lay people in its own community about medical advances

and to bring the fruits of discovery directly to those who need them. Excellence in care accompanies excellence in science. The promotion of effective outreach strategies and the fostering of cancer education complement the CCSG's focus on research excellence.

A new set of guidelines for CCSGs detailing the goals, policies, and procedures relating to the CCSG administered by NCI's Cancer Centers Program has just been completed. NCI's current formulation of and expectations for its centers program is heavily indebted to the Report of the CCPRG and the majority of its specific recommendations have been adopted as NCI policy and incorporated into the new guidelines, often with little or no modification in language. Thus, the CCPRG has had a fundamental influence on NCI's rethinking of what an NCI-sponsored cancer center should be, how it should be reviewed, and how it should relate to other centers and to the NCI. In addition to the CCPRG Report, the new statement of policies and review guidelines takes into account reactions to the Report by members of NCI's several advisory boards, by numerous individuals within the cancer centers themselves, and by NCI's leadership and staff.

Although NCI is an institution of science, its aspirations for the Cancer Centers Program do not end with discovery. Ongoing NCI initiatives enable the centers to design and evaluate increasingly effective outreach and education programs. NCI anticipates that the increased flexibility inherent in the new guidelines will result in the funding of new centers with a great variety of scientific agendas, including ones that exploit the opportunities afforded by the availability and needs of special populations. The disproportionate burden of cancer in certain minority groups, for example, is poorly understood and badly in need of attention from the research community. Planning grant initiatives will enable institutions in underserved communities and geographical areas to develop a critical mass of programs so that they may become more effective scientific institutions and better meet local and regional needs.

Since fiscal year 1992, the NCI has supported 16 cancer center planning grants (P20s) in regions of the country that were not supported by the NCI as either clinical cancer centers or comprehensive cancer centers, placing special emphasis on those developing centers that had the potential to bring the benefits of research to minority and rural populations. Additionally in fiscal year 1995, the NCI sponsored an initiative designed to support the important equipment and instrumentation needs of existing cancer centers and developing cancer centers. Seven awards were made to developing centers and 28 awards to existing centers throughout the nation. The total budget for this equipment and instrumentation initiative was $2.5 million. In addition, the Cancer Centers Program awards supplements to cancer centers at the end of each fiscal year that have important equipment and instrumentation needs. The NCI will continue to explore all feasible opportunities for coordinating with the NCRR. Current activities include the General Clinical Research Centers supported by NCRR and NCI Cancer Centers residing in the same institutions. There is also co-funding between the NCI and NCRR in support of vector production facilities important for human gene therapy.

At the present time, three institutions have planning grants with future year commitments remaining. However, eight of the 16 institutions that received planning grants submitted Cancer Center Support Grants. Two of the nine have been funded as NCI Cancer Centers and three or

four others are considered to have considerable potential for future success. The NCI considers the planning grant initiative for cancer centers a success. As a result of the CCPRG's Report, the NCI is considering making the Planning Grant a regular investigator-initiated grant mechanism, which would be the broadest and most consistent way to encourage the development of new cancer centers that can serve rural, minority and other special populations.

Item

DES -- The Committee continues to strongly support increased efforts to study and educate the public about the impact of exposure to the synthetic hormone diethylstilbestrol [DES]. NCI and other Institutes, along with the Office of Women's Health have developed a plan for expanded activities in this area. The Committee is pleased with the Institute's efforts in this area and expects NCI to continue its strong support for carrying out the recommendations of this plan. p. 75

Action Taken or to be Taken

NCI will continue to fund the five centers responsible for the follow-up of established DES-exposed populations (i.e., mothers, daughters and sons). Extensive analysis of the cancer experience of these populations will be done based on the results of the most recent follow-up effort.

The RFA-funded cooperative agreement, "DES and Cancer of Vagina/Cervix-- Collaborative Studies," involves re-contacting patients with clear cell adenocarcinoma (CCA) and identifying newly diagnosed cases. Clinical and epidemiologic data are being collected to assess factors related to survival and recurrence of CCA among DES-exposed (cases) and non-exposed (controls) women. Research efforts include investigating DNA microsatellite instability and DNA repair gene mutations, as well as the role of human papilloma virus (HPV) in CCA carcinogenesis. A meeting of investigators was held in December 1996 to discuss future research directions that utilize biological specimens and laboratory-based protocols.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42 USC241	Indefinite	> $2,112,747,000	Indefinite	> $2,173,063,000
National Cancer Institute	Sec 417 B(a)	42 USC286a-8	a/		b/	
National Research Service Awards	Section 487(d)	42 USC288(d)	a/	43,669,000	b/	44,419,000
Total, Budget Authority				2,156,416,000		2,217,482,000

a/ Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208).

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Appropriation History

Fiscal Year		Budget Estimate to Congress		House Allowance		Senate Allowance	Appropriation	
1989		1,468,256,000	2	1,596,536,000		1,591,036,000	1,571,879,000	
1990		1,494,741,000	3	1,652,666,000		1,668,473,000	1,657,161,000	4
1990	Sequester						(22,829,000)	
1991		1,694,059,000		1,749,392,000	5	1,747,462,000	1,714,784,000	6
1991	Sequester						(22,000)	
1992		1,810,230,000		1,830,509,000		2,010,230,000	1,962,587,000	7
1993		2,010,439,000		1,998,616,000		2,010,439,000	1,981,351,000	8
1994		2,142,122,000		2,082,267,000		2,082,267,000	2,076,382,000	
1995		9 1,967,709,000		1,917,929,000		1,917,929,000	1,919,419,000	10
1995	Rescission						(5,600,000)	
1996		9 1,994,007,000		2,025,294,000		1,972,757,000	2,029,591,000	11
1996	Rescission						(2,654,000)	
1997		9 2,060,392,000		2,161,395,000		2,102,949,000	2,156,416,000	12
1998		9 2,217,482,000						

1 Reflects enacted supplementals, rescissions and reappropriations.
2 The 1989 request excludes funds for AIDS research and education [$125,280,000] proposed for consolidation in the Office of the Assistant Secretary for Health.
3 The 1990 request excludes funds for the National HIV program [$151,332,000] proposed for consolidation in the Office of the Assistant Secretary for Health.
4 Excludes enacted administrative reduction of $6,839,000.
5 Excludes $35,793,000 for NRSA training programs not considered.
6 Excludes enacted administrative reductions of $42,568,000 and $8,972,000.
7 Excludes enacted administrative reductions of $22,255,000, $482,000, and $3,954,000.
8 Excludes enacted administrative reductions of $16,060,000; $9,933,000; and $139,000.
9 Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
10 Excludes enacted administrative reductions of $901,000, $116,000, and $1,482,000.
11 Excludes enacted administrative reductions of $1,546,000 and $1,108,000 and includes $6,951,000 transferred from the Director, NIH, one-percent transfer authority.
12 Excludes enacted administrative reductions of $1,095,000 and $38,000.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director..... Includes the Offices of Extramural and Intramural Management	542	542	542
Division of Basic Sciences.....	589	589	589
Division of Clinical Sciences.....	489	489	489
Division of Cancer Epidemiology and Genetics.....	105	105	105
Division of Cancer Treatment, Diagnosis, and Centers.....	187	187	187
Division of Cancer Biology.....	49	49	49
Division of Cancer Prevention and Control.....	143	143	143
Division of Extramural Activities.....	76	76	76
Total, NCI	2,180	2,180	2,180

	Average GS/GM Grade
1993	10.7
1994	10.5
1995	10.6
1996	10.7
1997	10.7
1997	10.7

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	0	0	0
ES-5	2	2	2
ES-4	9	9	9
ES-3	1	1	1
ES-2	3	3	3
ES-1	2	2	2
Subtotal	17	17	17
Total - ES Salary	$1,945,732	$2,009,941	$2,050,140
GS/GM-15	185	185	185
GS/GM-14	233	233	233
GS/GM-13	206	206	206
GS-12	271	271	271
GS-11	224	224	224
GS-10	10	10	10
GS-9	125	125	125
GS-8	84	84	84
GS-7	243	243	243
GS-6	60	60	60
GS-5	53	53	53
GS-4	58	58	58
GS-3	11	11	11
GS-2	8	8	8
GS-1	3	3	3
Subtotal	1,774	1,774	1,774
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	1	1	1
Senior Grade	60	60	60
Full Grade	57	57	57
Senior Assistant Grade	65	65	65
Assistant Grade	20	20	20
Subtotal	204	204	204
Ungraded	306	306	306
Total permanent positions	1,899	1,899	1,899
Total positions, end of year	2,301	2,301	2,301
Total full-time equivalent (FTE) employment, end of year	2,180	2,180	2,180
Average ES level	3.4	3.4	3.4
Average ES salary	$114,455	$118,232	$120,596
Average GS/GM grade	10.7	10.7	10.7
Average GS/GM salary	$51,019	$52,703	$54,284

WEDNESDAY, FEBRUARY 26, 1997.

NATIONAL EYE INSTITUTE

WITNESSES

CARL KUPFER, M.D., DIRECTOR

EDWARD McMANUS, DEPUTY DIRECTOR

JACK McLAUGHLIN, Ph.D., DIRECTOR, DIVISION OF EXTRAMURAL RESEARCH

CAROL LIPSON FIVOZINSKY, BUDGET OFFICER

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We are pleased this afternoon to welcome Dr. Carl Kupfer, the Director of the National Eye Institute.

Dr. Kupfer, it's very good to see you. I think I'm going to have you to myself. But why don't you proceed with your statement, and then we'll go into questions.

INTRODUCTION OF WITNESSES

Dr. KUPFER. Thank you, Mr. Chairman.

Perhaps before I begin I might just introduce those to my left who are representing the National Eye Institute also. To the far left is Ms. Carol Fivozinsky, who is our budget officer. Next to her is Mr. Ed McManus, who is the deputy director. And to my immediate left is Dr. Jack McLaughlin, who is the associate director for extramural programs.

OPENING STATEMENT

Mr. Chairman, the National Eye Institute continues to support research on the vast array of blinding eye diseases, but today I would like to focus on some of the exciting new areas of research that really impact upon the concerns amongst our older Americans.

It's a condition which is the main cause of visual disability and blindness. At present, there are 1.7 million Americans over the age of 60 who suffer from severe visual impairment and blindness, and by the year 2030 this number will be increased to about 6.3 million.

This is a condition called "age related macular degeneration," and then the term "age-related," that tells you why there's going to be such an increase as our baby boomers, who are just reaching age 50, will continue to go into the 60 and above age group.

We are pursuing a number of very exciting areas, and I'd like to just very briefly tell you what they are.

In the laboratory, we are very interested in the evaluation of growth factors, and these are factors that can rescue cells and allow regeneration to take place in the central nervous system and the retina, which is affected by age-related macular degeneration. The retina is part of the central nervous system.

The disease affects the macula, which is that part of the retina we use for straight-ahead vision. We use it for reading, for driving, for sewing. And, therefore, the individual who has age-related macular degeneration is unable to do these activities, but fortunately can still get about and ambulate, although the impact on quality of life is very severe.

We are very much interested in an item that Dr. Klausner brought up, and that is blood vessel growth. Just as blood vessels are important to maintain the integrity of a cancer, and if you could reduce the amount of blood vessels, you can kill the cancer. There are eye conditions—age-related macular degeneration being one and diabetic retinopathy being a second—where new blood vessels form. And we are actively engaged in looking at factors that prevent proliferation of new blood vessels—we, and people in the Cancer Institute, and the many other institutes who are interested in preventing abnormal blood vessel growth.

We are pursuing techniques for the introduction of genes into the retina, and this has been accomplished in experimental animals, and I think in the next two or three or four years we will begin to see these experiments done in patients.

We are very much interested in retinal cell transplants. This, again, is going to be primarily done in experimental animals for the foreseeable future, because there are many very important aspects of this type of work, including graft rejection, that must be overcome before we can assure that a clinical trial is worth doing.

And, finally, there is a condition in which the cell seems to commit suicide, and a number of diseases, including glaucoma and macular degeneration, appear to share this problem. We want to know what regulates this activity and how we can turn it off.

From a clinical point of view, we are well into our Age-Related Eye Disease Study, which involves some 4,700 patients, and from this study we will be able to assess the aging process of a retina, the potential risk factors that may predispose to the development of age-related macular degeneration.

We're very much interested in measuring the quality of life, and we do have an instrument, a questionnaire, that enables us to assess this very quantitatively.

And, finally, there is a clinical trial component to look at the effect of certain vitamins and minerals as to whether they can be of benefit in slowing down the degenerative process.

We are also beginning two new studies in which we're evaluating the genetic factors in macular degeneration. There are a number of families in which two or more members do have macular degeneration, either in the same generation or in two generations, and we're looking very aggressively at what the genetic factors might be.

I don't want to forget to mention that we are also very much interested in the infant and the young child. We recently announced the results of our retinopathy of prematurity study in which freez-

ing the outside of the eye has reduced blindness considerably, now that we're able to measure the vision at age five-and-a-half and six years.

As far as young Americans are concerned, we've had a very interesting experience with a pilot study in which patients with uveitis who are on large amounts of drugs, which do have adverse side effects, can have those drugs reduced by the introduction of a purified protein derived from the retina is actually fed to the patient.

The National Eye Institute is requesting for 1998 a budget figure of $330,955,000.

Mr. Chairman, I'd be happy to answer any questions.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of Director
National Eye Institute

Mr. Chairman, I am pleased to report that the NEI continues to conduct and support research leading to treatment for blinding eye diseases, including glaucoma, cataracts, and diabetic retinopathy. Furthermore, we also are pursuing exciting new avenues of research for one particular eye disease that is causing increased concern among older Americans , age related macular degeneration, or AMD.

The American eye is aging. The first group of "baby boomers" , those born between 1946 and 1964 , turned 50 last year. This group, by their sheer numbers, has changed, and continues to change, the fabric of American society. In 1995, these "baby boomers" numbered more than 79 million.

As this group of Americans marches toward their golden years, they will become more susceptible to serious eye diseases, such as AMD. AMD is a common eye disease of the macula, a tiny area in the retina that helps produce sharp, central vision required for "straight ahead" activities such as reading, sewing, and driving. A person with AMD loses this clear, central vision. AMD is the leading cause of severe visual impairment and blindness in the United States. It is estimated that AMD already causes visual impairment in approximately 1.7 million of the 34 million Americans over age 65, and its prevalence is expected to reach 6.3 million by the year 2030. Since fiscal year 1989, the NEI has devoted an increasing percentage of its annual appropriation to AMD research.

Technology has advanced greatly in recent years, and as a result, the NEI has identified several areas of research to learn what causes AMD and how it can be treated more successfully. Through NEI's Age-Related Eye Disease Study, researchers at 11 clinical centers around the country are assessing the aging process, potential risk factors, and quality of life of 4700 patients to pinpoint the earliest signs of AMD. Once such studies have helped us to determine how macular degeneration develops, we might be able to change its course; when we know for certain what risk factors contribute to development of the disease, we can caution patients to avoid them. This same study also includes clinical trials that will help determine the effects of certain vitamins and minerals in preventing or slowing the progress of AMD. In particular, researchers are examining whether vitamins C and E, beta-carotene, and zinc can provide the macula with greater protection, thereby preventing or slowing progression of the disease. If dietary supplements prove effective, it would have a huge impact on AMD treatment and reduce our nation's risk of visual impairment or blindness.

Another study begun last year is evaluating genetic and environmental factors related to AMD and examining an underlying hypothesis that genetic factors play a significant role in this complex chronic disease. Participating families in this study include those with both a single case of documented AMD and those who have at least two living siblings (or a parent) with documented AMD.

One of the risk factors that may be associated with AMD and vision loss is the presence of drusen, which are white, clumpy deposits that lodge under the retina. Early investigations suggest that these deposits might be a precursor to AMD, and this hypothesis is undergoing careful study to determine if drusen play a role in the development of macular degeneration.

Other approaches to solving the problem of AMD include laboratory, or basic, research. This research includes studies of genetic factors to gauge the role of heredity in the development of AMD. Genes involved in AMD already have been identified in three less common types of macular degeneration. In addition, genes associated with several other forms of macular degeneration have been localized to specific chromosomes. Knowing the genes will enable researchers to determine the gene product and how it brings about the degeneration.

NEI scientists also are trying to identify genes that could help regenerate damaged areas of the retina. This strategy may help to prevent much of the visual loss from later stages of AMD. Researchers are exploring the effects that gene replacement therapy may have on the treatment of macular degeneration, and scientists have already successfully placed genes into the retina of laboratory animals. Replacing diseased retinal cells with healthy ones is another promising area of research. NEI scientists are working to apply retinal cell transplants to treat retinal degeneration caused by AMD.

The NEI also sponsored a workshop that led to shared research ideas and consideration of the future direction of AMD research. This workshop, held last June, brought together academicians, clinicians, and representatives from biotechnology companies, all of whom were knowledgeable in growth factor cell biology. The discussion centered around the potential use of neurotrophins, or biological survival factors, to delay clinical indications of retinal cell degeneration in AMD and other eye diseases.

In addition to being a leading cause of blindness in the United States, AMD is also a leading cause of low vision, broadly defined as a visual impairment interfering with an individual's ability to perform activities of daily living. There are approximately three million Americans who suffer from visual conditions that are not correctable by standard glasses or contact lenses. People with low vision often cannot perform daily routine activities, such as reading the newspaper, preparing meals, or recognizing faces of friends.

As the leading source of vision research funds in the United States, the NEI is committed to furthering progress in the area of low vision research. During 1996, the NEI supported 18 extramural research projects related to low vision. In addition, the NEI, through the National Eye Health Education Program, is developing an education program aimed at addressing the needs of people with low vision. This new program will increase public awareness about the impact of low vision on daily living. Approximately 21 percent of those who have low vision and are aged 45 and older are unfamiliar with low vision clinical services. The low vision program will play a key role in informing Americans about the use of optical and adaptive low vision devices and services.

The NEI has been very active in pursuing treatments for a wide spectrum of eye diseases, including those affecting the youngest Americans. Last year we confirmed that a freezing treatment helps save the sight of premature babies with a potentially blinding condition called retinopathy of prematurity. After 5½ years of follow-up, this treatment increased the possibility of saving sight in affected eyes by about 24 percent. These results present solid evidence that this freezing treatment significantly reduces the number of infants who are blinded by retinopathy of prematurity.

NEI's fight against uveitis, a severe inflammation in the eye, is continuing. Uveitis causes about 10 percent of the severe visual impairment in the United States, and affects primarily children and young adults. Treatment of uveitis has usually revolved around potent drugs that block the immune system. In a recent intramural NEI study, we found that when a purified protein is fed to patients suffering from uveitis, they were able to be weaned off the strong drugs, with no negative side effects. A larger, more focused clinical trial is underway.

The NEI is also studying the effect of apoptosis, or "cell suicide," in retinal degeneration. Apoptosis is a controlled, orderly process by which the body eliminates unwanted cells; it is a mechanism to eliminate damaged cells, without harming healthier neighbors. Apoptosis appears to play a role in several retinal degenerative diseases. By understanding the process by which this programmed cell death occurs, scientists may be able to develop a method to inhibit the process and thus treat these diseases.

The NEI also is active in the area of cell rescue and regeneration. Severed nerve cells in the peripheral nervous system can survive and regenerate to some extent, but most central nervous system nerve cells do not. For years researchers have been trying to determine the basis for this difference, so that damage to either system could be repaired. Recent research on the development of the visual system indicates that the signals that promote the survival and growth of neurons in the central nervous system and peripheral nervous system may differ significantly. Studies have demonstrated that specialized nerve cells in the retina that are similar to brain cells, including those cells in the spinal cord, do not survive in a serum-free culture medium. However, these cells do survive in culture when the medium contains the required combination of growth factors and other constituents. Related experiments in animals show that the survival of these specialized retinal cells after damage is significantly increased by injection of these factors into the eye. These findings demonstrate that the retinal nerve cells have similar survival requirements in the living organism and in the test tube, suggesting central nervous system neurons can be rescued by activating the appropriate signaling pathways.

As the NEI continues its research, it is becoming apparent that many eye diseases and disorders share common denominators. For example, new blood vessel growth in the retina is associated with both diabetic retinopathy and age-related macular degeneration. The NEI is looking at the way these pathologic processes cut across many diseases and can be controlled by blocking new blood vessel growth.

Our investment in high quality clinical research has little real benefit unless the results and recommendations from such studies are widely and suitably incorporated into patient care. Results of research must be disseminated to the public so people can take

more proactive approaches to ensure their own health. One way this happens is through the National Eye Health Education Program (NEHEP), which is playing a role in educating Americans on the early detection and treatment of eye disease. For the past three years the National Eye Institute, through the NEHEP, has joined forces with the American Diabetes Association to make diabetic eye disease the major focus of National Diabetes Month activities, held in November. Through this successful public-private partnership, 11 organizations have disseminated important information to the 16 million Americans with diabetes and conducted community activities nationwide that emphasized the importance of an annual dilated eye examination. A related media campaign focusing on the connection between diabetes and eye care reached over 80 million people.

NEI's research program does more than fight eye disease , it also helps inventors with ideas on low vision aids develop those ideas for the marketplace. Inventors have few resources available allowing them to develop products that help people suffering from low vision. NEI's Small Business Innovation Research Grants Program gives inventors the opportunity to see their ideas turned into reality. For example, through this program, telescopic systems were developed that help those with low vision perform common tasks, such as walking down the street or reading signs. Another idea, a system called "Outspoken," magnifies text on a computer screen, making it easier for people with low vision to read. This product was recognized by the Smithsonian Institution for its unique way of using technology for the common good. A sister program, called the Small Business Technology Transfer Grant, encourages inventors in universities or research centers to form partnerships with small businesses. Between both programs, NEI expects to fund approximately 50 projects this fiscal year.

Mr. Chairman, the fiscal year 1998 budget request for the National Eye Institute is $330,955,000. I will be happy to answer your questions.

PROFESSIONAL JUDGMENT BUDGET

Mr. PORTER. Thank you, Dr. Kupfer.

I'm inclined to want to ask you first about the budget number. We understand that the request, including the OAR transfer, would be roughly $340.4 million, up about $8 million over the fiscal year 1997 appropriation. And I'd like to know what, in your professional judgment, your budget should be.

In other words, what could you reasonably really use? How much promising research is there in the area of the eye? And won't you, in fact, because of inflation, be actually working with less money in the next fiscal year if we were to fund you at the $340 million level than you have to work with right now?

Dr. KUPFER. I did mention in my opening statement those areas that are very promising that have to do with age-related macular degeneration. And, of course, they impact on other retinal diseases, such as retinitis pigmentosa.

And we would go ahead and take advantage of these research opportunities, no matter what. In fact, in the last three or four years we have increased the amount of money in age-related macular degeneration from $5 to $17 million, and the present level of support of retinal research is about $70 to $75 million.

[CLERK'S NOTE.—later corrected to "$16"]

But there are other opportunities. For instance, just in the last two weeks a gene for glaucoma was discovered, and the exciting thing about this is that usually when we find the gene, we aren't quite sure what it does, because we first have to find out what the gene produces in the way of a protein and determine what the protein does.

In this case we not only know where the gene is; we can identify the gene, we know what protein it produces, and we know what the protein does—it clogs up the out-flow channels in glaucoma.

And we can immediately apply this within the year to screening families that have this form of juvenile glaucoma—that is, they develop the blindness within the second and third decade of life—and identify quite convincingly those individuals who are at high risk of going blind.

So this is an area that should immediately be followed up very aggressively in terms of how does this finding apply to open-angle glaucoma, which is the main form of glaucoma throughout the United States and the world.

In particular, that happens to be a very major problem amongst African-Americans. It's about six times more common in African-Americans than Caucasians.

[CLERK'S NOTE.—"to seven" later added.]

So there are other opportunities.

In cornea research we now have for the first time identified channels in the cornea through which water is transported. And, of course, the whole trick in keeping the cornea clear is to keep it free of fluid, and therefore the ability to see the channels where water is continually being pumped out of the cornea becomes a very important point in preventing the cornea from becoming opaque.

In cataract there are new findings that should be put to hypothesis testing because we want to slow down the development of cataract. I mentioned before, if we could just slow down the development of cataract by ten years we'd reduce by about 45 percent the number of people who need surgery.

[CLERK'S NOTE.—"to 50" later added.]

Right now we, as taxpayers, support about $5 billion to do the 1.6 million cataract surgeries every year, and that's a major econoinic impact. Even though it's one of the most safe operations and most effective operations, it still represents a major economic impact.

So there are a number of opportunities, and I would say that we would pursue all of them at a slower rate. With additional resources, the rate could be increased.

GLAUCOMA GENE

Mr. PORTER. I always enjoy the interplay between the budget you really would like to have and the one the President has handed you, so I like to ask these kinds of questions.

We remember the painful retirement of Kirby Puckett from baseball last year because glaucoma had irreversibly damaged his right eye before it was detected.

Now recent scientific findings may result in new tools for early diagnosis of glaucoma. Researchers in Iowa have located a gene that causes a particularly virulent form of glaucoma which strikes young people, as you said. They expect to develop a test for the gene within a year.

This seems to be different from most cases when genes are discovered and years of work lie ahead before there is an impact on patients. Once tested, glaucoma patients could be diagnosed early and treated before any vision loss had occurred. Does this test also hold promise for people with more common forms of glaucoma?

Dr. KUPFER. Yes, sir. First, as far as the juvenile type, it's going to be a very effective way of really preventing blindness from ever occurring, because for this group, the use of a straightforward operative procedure before the disease really has taken away vision, will basically prevent the blindness from ever occurring.

In the case of open-angle glaucoma, I think we're going to have to see what additional genes are involved in addition to the one that has just been found, and I think in the next year or two or three we will identify those additional genes.

This finding has really spurred on the researchers. We have several groups working very hard in trying to identify additional genes.

So I think there will be a major impact on this disease.

Mr. PORTER. So that most eye diseases that are genetic are not single-gene conditions; they're more likely to be multiple?

Dr. KUPFER. Yes, sir. I think it is very clear that glaucoma, age-related macular degeneration, retinitis pigmentosa are multiple-gene diseases. We've got to find all the genes involved.

[CLERK'S NOTE.—Reference to "retinitis pigmentosa" later struck and "diabetic retinopathy" added.]

Mr. PORTER. And if you had more money, you could presumably find them faster?

Dr. KUPFER. Faster. Yes, sir.

NEURON SURVIVAL

Mr. PORTER. Your justification describes a protein found in cells that lie behind the retina which encourages neuron survival. The therapeutic potential of this protein is being explored for a variety of conditions in which neural cells die, such as stroke, traumatic brain injury, and Parkinson's disease. This seems to highlight the difficulty of ascribing research to one disease or another.

When you're asked to estimate your total expenditures for a list of diseases, how would you categorize the research on this protein? Would it be research on eye disease or Parkinson's disease, or stroke?

Dr. KUPFER. Well, if we do it on the basis of what seems to have the greatest impact, the experiments that have been done on the cells which are affected by Parkinson's disease show clearly a survival of these cells. They do not degenerate in tissue culture.

So I would say this is probably going to have initially a major impact on Parkinson's disease.

As a matter of fact, this research was done in collaboration with the investigators in the Neurology Institute.

We are trying to see what role it plays in cell survival in the retina, and, of course, that is being pursued very aggressively.

RADIAL KERATOTOMY VERSUS LASER TECHNIQUE

Mr. PORTER. In past years we've talked about RK surgery as a method to correct near-sightedness. Now physicians are heavily marketing a laser technique that is intended to correct myopia. What kind of clinical trials or approvals did this procedure undergo before marketing began? Has it been compared to RK in terms of safety and effectiveness? And what is your scientific opinion of this procedure and its effects, both in the long and short term?

Dr. KUPFER. You may remember, sir, that when radial keratotomy, RK, first appeared on the scene—which is now perhaps 15 years ago—we were approached by a number of investigators in the community that said, "We are very concerned about the safety and efficacy of this procedure, and we would like to submit a clinical trial."

We expedited the review. It was a very good review, and we supported the clinical trial and actually have ten-year data on the outcome of radial keratotomy.

So from both a scientific point of view and from a patient information point of view, the surgeon can tell the patient what to expect in terms of outcome.

This research data base does not exist with the laser studies to the same extent that it does with RK. These studies were done without support from the National Eye Institute. We were very interested in supporting animal studies and did so, but the clinical studies were supported primarily by the manufacturers of the lasers, and it is difficult to assess the long-term effects of these procedures because the longest data now is about two years.

So I think we will want to see what the long-term effects will be.

However, I do want to add that FDA has reviewed these studies and has given approval for the use of the lasers.

FDA APPROVAL

Mr. PORTER. When FDA has these matters before them, do they contact you for data that you might have?

Dr. KUPFER. Yes, sir. As a matter of fact, we usually have a member of the National Eye Institute on their outside review panel.

We have been working with FDA over the past five years and working with the private sector, the pharmaceutical companies, the device makers, and academia, trying to bring together the four components to make the translation from the laboratory to the clinic and eventual FDA approval a little more secure in terms of designing the very best clinical trial possible and then helping to see that it's carried out well.

And I think gradually we are moving in this direction, and I have great hopes that we will see more collaboration between FDA, National Eye Institute, the private sector, and academia.

MACULAR DEGENERATION

Mr. PORTER. In your testimony you mentioned that 1.7 million people are affected with macular degeneration today, and that you estimate that by—I think you said the year——

Dr. KUPFER. The year 2030.

Mr. PORTER [continuing]. 2030 it would be something like six million.

Dr. KUPFER. Approximately 6.3 million. Yes, sir.

Mr. PORTER. We're hearing from groups that are very concerned about macular degeneration that they say 13 million people are affected today.

Why is there a difference in this estimate?

Dr. KUPFER. When we quote the figure 1.7 million, we are saying that these are individuals who actually have severe visual disability or are legally blind. The larger figure are those who are at risk of developing age-related macular degeneration, and a certain subset of those individuals will go on to develop severe visual impairment, but not all of them.

Mr. PORTER. Mr. Stokes?

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Kupfer, it is nice to see you again.

Dr. KUPFER. Yes, sir.

GLAUCOMA GENE

Mr. STOKES. It is always a pleasure.

Doctor, according to your budget justification, approximately three million Americans have glaucoma, and at least half of those who have glaucoma are unaware of their condition. As many as 120,000 people now are blind from the disease.

Recent articles report that the gene associated with glaucoma was recently identified by NEI-supported investigators.

What are the major implications of this finding with respect to early treatment and detection of glaucoma?

Dr. KUPFER. The gene that was found and cloned and the protein product that it produces and what it does, primarily applies to a

subgroup of glaucoma that's called juvenile glaucoma because they develop during the first two decades of life.

In those individuals who are in families—and this is inherited as a dominant characteristic—we can now, within the year, test members of the family and determine very clearly whether they will go on to develop glaucoma or not.

The important thing is that when these individuals develop glaucoma they develop such high pressures in the eye that they can go blind in a matter of months, so early diagnosis is absolutely critical.

And if we can diagnose them early, we can do a surgical procedure to produce a new channel through which the fluid can leave the eye, and there's every expectation that they will then never get into trouble again.

Now, the real impact is how is this gene related to open-angle glaucoma, which accounts for about 85 percent of all the glaucomas, and that is being very actively pursued.

I think that it will be found that this gene does play a role in open-angle glaucoma, but there are other genes also involved, and those are the genes we are looking for now.

RETINOPATHY OF PREMATURITY

Mr. STOKES. What major progress do you have to report to our committee with respect to research on retinopathy of prematurity, the blinding eye disease that affects premature babies? What is the extent of this problem?

Dr. KUPFER. At the present time it has been estimated that about 4,000 infants weighing 3.3 pounds or less are born every year. And of those, it's estimated about 700 to 750 will become blind. We now can probably reduce that figure to about 400 by the treatment of freezing the outside of the eye.

We now have five-and-a-half year data on the first cohort of premature infants from a clinical trial begun about seven years ago, and we know that to actually prevent blindness, to restore good vision and keep vision, we can do that in about 25 percent of the children. And others may not have good vision but have useful vision.

So I think that we really have made major strides; however, we haven't stopped. We are continuing two other trials, one that deals with providing oxygen but at a very constant level. Technology has now enabled us to monitor the arterial oxygen levels continuously in premature infants lying in an incubator, so we can be sure that the level of oxygen stays constant.

There is the hypothesis that it's not just the level of oxygen but the changing level of oxygen that may be a risk factor in inducing retinopathy of prematurity.

And then there's another trial that is looking at the question whether there are other environmental factors that may contribute to the retinopathy of prematurity.

So we are very actively and aggressively pursuing this in conjunction with the Child Health Institute and with the Nursing Institute.

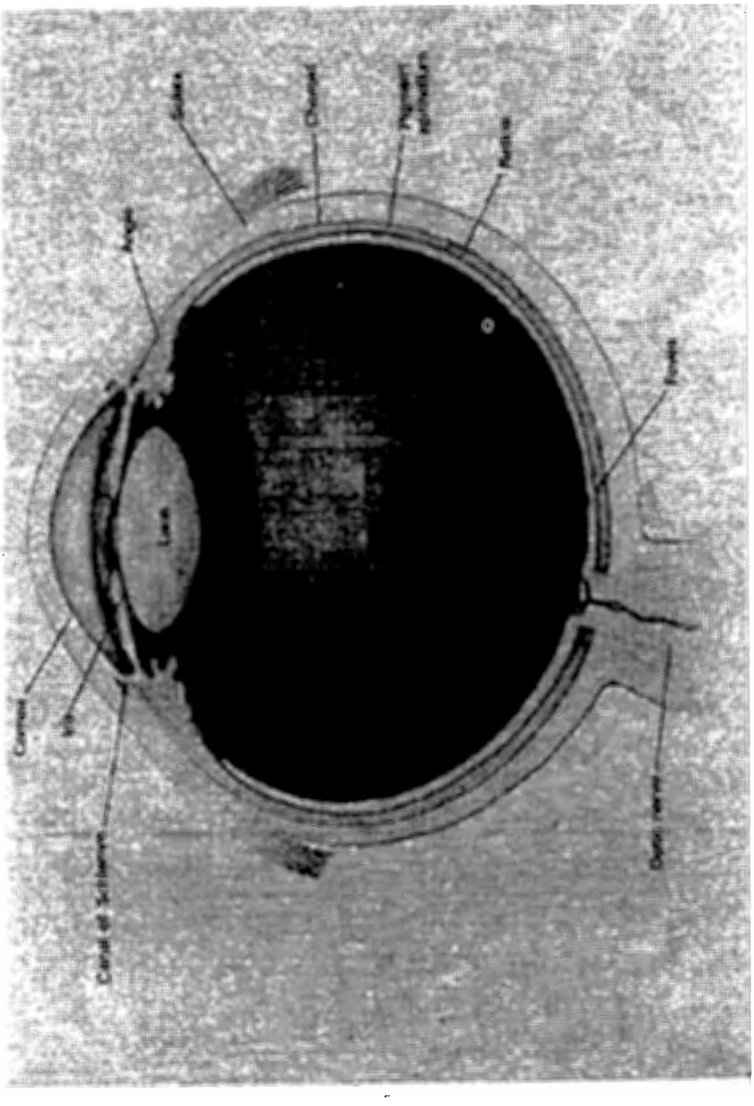
BIOLOGY OF THE BRAIN

Mr. STOKES. Doctor, as you know, the NIH has included the biology of the brain among its special emphasis areas, and, of course, you, Doctor, over the years have focused attention on the eye as the window to the brain.

What major research studies are underway at the Institute with respect to the biology of the brain? And, tell us—what are the implications of this work for furthering advances in neuro-degeneration and spinal cord injury.

Dr. KUPFER. I think that the seeing part of the eye, the retina—and perhaps I could just illustrate that with this figure. This is a cross-section of the eye, and the light comes through the cornea and is focused by the cornea and the lens onto the retina, and the retina is actually part of the brain. It's part of the central nervous system.

[The information follows:]


Sclera
Choroid
Retina
Angle
Fovea
Lens
Cornea
Iris
Canal of Schlemm
Optic nerve

So that the connection between the retina and the brain, which we call the "optic nerve," is quite comparable to the spinal cord. In fact, they are the same level of complexity and conveying roughly the same sort of information from the periphery to the central nervous system.

The research that is then going on in the optic nerve has a bearing on spinal cord injury, and this research is primarily looking at what growth factors are necessary to allow cells of the central nervous system to regenerate similar to what happens when one has an injury to a peripheral nerve. Those peripheral nerves usually regenerate.

We're trying to determine what is the difference between a peripheral nerve, which can regenerate, and a central nerve track that cannot.

Growth factors are involved. Genetic control is another. These central nerves will regenerate in a very, very young infant, but somewhere along the line the genetic control to allow regeneration to occur stops. And we want to know how to reactivate it.

We're interested in therapy of various drugs that will stimulate the development of central nervous tracks.

So this is a very major area of work.

In addition, all the diseases that affect the retina—retinitis pigmentosa, age-related macular degeneration, the juvenile dystrophies, they also need to be studied in terms of growth factors, gene replacement, transplantation, all the sorts of studies that underlie neuroscience at the present time.

Mr. STOKES. Doctor, considering the importance of this area, how much is included in the fiscal year 1998 budget request for the work in this area? How much are we currently investing?

Dr. KUPFER. I think in terms of the retinal disease, we're investing about $75 million. This will probably increase in fiscal year 1998 because we want to take advantage of these research opportunities and we will move funds in that direction.

Mr. STOKES. I think I have exceeded my time. Thank you, Mr. Chairman.

TRANSPLANTED RETINAL CELLS

Mr. PORTER. Thank you, Mr. Stokes.

Dr. Kupfer, the press has reported that surgeons in Chicago have transplanted retinal cells from aborted fetuses in an attempt to treat macular degeneration. Is this an approach you believe holds promise?

Dr. KUPFER. Mr. Porter, this technique has been used in various parts of the world during the last five to ten years. It has been used in Sweden. It has been used in India. I think this may be the first report in the United States.

My feeling is that we have so much more to learn in terms of what must be done for a transplanted tissue to survive, that perhaps these types of clinical studies may be a bit premature.

We are pursuing this in the laboratory very aggressively, and we will continue to do so. I think that there is a high probability in the next five, ten, fifteen years, that we will learn the surgical technique of transplantation, how to prevent rejection of the transplant, how to maintain the transplant long enough to begin to de-

velop connections with the retina and the brain, and then how to reorient these transplants so they can actually convey information that's going to be meaningful to the brain.

These are very major problems that have to be overcome before I think this sort of surgery will be useful.

FETAL TISSUE

Mr. PORTER. Is there evidence that fetal tissue is less likely to be rejected than adult tissue?

Dr. KUPFER. Yes, there is, sir, and I think that was the reason that the fetal tissue was used. But, nevertheless, I think there is still the possibility that fetal tissue may remain viable for much longer than if it were adult tissue, but eventually I think it is going to either be rejected or it will develop into a scar and not be functional. That would be my prediction at the present time.

MACULAR DEGENERATION

Mr. PORTER. Cigarette smoking has been shown to increase the risk of developing macular degeneration. Are you working with the CDC and the Cancer Institute to include that warning in their cancer control messages about the dangers of smoking?

Dr. KUPFER. These are results that recently came to our attention through three different studies. I think that, given the fact that cigarette smoking is a disaster for lung cancer and for cardiovascular disease and several other things, adding this additional piece of information is desirable, but I think it doesn't quite have the same urgency as those other areas.

But we are in contact with CDC through our National Eye Health Education Program, and I know the Cancer Institute is aware of these studies.

Mr. PORTER. Was it an NEI study that linked nutritional supplements like selenium and vitamins to a slowing of macular degeneration?

Dr. KUPFER. Slowing of macular degeneration—I think that the present clinical trial in which we are using some vitamins and minerals is the first systematic attempt to see if these are of any benefit.

MARIJUANA USE FOR GLAUCOMA

Mr. PORTER. This morning we discussed the debate about possible medical uses of marijuana. One disease for which marijuana is claimed to have a therapeutic affect is glaucoma. Is there a scientifically-validated basis for these claims?

Dr. KUPFER. In the early 1970s it was found that smoking marijuana reduces the pressure in the eye in normal individuals. Following that, a number of patients with glaucoma did report that their pressures did go down when smoking marijuana, and this was observed to be the case by eye care professionals.

There were a number of animal experiments done during the early 1970s. In 1978 we actually issued a request for applications to study this in patients. No applications came forth, so we really do not have any strong scientific basis on which to make a judgment.

I hasten to add that we do have a very large armamentaria of drugs that have been approved by FDA that do lower intra-ocular pressure and do not have some of the very serious side effects that marijuana does have.

But we would be prepared to conduct clinical trials if there was an interest upon the part of the research community and individuals with glaucoma.

PRIVATE FOUNDATIONS

Mr. PORTER. You suggested last August that your Institute and the Foundation for Fighting Blindness should jointly plan their research agendas to direct research funding more effectively. Is this a departure from usual practice at NIH, or is it common to coordinate research agendas with private foundations?

Dr. KUPFER. I think it's becoming more and more common, sir. As a matter of fact, one of the models that I'm most familiar with began with the Diabetes Institute, and that was a collaboration between the Diabetes Institute and the Juvenile Diabetes Foundation, where they jointly funded research grants.

We now have that same relationship with the Juvenile Diabetes Foundation, and we would like to have that same relationship with the Retinitis Pigmentosa Foundation.

The reason for that is that, although their resources are not as extensive, they have much more flexibility than we do, and therefore they can do certain things that we cannot do, and we want to look for areas where we can complement each other in that nature.

I think we're going to see more of this rather than less.

I don't know, Harold, if you want to make any comment about the——

Dr. VARMUS. I have urged Institute directors to take seriously propositions from private organizations.

We offer one very important component that is often difficult for them to provide, and that is an extensive, well-established peer review system that allows them to make the best possible use of the dollars they receive from donations and volunteers.

Mr. PORTER. How would you plan to coordinate your research portfolio, since you place heavy emphasis on investigator-initiated research rather than Institute-generated research?

Dr. VARMUS. Well, we would not want to subscribe to a program that we didn't think was in our interest, and, through discussions that have been held with a number of funding organizations, we have been able to agree that there are initiatives of mutual benefit we both would agree would be to the advantage of both sponsors and that we'd be happy to sponsor.

Dr. KUPFER. One could see at least two occasions. What we're doing with the Juvenile Diabetes Foundation is to co-fund RO–1s, research grants that we've reviewed but do not fund. They're very meritorious, but we do not have adequate funds to fully fund them. And the Juvenile Diabetes Foundation looks at these, makes their own decision. We notify the grantee that if they are going to accept this grant it's going to be co-funded, so that they are fully prepared, and then we move ahead.

The second area is to supplement our fellowship support. There are opportunities where to bring individuals into a particular area,

a supplementation of the NIH fellowship might be helpful in an individual, for instance, who has a very large debt and would need some additional financial resources. The private foundations can do this. We cannot.

NUTRITIONAL SUPPLEMENTS FOR RETINITIS PIGMENTOSA

Mr. PORTER. You're conducting clinical trials of a nutritional supplement to halt the progression of retinitis pigmentosa. Vitamin A has already been shown to delay the progress of RP. Reports suggest that, if successful, this treatment could allow patients to retain useful vision for their entire lives. How can a nutritional supplement stop the progression of an eye disease?

Dr. KUPFER. Perhaps I could answer that by first going back to the first study that you alluded to.

The first study actually used Vitamin A or Vitamin E or a combination of the two or a placebo, and it was felt, on the basis of many, many animal studies, that both Vitamin A and Vitamin E would be of value, Vitamin A because it is part of the molecule in the retina that captures the light, rhodopsin; Vitamin E because it's an antioxidant and is supposed to stabilize membranes. And the photoreceptor is made up of thousands of membranes, so it was felt that this would be very valuable.

As it turned out, the Vitamin A was of benefit, but the Vitamin E was not of benefit and actually caused an acceleration of the degenerative process.

So one must be very, very careful in testing these in a very well-controlled clinical trial, so the recommendation from that first study was that Vitamin A is of benefit, and we have an explanation.

The second trial is additional assessment of nutritional ingredients, and we will see how that turns out.

Mr. PORTER. And if this therapy turns out to be successful, it would be very low-cost, would it not?

Dr. KUPFER. Yes, it would be, just as Vitamin A is very low cost. Yes, sir.

LONG-RANGE RESEARCH PLAN

Mr. PORTER. Your Institute is in the early stages of developing your next long-range research plan. What would you consider the most significant ways the vision research field has changed since your last plan was released?

Dr. KUPFER. I think the areas of neuroscience, of genomics, the tracking down of genes, and the role of immunology are probably the three major changes. Automation has played a very major role. High-speed computers have allowed us to do things we weren't able to do.

I think we're going to see research done in a very different way in the next decade than we have previously.

I think we're also seeing that collaboration is absolutely essential. This article on finding the gene in glaucoma must have had 15 authors, and I think this is not unusual. Many of these articles require the skills of many, many different groups, and I think we're seeing more coordination of research activities, and I think we've got to shape our research grant support in that direction.

CATARACT SURGERY

Mr. PORTER. Apparently, many people who have cataract surgery must have a second operation because the cataract forms again as a response to the residual lens cells remaining after the surgery. What share of those undergoing cataract surgery face this problem and how much could be saved if drugs or better surgical techniques could prevent the formation of the second cataract?

Dr. KUPFER. Yes, sir. It has been estimated that about 25 percent of the individuals who undergo cataract surgery have this proliferation of cells that occlude the vision, and therefore a laser treatment is necessary to sort of punch a hole in this membrane.

If we assume that there are about 1.5 million or 1.6 million cataracts done a year, and about 25 percent of those, that's about 300,000 to 400,000 develop this problem, and the average cost, with hospitalization and return visits, is about $1,000. We're talking about $300 to $400 million.

CONTACT LENSES

Mr. PORTER. How many Americans are contact lens wearers? Do we know that?

Dr. KUPFER. That's a very good question. The problem with the answer is we know how many people purchase contact lenses, but we don't know how many people are wearing them. It has once been said there are more contact lenses in the top bureau drawer than in the eyes of people.

I would guess—and I could correct this when I look at the transcript—somewhere between 5 and 10 million people are wearing contact lenses.

[CLERK'S NOTE.—later corrected to "24."]

Mr. PORTER. And are there any long-term studies of the effects, the possible negative effects of wearing such lenses?

Dr. KUPFER. Yes, sir, there are. Many of the studies have dealt with what was the original type of lens, the hard lens, and they have given way almost completely to the soft lens. The hard lenses do have some complications after about 15 to 20 years of wearing, but the soft lenses so far are being watched very carefully.

The main problem with soft lenses is that they are so comfortable that people forget to take them out at night and will sleep with them—in fact, may keep them in three or four days—and then corneal ulcers can develop, and that's a major complication.

VISION CONDITIONS NEEDING MORE RESEARCH

Mr. PORTER. We talked about glaucoma and the tools to detect and prevent it. We seem to have a much more limited stockpile of weapons against other eye diseases. For which vision conditions would you say we know the least about treatment and prevention?

Dr. KUPFER. In terms of the public health impact, it's age-related macular degeneration. Of the cases, 90 percent are what we call "the dry type." That is, there is breakdown of the retina very slowly. The wet type is 10 percent. That's where new vessels develop. But it's that 10 percent that causes legal blindness.

And we can only treat successfully about 15 percent of those patients, so we really do not have an awful lot to answer. That's our major concern at the present time.

Mr. PORTER. And that, in a sense, is a result of being successful in other fields and having people live longer and healthier to later ages and then develop diseases like age-related macular degeneration.

Dr. KUPFER. That is it completely.

Mr. PORTER. Or Alzheimer's disease.

Dr. KUPFER. That's right.

Mr. PORTER. Well, we thank you very much, Dr. Kupfer, for your good testimony.

I'm going to ask Dr. Varmus if he would stay just a moment, because I have several questions left over from this morning that I'd like to pose to him. But thank you for your good testimony. Thank you for your excellent work at the National Eye Institute. You do a wonderful job there and we appreciate the candid and good testimony that you give us and insights into what is being accomplished in your field.

Thank you very much.

Dr. KUPFER. Thank you, Mr. Porter.

ANGIOGENESIS AND CANCER

Mr. PORTER. Some of these questions probably are for Dr. Klausner, but since he's not here——

Dr. VARMUS. We can call him back. He's still in the building.

Mr. PORTER. I thought you might be able to answer them.

We talked earlier about reducing the blood flow to certain cancers.

Dr. VARMUS. Right.

Mr. PORTER. And the promise that that has. I wonder if you know whether that is NCI-supported research that led us to where we are?

Dr. VARMUS. Most of it is. Yes. There are actually two approaches that are being taken. One is based on the idea that the process of blood vessel formation, like so many things that go on in the body, is a ying and yang process. There are factors that promote blood vessel development and there are factors that inhibit it.

Dr. Judah Folkman at Harvard, who is one of the pioneers in this field and a long-term NCI-supported investigator, has, for example, identified at least two or three compounds, natural products of the body—indeed, in some cases natural products of tumors—that can inhibit blood vessel growth and have been used in treatment of tumors in animals, and have, indeed, been proposed for clinical trials.

The other avenue is to make use of clotting mechanisms to induce thrombosis, clots, in blood vessels that lead to tumors.

I'm not sure who sponsored those experiments. There was a paper recently published in the journal, "Cell," describing the use of this approach in an experimental tumor in an animal, in mice. We could find out for you who supported that.

CONSOLIDATED AIDS APPROPRIATION

Mr. PORTER. Dr. Varmus, your budget again proposes a consolidated appropriation for the Office of AIDS Research. I know you're obligated to support the President's budget request, but could you tell me if the approach we used in fiscal year 1997 for AIDS funding was workable? Did our language prevent you from doing anything that you wanted to do in managing AIDS research?

Dr. VARMUS. It did not prevent us from doing anything. The budget was, of course, allocated according to the plan worked out by the Office of AIDS Research. It was slightly cumbersome in its operation, in that the money went to the institutes, back to the office, then back out to the institutes, but it was a paper transfer and it worked efficiently and everybody was happy.

AIDS TRANSFER AUTHORITY

Mr. PORTER. Do you and Dr. Paul intend to use the transfer authority we gave you in this fiscal year to move AIDS funds between institutes?

Dr. VARMUS. You're referring to the 3 percent transfer authority?

Mr. PORTER. Yes.

Dr. VARMUS. At the moment we don't have any expectations of using it. As you probably know or will soon know, we have identified a number of projects that will be funded by use of my 1 percent transfer authority, assuming that the committee is willing to approve that request. None of those are in the AIDS area.

I believe one of the reasons we've had so little need for it is that the planning process was carried out right up to the time when the allocations were made, and, as a result, I think the appropriations were appropriate.

And, given Dr. Paul's discretionary budget, I think in toto we were able to operate effectively without using this transfer authority. If there is a need as an emergency later in the year, we, of course, would employ the transfer authority.

EARMARKS FOR DISEASES

Mr. PORTER. I wish I'd had an opportunity to say this earlier, but I want to put it in the record.

Dr. Varmus, we fight hard to keep our bill and our report free of disease earmarks. We've heeded your warnings that this is destructive to the scientific enterprise, and I'll continue to fight to preserve this principle, despite what is a growing rebellion in some quarters of the Congress.

I have to say the President's pronouncements last year pledging specific dollar amounts to spinal cord injury research, for example, have the effect of undermining these kinds of efforts.

How can you and the scientific community expect Congress to continue "letting science decide" when the President of the United States seems to be leading a charge in the opposite direction?

That's more of a statement than a question.

Dr. VARMUS. Thank you.

Mr. PORTER. I think that it does us a great deal of harm for the White House to work in the direction that takes discretion away from science, from you in determining the proper allocation of

funds, and we would like to give you the maximum discretion in doing that.

While all of us have strong feelings, as does the President, we do our very best to try to keep them out of the bill and only in the report where they belong.

Dr. VARMUS. I perhaps should say, Mr. Porter, that there was a happy confluence of events in that circumstance, because there have been some recent developments in the study of central nervous system injury that allowed us to make extremely good use of those additional allocations.

PRIORITY SETTING

Mr. PORTER. In each year that I've been chairman of the subcommittee, I've been approached by advocacy groups concerned that NIH spending in certain diseases is out of balance with its incidence and associated health care costs, and I think Representative Istook raised some of those questions earlier.

Some feel that political pressures are applied to NIH spending decisions. Can you lay out for us your response to these concerns?

For example, when the committee provides more funding for NIH than was requested by the President and we ask your advice in allocating the increase, what guides your decision about distributing the funds among the institutes?

Dr. VARMUS. You ask me to do that here or for the record?

Mr. PORTER. No. Here.

Dr. VARMUS. There are several things. I have to say, Mr. Porter, as we think through priority setting, it is an imperfect process. When we're given money to spend on research, we have to depend upon subjective estimates and our judgment, and ultimately I suppose we come back to the idea that those of us who have been entrusted with positions such as director of NIH or director of an institute have the judgment that allows us to make the best possible guess about how the money can be well spent.

When we have an increased amount of money, there are two kinds of things that can be done. One is simply to fund more grants than we could otherwise fund. As you know, we have a list of grant applicants with different priority scores.

Currently, in some institutes, grants that received extremely high priority scores, perhaps ranking among the top 20 percent, but with scores that indicate a very high degree of excellence as perceived by the study sections, don't get funded, and we are able to fund those.

That's just a simple lowering of the threshold so that we have a higher success rate.

The other thing that happens is in the programmatic allocations by each institute—an allocation that is made differently in different institutes. Some institutes will fund the top 80 percent of their grant applicants and then look at the distribution of grants among programs and decide to reach lower in the priority list among grants to make sure that there's adequate support in various areas. Others divide the grants by program and fund to certain levels within each program.

Regardless of how that's done, when additional money is available the director of the institute, in consultation with outside ex-

perts, with members of his program staff, with his National Advisory Council that's composed of both consumers and scientists from the outside, will decide whether to go further in funding certain programmatic areas.

Now, when I say "program," I'm referring both to funding in certain categories—be it basic research or disease-specific research—or sometimes it means providing more funding for certain kinds of mechanisms—for training grants, for construction.

SHARED INSTRUMENTATION

You will recall that we've had discussions here before about the amount of money we're able to spend on extramural construction or on shared instrumentation. Shared instrumentation is a very useful item to talk about, because, as you're aware, we cut back on our support for shared instrumentation. I, myself, believe that's one of the most potent ways we can advance science, especially at centers where equipment does get used by a large number of individuals. And that's one of the things that tends to get cut when the money is tight, because we're not funding an individual investigator; we're funding the purchase of equipment that services many different investigators. But when we have more money, we're liable to say we will support the shared instrumentation grants or other endeavors that benefit a group of investigators.

AREAS OF SPECIAL EMPHASIS

Mr. PORTER. I thought I heard you earlier in the day refer to budgeting at various levels—in other words, I'm interested in at what point you do this.

Obviously, you've worked out a budgeted 2.4 percent increase. Do you also have in place where you might go if the funding were at 4.8 percent or 5 percent or——

Dr. VARMUS. Yes, I do.

Mr. PORTER. It's all done in advance?

Dr. VARMUS. This year, in particular, I went through, in painstaking detail, with each institute director the kinds of projects they would identify as falling within areas of special emphasis, areas where they could foresee—as, for example, Dr Kupfer could see increased interest in glaucoma as a consequence of cloning the glaucoma gene this year. He would tell me that there were three or four areas which he would like to expand because of new, recent discoveries or because of some pressing scientific need or because of a resurgence of a disease.

I have a list of initiatives that the institute directors would like to advance. As a result of our discussions, I have, by a semi-subjective and semi-informed process, developed my sense of what the most urgent items and the most productive items on that list are likely to be.

And I, in order to sustain our commitments and also initiate some new endeavors, have tried to put together a budget that's fair to the various institutes, fair to our existing grantees, and still allow initiatives to be started for various budget levels, not knowing where the actual outcome will lie. So I have some sense of how much we'll be able to put into these new projects if we have various levels of support.

Obviously, if we had this professional judgment budget, we would be able to support virtually all of the initiatives. If we have a more modest budget that is constrained by the budgetary issues we've agreed exist, we will support fewer of those or support them with less money than we might otherwise do.

ROYALTIES FOR DRUG PRODUCTS

Mr. PORTER. Dr. Varmus, we've been approached about a legislative provision that would extend five additional years of market exclusivity to unpatented drug products which are the subject of a CRADA with NIH. In return, the pharmaceutical companies would pay a royalty to NIH to enhance appropriated research funding. What is NIH's view of this proposal?

Dr. VARMUS. Well, we're willing to look at it, but I've only heard it described in the kind of detail you just provided. And until we see it in further detail, I would be hesitant to endorse it. We would be perfectly willing to work with whomever is proposing it and look at the details of the proposition.

GOVERNMENT PERFORMANCE AND RESULTS ACT

Mr. PORTER. Thank you.

From Department documents, we understand that NIH has determined that it will need to ask OMB for permission to develop an alternative approach to the Government Performance and Results Act performance measures for its research activities. Understanding the difficulty of establishing performance measures for investigator-initiated basic research, what alternative measures are you considering? And what approaches to GPRA are the other Federal science agencies contemplating, if you know?

Dr. VARMUS. Yes. Well, I do know something about that.

As you know, Neal Lane and I chair the Fundamental Science Committee of the National Science and Technology Council, and about two years ago, in preparation for the implementation of GPRA, we gave some thought to how the agencies that do fundamental science would be able to evaluate their programs in accord with GPRA.

In thinking through this process on the behalf of NIH, we came to the conclusion that we could develop some quantitative measures for our activities in support of training and in support of facilities and other infrastructure, so we plan to do that, to develop a logarithm that will allow us to make some judgments about how we're doing in those areas.

But, as you point out, with respect to fundamental research it is a good deal more difficult.

There are a number of qualitative measures that we can imagine. We can imagine descriptions of specific scientific advances as a way of portraying what we do. We can talk about the impact of our science on industry, on the biotechnology and pharmaceutical industries. We can talk about how basic science has benefitted clinical practice. We can talk about the impact of our research on improved health, on the reduction of hospital days or on the development of procedures that have been shown to be effective in the treatment of various diseases.

There is the possibility of some more quantitative measures. I, myself, find them rather unsatisfactory—for example, patent applications, citation indices, and other measures which I think are less instructive and less pertinent to what we do than actual descriptions of discovery.

MANAGED CARE

Mr. PORTER. This morning you touched on this question. I have been concerned for a long time about the changes in our health care delivery system that are leaving our teaching hospitals without the resources that they need, because in many instances managed care plans simply bypass those kinds of facilities because of their higher cost.

I'm also concerned as to what managed care organizations will do to contribute to the cost of biomedical research. I think you've had some discussion with representatives of the managed care industry recently about this. Can you fill us in, in a general way, on what you see?

Dr. VARMUS. Sure. We've met twice now with representatives of Kaiser Permanente, the Puget Sound Health Care Program, and several others.

Mr. PORTER. Did you initiate those meetings or did they?

Dr. VARMUS. Well, I guess we did at one level, but there were a couple of preliminary conversations, some of them initiated by Dr. David Nathan, who is the head of my clinical research panel. But I asked them then to come to NIH.

But it was clear from our preliminary conversations that they were interested in having these conversations.

As you know, the managed care industry includes a number of organizations that have been in existence for a long time, have a strong research record, receive NIH money, do interesting research, and have connections in many cases to academic health centers. And we see those connections strengthening.

Managed care organizations have much to offer the NIH. They have large stable patient populations that are easy to track, and particularly useful from the perspective of epidemiology and health services or outcomes research, or for the conduct of clinical trials.

I think there's a difference in overall program in that managed care organizations, for fairly obvious reasons, are less interested in the fundamental research than we might be, but we have many areas of shared interest.

And it's to their advantage, I think, to form partnerships with us because they know that their staff appreciates the chance to participate in research, they recognize that there are benefits to the kinds of research we're describing for their planning and for benefitting patients who are enrolled.

PARTNERSHIPS WITH MANAGED CARE ORGANIZATIONS

One of the things that we recognize as a joint concern is how they make their contribution to research without being penalized in what is currently a fiercely-competitive market.

Therefore, one of the players that needs to be brought into this discussion, but has not yet been brought in as actively as I would

like be done—the employers who are the ultimate purchasers of these health care plans.

If we were to persuade a managed health care provider to join with us and to provide some of the resources necessary to carry out more clinical research at our academic health centers, it would be necessary to pass on some of those costs to those who pay for the health care that's provided.

We believe that the benefits accrue both to those who are in those health care plans and to the Nation at large, and that either by force of persuasion of the employers who pay for these plans, or perhaps by persuading Congress to help us in finding ways to achieve means to ensure that health care plans include some allocation for research, that we can achieve the benefits that I think are to be gained by the managed health care revolution.

Mr. PORTER. Let's say that Congress did that. Let's say Congress directed all managed care plans to allocate 1 or 2 percent of their revenues to research. What effect would that have in directing research? And maybe you can talk generally about where we are in reference to basic research as opposed to research that tends to be more directed toward a specific end.

Dr. VARMUS. Well, I believe that money would be most appropriately spent largely on clinical activities, and I believe that because that is what the managed care organizations are going to be interested in, in part because a very significant part of the erosion of support of academic health centers has affected clinical research. Not all of it, because, as you know, patient care revenues that have traditionally gone to academic health centers have frequently gone into either a departmental fund or a dean's fund, which ends up supporting both basic and clinical research.

So I want to emphasize that the loss of revenues has affected both basic and clinical activities. But I think the expectation would be that whatever is provided from the managed care industry would go largely to clinical activities.

What I then imagine happening is that proposals that could be jointly funded by the NIH and by managed care would be supported through both avenues. I've not thought through in great detail exactly how that would be done, whether it would achieve the kind of partnership, we just discussed, with some of the voluntary organizations—for example, the Diabetes Foundation—or whether we would prefer to work with separate pots of money with managed care industry picking up some proposals and us picking up others.

RESEARCH PARTNERSHIPS

Mr. PORTER. It seems to me that we are—Dr. Kupfer referred to this—we are increasingly looking for partnering in one way or another with foundations or even with industry, and that at some point we end up with a great deal of research that is directed to specific ends and less perhaps resources than we ought to have on basic research.

Is that possible?

Dr. VARMUS. I wouldn't jump to that conclusion, Mr. Porter.

Mr. PORTER. Good.

Dr. VARMUS. Because if you look at the research in basic sciences these days and look at the acknowledgements in research papers, as I frequently do as someone, of course, looking for acknowledgement that NIH helped to support the research, what you find almost inevitably is support from a variety of institutions.

In fact, since it's frequently the case that NIH is the major supporter, it sometimes seems to me that the attribution to NIH is somewhat buried among a long list of foundations and other organizations that have provided support for post-doctoral training and for fairly modest amounts of money, but we all have supported the research.

So virtually everything that's done these days is a partnership, and the question is whether you allow those partnerships to be brokered independently by the investigator who has gone out to six places to get the money, or whether the investigator can go to one place and get support for a project from two organizations at the same time, as we do in the case of some of the projects co-supported by the Juvenile Diabetes Foundation and certain institutes at NIH.

Mr. PORTER. Dr. Varmus, thank you for your patience and for your very candid and direct answers to all of our questions.

We will now stand in recess until 10:00 a.m. tomorrow.

Dr. VARMUS. Thank you very much. I appreciate your interest.

[The following questions were submitted to be answered for the record.]

SPENDING ON EYE DISEASES

Mr. Porter: Identify FY96-98 spending on the following: Retinitis pigmentosa, glaucoma, diabetic retinopathy, macular degeneration, cataract, and CMV retinitis. Identify direct and related spending separately (understanding that there may be duplication of related spending between diseases).

Dr. Kupfer: The following table provides NEI FY 1996 - 1998 direct and related spending, for the eye diseases named.

	Fiscal Year		
	FY 1996	FY 1997	FY 1998
	(Dollars in thousands)		
Retinitis Pigmentosa			
Direct	$14,929	$15,861	$16,232
Related	25,783	27,397	28,042
Glaucoma			
Direct	30,412	32,372	33,195
Related	10,966	11,673	11,970
Diabetic Retinopathy			
Direct	14,944	15,855	16,203
Related	6,565	6,976	7,140
Macular Degeneration			
Direct	15,492	16,491	16,910
Related	55,619	59,100	60,492
Cataract			
Direct	11,883	12,648	12,969
Related	23,538	25,011	25,600
CMV Retinitis			
Direct	6,635	7,060	7,236
Related	4,664	4,956	5,073

DIABETES

Mr. Bonilla: Please explain NIH's Areas of Research Emphasis in particular, the "new approaches to pathogenesis" and its relation to diabetes.

Dr. Kupfer: One of the research areas the NIH has chosen for special emphasis during fiscal years 1997 and 1998 is "new approaches to pathogenesis." This area encompasses studies that seek to determine the pathological consequences of disease processes, as well as the mechanisms of injury. Some of the NEI-supported research on diabetic retinopathy, a sight-threatening complication of diabetes, falls within this area of emphasis. Recently, scientists have reported progress in this area while studying a particular protein, belonging to a family of proteins that control several important functions in blood vessels, such as blood flow. They found that the activity of one particular form of this protein is increased in the retina and in other tissues of diabetic animals. An orally-administered inhibitor of this form of the protein has been developed and shown to be effective in improving retinal blood circulation and several other vascular abnormalities in diabetic rats. This inhibitor may have therapeutic implications in preventing the abnormal growth of blood vessels that occurs in diabetic retinopathy.

Mr. Bonilla: The State of Texas participated in National Eye Care Month last month. Governor Bush encouraged Texans to have eye examinations as their New Year's resolution throughout the state. Did NEI conduct any outreach programs targeting minority populations?

Dr. Kupfer: The NEI conducts outreach programs for minority populations through its National Eye Health Education Program (NEHEP). The NEHEP is strengthening its relationship with those organizations that reach the African American population. One example is the National Black Nurses Association's (NBNA) collaboration with the NEHEP to educate its members about eye disease. In June 1997, the Cleveland chapter will pilot a continuing education program that, upon completion, will be promoted to all NBNA chapters at their annual meeting. In addition to the continuing education program, the chapter will conduct health education and eye screening for the community. Another example of our minority outreach efforts is through the work of The Links, an African American women's organization. The Links chapters throughout the country have been involved in National Diabetes Month activities and have worked to integrate eye health education into all their health and wellness programs. The NEHEP also continues to work with the African American media to highlight the importance of protecting one's vision.

Another one of NEHEP's important target audiences is Hispanics. This audience is reached through the *Ojo Con Su Vision* program, which is designed to educate Hispanics with diabetes about the importance of dilated eye exams to prevent vision loss that often results from their condition. The program's public service announcements for television, radio, and the print media continue to receive coverage, reaching millions of Hispanics with sight saving information. Coverage was especially high in key states including Texas, California, and New York. To complement the media activities, community kits

were distributed to more than 700 individuals or organizations that serve the Hispanic population. Working through these national, regional, and local organizations, the NEI staff is providing the Hispanic community with technical assistance and educational materials. Over 50,000 *Ojo Con Su Vision* booklets have been distributed, thus far. In addition, NEI staff continues to work with the National Council of La Raza to incorporate the NEHEP materials into their diabetes program. Plans are also underway to increase outreach to the Hispanic community through the use of Spanish-language radio and pilot programs with several community-based organizations.

Mr. Bonilla: Last year NEI sponsored a National Eye Health Education program (NEHEP) which included a strong emphasis on diabetes education in the Hispanic community. A TV station in my district in Eagle Pass, Texas received a PSA that the NEHEP developed and said they aired it daily and it appeared 28 times. They commented that the information was great and that they would welcome more tapes. Please update the committee on the progress of this program.

Dr. Kupfer: The *Ojo Con Su Vision* program has been extremely effective in educating Hispanics with diabetes about the importance of annual dilated eye exams to prevent vision loss that often results from their condition. The program's public service announcements for television, radio, and the print media continue to receive coverage, reaching millions of Hispanics with sight saving information. Coverage was especially high in key states including Texas, California, and New York. To complement the media activities, community kits were distributed to more than 700 individuals or organizations that serve the Hispanic population. Working through these national, regional, and local organizations, the NEI staff is providing the community with technical assistance and educational materials. Over 50,000 *Ojo Con Su Vision* booklets have been distributed. NEI staff continues to work with the National Council of La Raza to incorporate the NEHEP materials into their diabetes program. Plans are also underway to increase outreach to the Hispanic community through the use of Spanish-language radio and pilot programs with several community-based organizations.

AGE-RELATED EYE DISEASE STUDY

Ms. Northup: Please provide more detail on the Age-Related Eye Disease Study. Where are the 11 centers located? When did the study start and when do you expect results?

Dr. Kupfer: The Age-Related Eye Disease Study (AREDS) is divided into two Phases: Phase I began in March 1990 and ended in November 1992, and Phase II began in November 1992, and is expected to end in March 2000. The first six months of Phase I were devoted to planning the study. The remainder of Phase I was focused on screening and identifying potentially eligible study participants, developing the detailed study protocol, and preparing for Phase II. Various advisory groups made recommendations in Phase I regarding the study design and operational details for Phase II. The operational objectives of Phase II were to enroll 4,600 eligible participants and to follow them for the next six to seven years. A total of 4,734 participants have been randomized into AREDS and participating clinical centers have completed a total of 21,344 study visits, with patients being seen every six months. Patient follow-up is projected to continue until March 2000. The Data and Safety Monitoring Committee, an independent oversight board, reviews annually the accumulating study data and advises the NEI and study investigators on study matters.

The eleven AREDS participating centers are located as follows:

Massachusetts Eye and Ear Infirmary - Boston, Massachusetts
Associated Retinal Consultants, P.C. - Royal Oak, Michigan
Albany Memorial Hospital - Albany, New York
Devers Eye Institute - Portland, Oregon
The Eye and Ear Institute of Pittsburgh - Pittsburgh, Pennsylvania
University of Wisconsin - Madison, Wisconsin
Emory University - Atlanta, Georgia
Ingalls Memorial Hospital - Chicago, Illinois
The Johns Hopkins Hospital - Baltimore, Maryland
Elman Retina Group - Baltimore, Maryland
National Eye Institute, NIH Clinical Center - Bethesda, Md.

Ms. Northup: What type of environmental effects are you seeing in the formation of age-related macular degeneration (AMD)?

Dr. Kupfer: The Age-Related Eye Disease Study is designed to assess the association of a number of risk factors on the formation and progression of age-related macular degeneration. The specific environmental factors that will be evaluated are: nutrition (diet and biochemical factors), effect of antioxidant nutrients and zinc, cigarette smoking, use of alcohol, medications, supplement use, and sunlight exposure. In addition, medical factors will be evaluated, such as a history of cardiovascular disease,

diabetes, skin cancer, and poor nutritional status. The study results will be available after patient follow-up is completed and information is available on the development and progression of age-related macular degeneration.

LOW VISION VS. BLIND

Ms. Northup: In my district there are many services for the blind including the Kentucky School for the Blind, as well as the Kentucky Printing House for the Blind. Constituents of these services have spoken to me about their concern that we focus too much through education programs and other government programs on persons with low vision, rather than the blind. For many of the blind, they start with low vision problems which lead to blindness. In your testimony you mentioned an education program aimed at addressing the needs of people with low vision. Is there a similar education program for the blind under your agency?

Dr. Kupfer: The NEI conducts and supports research aimed at preventing, reducing, and possibly even eliminating blindness and visual impairment resulting from a wide variety of diseases and disorders. Our health education programs, targeted at those at risk for certain eye diseases, focus on preventing vision loss and blindness through regular dilated eye examinations and timely treatment. Although the NEI does not have any plans at this time to develop an education program for the blind, many people with low vision are legally blind. Therefore, they are expected to benefit from the health education program for low vision that is currently under development. This new program will increase public awareness about the impact of low vision on daily living. Approximately 21 percent of those who have low vision and are aged 45 and older are unfamiliar with low vision clinical services. The low vision education program will play a key role in informing Americans about the use of optical and adaptive low vision devices and services.

Ms. Northup: Do you educate about the likelihood of this disease progressing to blindness?

Dr. Kupfer: Low vision is not a disease, but a consequence that may result from many different eye diseases and disorders. For the past five years, the NEI's National Eye Health Education Program (NEHEP) has developed many educational programs and activities for those at risk of low vision or blindness from glaucoma or diabetic eye disease. These programs alert those at risk for these blinding eye diseases to the benefits of regular dilated eye examinations. In addition, the NEI handles more than 15,000 public inquiries each year on a wide variety of topics. Often, these inquiries concern blinding eye diseases and disorders, and information is provided to help individuals learn more about their specific problems.

Ms. Northup: Do you work in conjunction with physicians in developing and pursuing this education program?

Dr. Kupfer: We work with physicians and other eye health professionals in the development, implementation, and evaluation of all NEI-sponsored eye health education programs.

RETINOPATHY OF PREMATURITY

Ms. Northup: The work to help premature babies is extremely interesting. While the research end is moving forward, I am wondering what evidence is there that the practical use of this treatment is moving forward. Specifically, at what point is a baby diagnosed with this condition and are you working with physicians on education about this disease and treatment?

Dr. Kupfer: In the wake of the widely-disseminated report of results from the NEI-supported CRYO-ROP Study, there has been rapid, worldwide acceptance of cryotherapy as an important part of the clinical management of retinopathy of prematurity (ROP). Because ROP can progress to blindness during the first three months of life and treatment is currently available to arrest it, a screening examination of the eyes of premature infants occurs during this span. The CRYO-ROP investigators have been active in educating physicians and nurses about ROP through several avenues including conducting continuing medical education courses; publishing treatment recommendations in professional journals, medical books and in the lay press; presenting results at scientific meetings; developing patient newsletters; and conducting press releases and television news broadcasts.

SMALL BUSINESS INNOVATION GRANTS

Ms. Northup: What level of funding have you designated to the innovation grants and the technology transfer grant?

Dr. Kupfer: In FY 1997, $7,084,000 has been designated for the Small Business Innovation Research grant program, and $425,000 has been designated for the Small Business Technology Transfer grant program.

Ms. Northup: Are these grants focusing only on low vision services and inventions, or can you describe some innovations which can be used by individuals who have no sight?

Dr. Kupfer: The NEI has used the SBIR grant mechanism to support the development of technologies and devices for the blind. Examples include electronic Braille production systems, full page Braille displays, refreshable Braille systems, electro-tactile display systems for computer graphics, and tactile graphic printers. These devices also include examples of a variety of navigation aids such as sonar-based wayfinding systems, spoken language systems applied to wayfinding functions, auditory-interactive maps, virtual reality based maps, devices for the production of tactile maps, ultrasonic spatial sensing aids, and GPS satellite-based navigation aids.

AGE-RELATED MACULAR DEGENERATION

Mr. Stokes: According to the Institute's budget submission, age-related macular degeneration is a leading cause of blindness in the United States, and is also a leading cause of low vision. Media coverage regarding age-related macular degeneration often focuses on "low vision" as a visual impairment that interferes with an individual's ability to perform daily activities, and which cannot be corrected by standard glasses or contact lenses. How extensive a problem is "age-related macular degeneration" in the United States, and what is the cost to the nation?

Dr. Kupfer: Age-related macular degeneration or AMD is a sight-threatening degeneration of the photoreceptor cells in the macula--the tiny part of the retina responsible for sharp central vision. Although we do not know the financial cost to the Nation for AMD, the human cost in terms of its effect on the quality of life of our older citizens, is enormous. An estimated 1.6 million of the 34 million Americans over age 65 have some degree of vision loss from AMD, and another 100,000 Americans have difficulty performing even routine visual tasks, such as driving, reading printed material, or recognizing faces. We are particularly concerned that AMD will be an even greater public health problem, as the size of the population over age 65 increases. Current estimates indicate that the prevalence of AMD will increase to 6.3 million by the year 2030.

Mr. Stokes: According to your opening statement, genes involved in AMD already have been identified in three less common types of macular degeneration. In addition, genes associated with several other forms of macular degeneration have been localized to specific chromosomes, and NEI scientists are trying to identify genes that could help regenerate damaged areas of the retina. Could you tell us a little more about this area of research and the benefits expected to be achieved. What other major basic and clinical research initiatives are underway at the Institute to study and unravel this disease?

Dr. Kupfer: The NEI has identified several areas of research to learn what causes AMD and how it can be treated more successfully. Through NEI's Age-Related Eye Disease Study, researchers at 11 clinical centers around the country are assessing the aging process, potential risk factors, and quality of life of 4,700 patients in order to pinpoint the earliest signs of AMD. Once such studies have helped us to determine how macular degeneration develops; we might be able to change its course; when we know for certain what risk factors contribute to development of the disease, we can caution patients to avoid them. This same study also includes clinical trials that will help determine the effects of certain vitamins and minerals in preventing or slowing the progress of AMD.

A number of projects are being conducted to evaluate genetic and/or environmental factors related to AMD and to examine the underlying hypothesis that genetic factors play a significant role in this complex chronic disease. Participating families in these studies include those with both a single case of documented AMD and those who have at least two living siblings (or a parent) with documented AMD. Genes involved in AMD already have been identified or localized to specific chromosome regions in several less common forms of macular degeneration. The identification of genes involved in macular degeneration will help researchers to determine the gene product and its role in the disease process.

NEI scientists also are trying to identify biological factors and associated genes which could help retinal cells to survive damage and, perhaps, to stimulate surviving retinal cells to divide, differentiate, and to repopulate areas of damaged retina. This strategy could help to prevent much of the visual loss from later stages of AMD. Researchers are exploring the effects that gene replacement therapy may have on the treatment of macular degeneration, and scientists have already successfully placed genes into the retina of laboratory animals. Replacing diseased retinal cells with healthy ones is another promising area of research, and scientists are working to apply retinal cell transplants to treat retinal degenerations.

The NEI also sponsored a workshop that led to shared research ideas and consideration of the future direction of AMD research. This workshop, held last June, brought together academicians, clinicians, and representatives from biotechnology companies, all of whom were knowledgeable in growth factor cell biology. The discussion centered around the potential use of neurotrophins, or biological survival factors, to delay clinical indications of retinal cell degeneration in AMD and other eye diseases.

Mr. Stokes: How much is included in the FY 1997 budget for these activities, and how does this compare with the FY 1998 proposed investment in AMD research?

Dr. Kupfer: In FY 1997, the NEI expects to spend approximately $75 million on macular degeneration. Of this amount, approximately $16 million will be directly related to AMD. At the proposed FY 1998 budget level, the NEI expects to devote approximately $77 million to macular degeneration, including approximately $16 million for age-related macular degeneration.

Mr. Stokes: What is the NEI doing for those individuals who have already lost vision because of age-related macular degeneration?

Dr. Kupfer: Individuals with AMD very often have "low vision," broadly defined as a visual impairment interfering with an individual's ability to perform activities of daily living that cannot be corrected by standard glasses or contact lenses. People with low vision often cannot perform daily routine activities, such as reading the newspaper, preparing meals, or recognizing faces of friends.

As the leading source of vision research funds in the United States, the NEI is committed to furthering progress in the area of low vision research. During 1996, the NEI supported 18 extramural research projects related to low vision. In addition, the NEI, through the National Eye Health Education Program, is developing an education program aimed at addressing the needs of people with low vision. This new program will increase public awareness about the impact of low vision on daily living. Approximately 21 percent of those who have low vision and are aged 45 and older, are unfamiliar with low vision clinical services. The low vision program will play a key role in informing Americans about the use of optical and adaptive low vision devices and services.

Also, the NEI's research program helps inventors with ideas on low vision aids develop those ideas for the marketplace. Inventors have few resources available that will allow them to develop products that help people suffering from low vision. NEI's Small Business Innovation Research Grants Program gives inventors the opportunity to see their ideas turned into reality. For example, through this program, telescopic systems were developed that help those with low vision perform common tasks, such as walking down the street or reading signs. Another idea, a system called "Outspoken," magnifies text on a computer screen, making it easier for people with low vision to read. This product was recognized by the Smithsonian Institution for its unique way of using technology for the common good. A sister program, called the Small Business Technology Transfer Grant, encourages inventors in universities and research centers to form partnerships with small businesses. Between both programs, NEI expects to fund approximately 50 projects this fiscal year.

Mr. Stokes: I understand that there is a link between smoking and age-related macular degeneration. Could you elaborate on this relationship?

Dr. Kupfer: Yes. According to two different studies funded by the NEI, this correlation was found to exist. In one study, it was found that women who were current or past smokers had a significantly greater risk of AMD, compared to women who had never smoked. In the other study, it was found that men who smoked one pack or more of cigarettes daily had a two- to three-fold increased risk of AMD, compared with those who had never smoked.

Mr. Stokes: Are there outreach activities underway in age-related macular degeneration? Explain.

Dr. Kupfer: Individuals with age-related macular degeneration have low vision. The NEI, through the National Eye Health Education Program (NEHEP) is developing an education program aimed at addressing the needs of people with low vision. This new program will increase public awareness about the impact of low vision on daily living for many Americans. Approximately 21 percent of those who have low vision, aged 45 and older, are unfamiliar with low vision clinical services. The low vision program will play a key role in informing Americans about the use of optical and adaptive low vision devices and services.

In August 1996, a meeting was held that brought together low vision researchers, health professionals, and consumers to provide recommendations to the NEI on the development of this new program. Building on a national survey on vision loss conducted by The Lighthouse, Inc., the NEI is conducting ten focus groups to learn more about the target audience's knowledge, attitudes, and practices related to vision loss. Groups are being conducted in Washington, DC, Milwaukee, and Los Angeles. In addition, two groups will be conducted with care givers of people with low vision. Following the focus groups, the NEI will meet with other public and private organizations to review the information and design a program that will complement existing programs and help these organizations expand their activities. The program is expected to be launched early in 1998.

EYE DISEASE IN AFRICAN AMERICANS

Mr. Stokes: What are the most serious eye diseases and disorders affecting the African Americans and other minorities? What is the extent of the problem in these populations compared to the general population?

Dr. Kupfer: Open-angle glaucoma, the most common form of glaucoma, is a leading cause of blindness in the United States and the number one cause of blindness in African Americans. Although open-angle glaucoma can affect anyone, it is most prevalent in African Americans over age 40 and anyone over age 60. In fact, five to six times as many African Americans have this disease, compared to the general population. A total of three million Americans have open-angle glaucoma. The NEHEP recommends that people at high risk have a dilated eye examination every two years.

The Hispanic and Native American populations have a high incidence of diabetes. About one in ten Hispanic adults living in the U.S. has diabetes, which means that nearly two million of these individuals are at risk of developing diabetic eye disease. The prevalence of diabetes is twice as high among Native Americans than the general population and reported to be approximately 70 percent in the Pima tribe.

NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr. Stokes: Concentrated use of computers, video games and other technologies appear to accelerate vision impairments. What is the Eye Institute doing to educate young people about the importance of taking care of their vision?

Dr. Kupfer: The NEI has developed a school curriculum program for grades four through eight. The program consists of three lesson plans, interactive classroom activities, and pre- and post-visit exercises. Topics include the anatomy and physiology of the eye and visual system, common eye diseases and disorders, and eye safety. The program is designed as a supplement to any science health curriculum and can be used by

classroom teachers or their guest speakers, such as vision researchers or eye care professionals. Within the last year, the curriculum has been distributed to more that 35,000 eye care professionals, scientists, and teachers.

UVEITIS

Mr. Stokes: According to your opening statement, uveitis causes about 10 percent of severe visual impairments in the United States and affects primarily children and young adults. You also mention that treatment of uveitis has usually involved the use of potent drugs that block the immune systems. What is the age group of those most seriously impacted by the disease?

Dr. Kupfer: Most patients with uveitis fall into the 25 to 45 year-old age group. In terms of sheer numbers, these patients are seriously impacted by the disease. However, it is important to note that uveitis also affects children from four to12 years old with childhood diseases such as juvenile rheumatoid arthritis which can cause blinding uveitis. Although the latter constitute fewer patients, the impact is also very serious because the disease has a significant impact on the children's visual function and overall function--for lifetime.

Mr. Stokes: What major basic and clinical research initiatives are underway to further advances in the treatment, early detection, and prevention of uveitis? Are we making much progress in each of these areas?

Dr. Kupfer: A large clinical research initiative is underway in the NEI intramural program to improve early diagnosis, treatment, and prevention of uveitis. Several clinical studies are currently in process, some of which focus on ways to improve the diagnosis of the disease. Early diagnosis and prompt therapy can prevent permanent loss of vision in these patients. One of the studies is developing improved diagnostic tests for sarcoidosis, a disease that causes uveitis. This disease appears to be more common in African Americans and may involve other organs such as the skin and lungs. Other studies are determining whether there is a genetic predisposition to certain forms of uveitis, and also which clinical parameters predict its related vision loss. These studies would allow physicians to identify patients most at risk and in need of early therapy to prevent ocular inflammation and vision loss. Cataracts are common in patients with uveitis, however cataract surgery is complicated by inflammation in these patients. Intraocular lens implants that may reduce these complications, are being evaluated. A number of studies seek to define the pathophysiology of uveitis so that new therapies can be developed. These studies have helped to improve the detection of lymphoma in the eye, which can cause a secondary uveitis. This has allowed early detection and treatment of this sight-threatening and life-threatening disorder.

Steroids remain the mainstay of therapy for uveitis, however, many patients are resistant or intolerant of steroid therapy. The NEI intramural program has developed a number of new therapies for uveitis. Cyclosporine, a drug for the treatment of transplant rejection,

was first used for the treatment of uveitis in the intramural program. Use of this drug alone or in combination with steroids has been effective in preventing vision loss in many patients with uveitis. The intramural program is now concentrating on developing new immunologic therapies for uveitis that will have greater efficacy with fewer side effects. An intramural study showed that oral tolerance, where antigens from the retina are fed to patients, can be used to effectively treat patients with uveitis. Importantly, the therapy had no discernible side effects. A trial is now being planned to test this approach for children with uveitis caused by juvenile rheumatoid arthritis. An antibody against the IL-2 receptor, a molecule found in activated immune cells, is also being tested as a new therapy for patients who have had problems with conventional therapy.

With regard to basic research, the following initiatives are among those being pursued: studies to determine the unique characteristics of the ocular immune response; studies on the relationship between the environment and the ocular immune system; development of new laboratory techniques for the elucidation of animal models of uveitis and the application of these techniques to the human situation whenever appropriate; and, investigations of ocular immune barriers to transplantation.

National Eye Institute intramural scientists are studying the cellular and molecular mechanisms involved in T cell-mediated autoimmunity affecting the retina in animal models of experimental autoimmune uveoretinitis. These researchers hope to gain a greater understanding of the mechanisms governing the normal development and maintenance, as well as pathological breakdown, of self-tolerance to retinal antigens. The goal of this line of research is to identify the immunologic factors predisposing to uveitic disease, learn about pathogenic mechanisms involved, characterize the immunoreactive cells and their mediators, and finally to use this knowledge for designing novel and rational approaches to immunotherapy. Another NEI-intramural project is focusing on learning about the role of ocular antigens ability to initiate pathogenic autoimmune processes in the eye. To date this research has found that small amounts of retinal antigens are expressed in mouse thymus and are responsible for the partial resistance of mice to autoimmune eye diseases by rendering these animals unresponsive to ocular antigens. This research has also shown that mice deficient of alpha-A-crystallin due to genetic manipulation resembled their wild-type controls in being tolerant to mouse alpha-A-crystallin. Although no alpha-A-crystallin was detected in their lens, the deficient mice contained alpha-A-crystallin mRNA in their thymus, thus providing a putative mechanism for tolerance in these animals.

Mr. Stokes: How much is included in the FY 1998 budget to address uveitis, and how does this compare with the current funding level?

Dr. Kupfer: The NEI FY 1998 budget proposes to spend approximately $18.4 million, to address uveitis. In FY 1997, the NEI expects to spend approximately $18.0 million.

VISION RESEARCH--A NATIONAL PLAN 1994-1998

Mr. Stokes: As you approach the final year of the 1994 to 1998 National Vision Research plan, what is the Institute's assessment of the goals and objectives as identified by the plan and that you were able to accomplish?

Dr. Kupfer: There is little question that evaluation or assessment of progress in achieving program goals and objectives is difficult to undertake. At the NEI, we have long believed that the best form of assessment of progress has been the review of the program by expert panels. As part of the NEI planning process, the panels are asked to identify the most important research accomplishments that have occurred within the program since the issuance of the last plan, in addition to consideration of the needs and opportunities. This is currently being done as part of the development of our next strategic plan. Additionally, we are asking for broader input on identification of the key areas of progress from the research community through the NEI home page on the world-wide web. The most significant areas of progress will be identified in the final plan.

Mr. Stokes: How long has the Institute been using this planning mechanism to help focus the direction of its research, research training, and outreach activities, and over the years what lessons have you learned from this process?

Dr. Kupfer: The Institute began work in 1974 on its first planning document, Vision Research Program Planning, which was published in 1975. The current plan is the sixth in this series of planning documents. One of the most important lessons we have learned is the value and importance of involving the research community in the process. The involvement of the vision research community has not only continued throughout the years, but it has increased substantially since the issuance of the first plan, rising from 25 panel members for the first plan to about 425 panel members, consultants, and reviewers for our latest effort.

Mr. Stokes: What is the status of the development of the Institute's next strategic plan?

Dr. Kupfer: We are currently in the early stages of the plan's development. Panels of experts have been formed and will be meeting over the next two months. We are hoping to complete the plan late in this calendar year.

DIABETIC RETINOPATHY

Mr. Stokes: An estimated 16 million Americans have diabetes and nearly half of them are not even aware that they have the disease. What is the extent of diabetic retinopathy in the United States, and what is the cost to the nation?

Dr. Kupfer: Nearly one-half of the 16 million Americans with diabetes have early signs of diabetic retinopathy. Approximately 24,000 Americans lose their sight each year, due to diabetic retinopathy. The costs associated with blindness due to diabetic retinopathy total $2.8 billion, in 1992 dollars.

Mr. Stokes: According to the budget justification, the most important causal factor in the development of diabetic retinopathy is increased blood sugar or hyperglycemia. What major basic and clinical research is underway with regard to diabetic retinopathy, and what is on the horizon?

Dr. Kupfer: The NEI is supporting a number of projects aimed at understanding how high levels of glucose damages retinal blood vessels and surrounding tissues. For example, investigators are examining the role of the natural barrier that exists between the retina and blood vasculature, called the blood-retina barrier, to determine how it is compromised in diabetes, resulting in leakage of blood into the eye. The way that hormones regulate retinal vascular circulation is also being studied. One specific hormone called endothelin is found in the retina and appears to play a role in regulating retinal circulation. An important discovery has been that endothelin is affected by insulin, so investigators are trying to determine the mechanism of this effect at the genetic and cellular level. Another avenue of study is the way vascular cells communicate information received from outside the cell into signals controlling normal function inside the cell. Glucose can cause an increase in the production of diacylglycerol, resulting in activation of the protein kinase C biochemical pathway that may be involved in vascular cell pathology. Investigators have recently discovered an inhibitor of this pathway that may prove useful in the treatment of diabetic vascular complications.

Growth factors are also being explored. They are small molecules that can have important consequences on the behavior of cells. One such factor is vascular endothelial growth factor or VEGF, which has been shown to increase in concentration under conditions of reduced oxygen as occurs in diabetic retinopathy when blood flow to the retina becomes compromised. The mechanism by which VEGF is related to blood vessel proliferation is a current area of intense investigation. On the horizon, a number of related areas appear promising. These include developing anti-angiogenic compounds that can reverse the effects of growth factors like VEGF. In addition, inhibitors of the enzyme aldose reductase may yet prove to be useful in the treatment of diabetic retinopathy and investigators are attempting to design more effective compounds with fewer side effects.

Mr. Stokes: How successful has the National Eye Health Education Program been in conducting outreach focusing on diabetic retinopathy?

Dr. Kupfer: The National Eye Institute (NEI) is extremely committed to educating people about diabetes and its complications through its National Eye Health Education Program (NEHEP). For example, for the past three years, the NEI has been collaborating with the American Diabetes Association (ADA) during National Diabetes

Month. The ADA and the NEI coordinated activities with ten other organizations in the NEHEP Partnership to encourage people with diabetes to have an annual dilated eye examination, thus enabling eye care professionals to detect and treat diabetic eye disease more effectively. This year, over 8,000 National Diabetes Month kits were distributed to community-based organizations to help them plan local activities. In support of these activities, more than 1.5 million NEI brochures on diabetic eye disease were distributed. In addition, a media campaign for television, radio, and newspapers was successful in reaching more than 60 million people with sight-saving information for people with diabetes. In addition to the ADA, The Links, Inc., and the Lions Clubs International have been conducting diabetes awareness programs through their chapters and clubs nationwide. Building on the national network established by the NEHEP, these organizations have been able to reach out more effectively in their local communities, thus contributing to our outreach program's success.

SBIR

Mr. Stokes: The NIH recently convened a Small Business Innovation Research grants conference. I noticed from your opening statement that the Eye Institute has found the SBIR funding mechanism useful in giving inventors with ideas on low vision aids the opportunity to develop those ideas for the marketplace. Through the program, telescopic systems were developed that help those with low vision perform common tasks, such as walking down the street or reading signs. Another idea, a system called "Outspoken," magnifies text on a computer screen, making it easier for people with low vision to read. The use of these technologies to improve the quality of life for those suffering from low vision is encouraging. In your statement, you also mention the Small Business Technology Transfer Grant Program. Would you elaborate on how these programs can be used in combination to effectively further the commercialization of technological advances?

Dr. Kupfer: The Small Business Innovation Research (SBIR) program is intended to support small business innovative research that results in commercial products or services that benefit the public. Innovation and probability of commercial success are both important factors in funding decisions. Allocation of a small business concern's funds or resources and those of an investor or partner organization is viewed as an important and meaningful commitment to a project's commercial success and as a mechanism for leveraging federal SBIR investment. The Small Business Technology Transfer Program is intended to (1) stimulate and foster scientific and technological innovation through cooperative research and development carried out between small business concerns and research institutions; (2) foster technology transfer between small business concerns and research institutions; (3) increase private sector commercialization of innovations derived from federal research and development; and, (4) foster and encourage participation of socially and economically disadvantaged small business concerns and women-owned small business concerns in technological innovation.

OUTREACH AND DISSEMINATION OF RESEARCH RESULTS

Mr. Stokes: As you stated in your opening statement, "Our investment in high quality clinical research has little real benefit unless the results and recommendations from such studies are widely and suitably incorporated into patient care." Dr. Kupfer, I strongly agree with your statement. Over the years, we have often discussed the activities of both your National Eye Health Education Program and the Institute's activities with regard to clinical alerts. What major activities are currently underway at your Institute to strengthen outreach, and to accelerate the dissemination of results stemming from clinical research?

Dr. Kupfer: At the National Eye Institute, information dissemination is viewed as the final step in the research continuum, where the results of research are shared with health professionals, patients, and the public. In fact, one might argue that research results are somewhat meaningless if they are not transmitted to those who can benefit from them. Our dissemination and outreach activities fall into several areas.

Of significant importance is the dissemination of the results of clinical trials and other NEI-supported research. The NEI currently conducts and supports 18 extramural and intramural clinical trials, and a wide variety of other extramural and intramural basic and clinical research activities. Many of these clinical trials have reported results within the past few years, and basic researchers also are reporting significant advances with tremendous public health importance. These results are disseminated in a variety of ways, from articles in the professional literature to a very extensive process that might involve clinical alerts, news releases, news conferences, and extensive media coverage. We have developed a list of guiding principles that are followed when research results are obtained, and a dissemination plan is developed for all target audiences needing the information.

To aid in the timely dissemination of research results, the NEI recently has formed two Public Affairs Network groups, one for eye institutes and departments of ophthalmology, and one for schools and colleges of optometry. The purpose of these networks is to develop an ongoing program to inform and educate the public about vision research. Members include public information and education professionals at NEI grantee institutions who share information, pool resources, and collaborate on programs. Using Listserve, a capability within electronic mail, members of the groups are linked, enabling rapid dissemination of research results and other information.

For the past few years, the NEI has been involved in public outreach activities surrounding the Celebration of Vision Research, to commemorate the NEI's 25th anniversary. These activities have been so successful that the Institute has decided to extend the Celebration to the end of 1998, the NEI's 30th anniversary. The success of this project has been attributed to the NEI's development of **VISION**, a 2,000 square-foot traveling science museum exhibit, which is being offered to NEI-grantee institutions to host in their regions. These institutions have gone on to form unprecedented

coalitions to sponsor the exhibition. To date, more than 2.5 million people have visited the exhibit in science museums and other venues in 13 cities, and have learned how their tax dollars have been invested in vision research.

The second main activity of the Celebration is the VISION school program. This is a curriculum for grades four through eight, designed for use by classroom teachers or their guest speakers, such as vision researchers or eye care professionals, to teach children about the visual system and eye diseases, and to interest students in visual sciences. More than 25,000 copies of the program have already been distributed to teachers and health professionals.

Finally, the NEI's National Eye Health Education Program has conducted and facilitated many recent public outreach activities for a variety of audiences. For example, to reinforce media campaigns and sustain the blindness prevention message to at-risk populations, the NEHEP has developed brochures on glaucoma and diabetic eye disease. These publications are written in an easy-to-read format, and provide disease information and the steps an individual can take to protect their vision. The Program is also strengthening its relationship with those organizations that reach the target audiences at risk for glaucoma, including African Americans over age 40, and everyone over age 60. The *Ojo Con Su Vision* program has been extremely effective in educating Hispanics with diabetes about the importance of a dilated eye exam to prevent vision loss that often results from their condition. For all people with diabetes, the NEI has collaborated for the past several years with the American Diabetes Association and other organizations to sponsor National Diabetes Month, with a focus on diabetic eye disease. This year, over 8,000 National Diabetes Month kits were distributed to community-based organizations to help them plan local activities. In the future, a new program on low vision will be added to the NEHEP, which will play a key role in informing Americans about the impact of low vision on daily living and how they can make the most of remaining vision through optical and adaptive low vision devices and services.

Mr. Stokes: How much is included in the FY 1998 budget request for this effort, and how does it compare with the funding level for FY 1996 and FY 1997?

Dr. Kupfer: The FY 1998 budget includes approximately $1,095,000 for outreach and dissemination of research results. In FY 1996, the NEI spent $995,000 and expects to spend $1,072,000 in FY 1997.

CLEVELAND BLACK NURSES

Mr. Stokes: I understand that the Cleveland Council of Black Nurses has entered into a partnership agreement with the Eye Institute to develop a pilot education program for health care professionals and the public. As you may know, I am quite proud of that organization. Can you tell me a little more about the partnership project?

Dr. Kupfer: The Cleveland Council of Black Nurses (CCBN) plans to design a program that provides information on prevention, early detection, and treatment of eye diseases that affect the African American community. The goals of the program are (1) to provide a learning environment for professional/community understanding of eye diseases that contribute to loss of vision in minority communities and (2) to provide specific information to guide health care givers in the prevention, early detection, and treatment of eye diseases for which minorities are at risk.

Participants will be involved in didactic presentations by an ophthalmologist and internist who will cover the pathophysiology of the eye. The lectures will be followed by small group discussions on prevention, assessment and management and how persons from various specialty areas can contribute to community and professional education regarding vision. Continuing education credits will be given to participants.

A health fair will be held for the community which will provide a variety of health screenings and education. Plans are to have six to ten agencies participate in the screenings.

The CCBN has entered into a partnership agreement with the National Eye Institute to develop the curricula and materials for an eye health educational program for health care professionals and the public. The pilot program will be presented in June 1997. The program will be held at the Cleveland Health Museum, which is located in the heart of the African American community, and contains many exhibits supportive of the goals and objectives of NIH, NEI, and CCBN. The NEI is providing technical assistance and funding in support of this pilot project.

In August 1997, at the annual meeting of the National Black Nurses Association, the CCBN will present the results of the pilot to other NBNA chapters and encourage their participation in similar eye health education activities.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists' cloning of adult sheep. These articles expressed excitement with regard to opportunities for advances in medical treatments, and concern with regard to misuse of the technology and the possibility of human cloning. This is another area where we must now be certain to assess and address the ethical legal, and social issues of research on the front end. As a leading researcher and as the Director of the National Eye Institute, what is your professional opinion of this technology and what are your most serious concerns?

Dr. Kupfer: I think this technology could have important uses medically, but it also raises a number of ethical concerns which need to be addressed in a forthright and public manner. President Clinton has asked the National Bioethics Advisory

Commission to review the issues and to prepare a report on the matter. I think this was a very good decision on his part.

Mr. Stokes: With regard to eye diseases and disorders, what are the most significant benefits that the cloning technology would yield?

Dr. Kupfer: I can envision some new approaches to eye diseases that would be made possible by this technology. However, I think we need to have much more public debate and a resolution on the ethical issues involved in advance of moving any of these ideas to the laboratory.

VISUAL FUNCTION QUESTIONNAIRE

Ms. DeLauro: The NEI is funding the development of a survey to assess "visual functioning and its impact on the health-related quality of life." How will the results of this survey affect basic biomedical research at NEI?

Dr. Kupfer: The NEI has and is funding the development of measures of vision function and quality of life in order to assess the impact of vision loss and blindness on patients and the U.S. population in general. Much of the research that leads to the development of new devices for vision and treatments for vision problems and blindness is supported by NEI, NIH research. Before the drugs, devices and treatments that are developed as a result of this research are made available to the public, they need to be carefully evaluated for efficacy and safety, usually in clinical trials. The development of new efficacy end points, such as patient self-reporting of visual function, can advance comprehensive approaches for assessing these new products. For example, it is important to demonstrate that new refractive surgical techniques can do more than just correct visual acuity, since glasses and contact lenses can also do that. Somehow, the increments in vision function and related quality of life gained from these new technologies must be objectively assessed. That is the purpose of these newly developed instruments.

EYE DISEASES UNIQUE TO WOMEN

Ms. DeLauro: Your budget mentions that your "New Approaches to Pathogenesis" initiatives is addressing AQP5, which may play a role in dry eye, a women's health problem. What other eye problems that are unique to women are being addressed by your institute?

Dr. Kupfer: Most of the major causes of blindness (glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However in the U.S., women live longer than men do on average and therefore, more women than men are affected by these age-related eye diseases. Additionally, there appears to be a slightly greater risk of cataract and macular degeneration for women than for men.

Although not unique to women, several eye conditions affect women significantly more frequently than men. These conditions include: optic neuritis, a demyelinating disease of the optic nerve that may be a precursor of multiple sclerosis; corneal endothelial dystrophy, a slowly progressive disease that occurs when endothelial cells deteriorate as a result of cell loss, age, or trauma; and keratoconus, a visually disabling thinning disorder of the central cornea that results in irregular astigmatism, progressive cornealdistortion, and corneal scarring. All of these conditions are being addressed within our research program.

Ms. DeLauro: What kinds of strides has NEI made to include women in clinical trials? How is the inclusion of women in clinical trials addressed in your FY 98 budget request?

Dr. Kupfer: The NEI has not experienced problems in recruiting women into its conducted or supported clinical trials. As of February 1997, the overall percentage of women involved in the 17 ongoing NEI Phase III clinical trials was 53 percent. These recruitment efforts will continue in FY 1998. Of special interest, the FY 1998 budget request would allow for the collection of long-term follow-up data in the Longitudinal Optic Neuritis Study. Optic neuritis is a disease which affects significantly more women than men. In addition, the NEI has recently funded a pilot study to plan for a series of full-scale projects in FY 1998 which will address the prevalence, clinical course, and risk factors for dry eye, another debilitating eye condition which affects women disproportionately. The Collaborative Longitudinal Evaluation of Keratoconus Study, another study that focuses on an eye disease that disproportionately affects women, has been initiated and will be in an active recruiting phase in FY 1998.

PEDIATRIC RESEARCH

Ms. DeLauro: I am happy to see that NEI has identified several important pediatric research areas, and I am pleased with the work you have been doing on determining the function of the retinoblastoma gene product at both the cellular and the molecular level in the etiology of retinoblastoma. However, given that I co-sponsored the Clinical Research Enhancement Act, which advocates increased funding for clinical research, can you explain how this research will be used by American doctors to treat our youngest patients?

Dr. Kupfer: Retinoblastoma is a rare eye cancer that results from the loss of function of a tumor suppressor gene whose normal role is to restrict cell proliferation. For retinoblastoma to develop, an individual must lose the function of both maternal and paternal copies of the retinoblastoma gene. Knowledge of the retinoblastoma gene sequence and gene product should allow early identification of individuals who are genetically predisposed to retinoblastoma. However, technology for accurate and cost-effective molecular diagnosis of the genetic predisposition to retinoblastoma needs to be improved. This is an active area of investigation. Current treatments have yielded survival rates better than 90 percent, but survivors must cope with long-term visual and systemic morbidity. Treatment of children who have a genetic predisposition to retinoblastoma with external beam radiotherapy increases both the risk of secondary cancers as well as likelihood of cosmetic deformity and cataracts. One area that seems promising is the use of chemotherapy as a primary treatment. Several medical centers in both the U.S. and Canada have recently reported that chemotherapy in combination with other treatment modalities such as radiation, laser, thermotherapy, and cryotherapy may be effective in treating retinoblastoma while reducing side effects. More studies need to be done to confirm these initial clinical reports and to develop new approaches for treating this disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

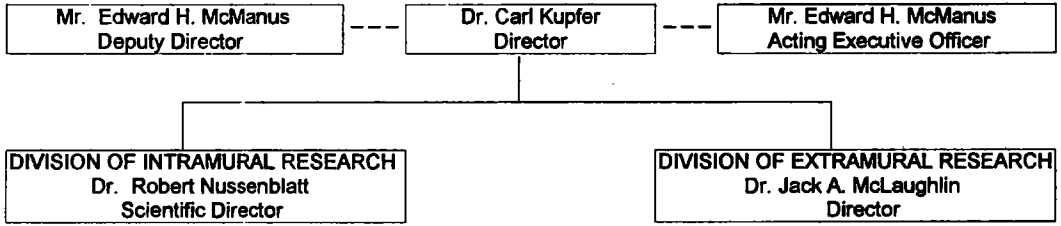
National Eye Institute

FY 1998 Budget	Page No.
Organization Chart	2
Appropriation Language	3
Amounts Available for Obligation	4
Justification Narrative	5
Budget Mechanism Table	18
Budget Authority by Activity	19
Summary of Changes	20
Budget Authority by Object	22
Administrative Costs	23
Significant Items in House, Senate, and Conference Appropriations Committee Reports	24
Authorizing Legislation	25
Appropriation History	26
Detail of Full-time Equivalent Employment (FTE)	27
Detail of Positions	28

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Eye Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to eye diseases and visual disorders, [$332,735,000] *$330,955,000*.

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1997, P.L. 104-208.)

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$314,185,000	$332,735,000	$330,955,000
Rescission in accordance with P.L. 104-134	(202,000)	0	0
Reduction in accordance with P.L. 104-208		(138,000)	
Subtotal, Adjusted Appropriation	313,983,000	332,597,000	330,955,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority	(824,000)	0	0
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	(9,125,000)	(9,450,000)	0
Subtotal, adjusted budget authorit	304,034,000	323,147,000	330,955,000
Unobligated balance, lapsing	(101,000)	0	0
Total obligations	303,933,000	323,147,000	330,955,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1996 - $10,634,000; FY 1997 - $12,000,000; FY 1998 - $12,000,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research:
FY 1998 - $9,476,000

Note: Excludes $6,000 in FY 1996 for royalties.

Justification

National Eye Institute

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be proposed.

Budget Authority:

FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
233	$304,034,000	233	$323,147,000	233	$330,955,000	0	+ $7,808,000

This document provides justification for the FY 1998 Non-AIDS activities of the National Eye Institute. Justification of NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

Out of concern for the thousands of Americans who were blinded each year by eye diseases and disorders of vision, Congress established the National Eye Institute (NEI) in 1968, giving it broad responsibility to conduct and support research, training, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight and the special health problems of individuals who are visually impaired or blind. Subsequently, Congress added health education responsibilities to the mission of the NEI and appropriated funds to allow the Institute to increase its commitment to the prevention of blindness through public and professional education programs and the encouragement of regular eye examinations.

Diseases and disorders of the eye and visual system affect men and women, young and old, and cost our Nation an estimated $22.3 billion in direct costs and $16.1 billion in indirect costs each year. These statistics are according to the analyses of Dr. The-Wei Hu, published in "Economic Costs of Visual Disorders and Disabilities," and subsequently updated with economic indicators. Diseases and disorders of the eye have pronounced effects on quality of life, as indicated by the numerous surveys that have repeatedly demonstrated that Americans fear loss of vision more than any other disability.

Story of Discovery

The light-sensitive photoreceptor cells of the retina, the rods and cones, are responsible for the capture of light and the initiation of the electrical signals utilized by the brain in processing visual

information. Building upon the discoveries made through several decades of intense basic research, scientists have defined this process and have established in great detail all of the key molecular components and events that generate these electrical signals. Armed with this tremendous wealth of information, researchers began to focus their efforts on determining the genetic regulation of the photoreceptor proteins involved in the signaling process. Their intuition was that this line of research would lead ultimately to a better understanding of why photoreceptors are so fragile and easily damaged by sight-threatening diseases, such as retinitis pigmentosa and age-related macular degeneration, toxic agents, overexposure to light, and dietary deficiencies.

The "payoff" from this investment in basic research on photoreceptor signaling proteins has already begun. Scientists have made the unexpected discovery that at least four different genes for proteins involved in photoreceptor signaling are mutated in various forms of retinitis pigmentosa. In laboratory mice and fruit flies that carry some of these gene defects, gene therapy was successful in delaying the onset of retinal degeneration. The next objective in this continuing story of discovery is to determine the precise mechanisms by which these gene mutations bring about the death of retinal photoreceptors. This information has already begun to generate a number of potential therapeutic approaches for treating retinitis pigmentosa and related diseases, and the future looks very promising.

Science Advances that Highlight the Benefits and Impact of Research

Retinal Diseases

The retina is the delicate, light-sensitive neural tissue at the back of the eye. Highly-specialized and metabolically active photoreceptor cells in the retina respond to light by emitting chemical and electrical signals. These signals are received by other retinal cells which process the signals and transmit visual information to the brain via the optic nerve. Diseases and disorders of the retina and the choroid, the underlying layer of blood vessels that nourish the retina, are the leading causes of blindness in the U.S. These sight-threatening conditions include age-related macular degeneration, diabetic retinopathy, retinitis pigmentosa, retinal detachment, and uveitis (ocular inflammation).

Retinitis Pigmentosa. Retinitis Pigmentosa (RP) is the name given to a heterogeneous group of inherited eye diseases in which the rod and cone photoreceptors in the retina degenerate, causing progressive visual loss. Our understanding of RP has progressed rapidly with the discovery of many genetic mutations in key photoreceptor genes in several forms of RP. While the search for other mutations continues, NEI-supported investigators have made progress towards the next objective, that of understanding the precise mechanisms by which these gene mutations bring about the death of photoreceptors.

Most cases of familial RP are inherited in an autosomal recessive pattern, i.e., both copies of a specific photoreceptor gene must be defective. Another form of the disease that is much less frequent is linked to the X chromosome. The X-linked form, XLRP, is the most severe form of RP and accounts for 10-25 percent of the RP affected families. Most affected individuals with

XLRP show early onset of visual symptoms with night blindness before the age of 20 and complete blindness at middle age. The isolation of the XLRP diseased genes has been difficult. Scientists have identified four regions on the human X chromosome where the diseased genes are located. Recently, NEI-supported scientists refined the location of one of the genes in an American family with XLRP. This information has led to defining the precise location and identification of the gene for this most common form of XLRP, which accounts for more than 70 percent of the XLRP.

An unusual inheritance pattern of RP, known as digenic retinitis pigmentosa, exists in which mutations in two different photoreceptor genes are necessary to produce the disease. This is a novel finding since in all other RP families studied, only one defective gene is thought to be involved. The genes that are defective in this digenic form of the disease, normally code for proteins that are thought to be important in forming and maintaining the proper structure of specific photoreceptor cell membranes.

Structural Biology of Key Retinal Proteins. The visual process through which the photoreceptor cells of the retina--the rods and cones--capture light and initiate electrical signals to the brain is known as visual phototransduction cascade. Biochemical and physiologic explorations have established the molecular description and key components of the pathway. Recent studies have determined the molecular events and key protein components of the pathway. Current research has turned to defining the detailed molecular structure of these proteins.

Scientists have now obtained three dimensional structural information on two key phototransduction cascade proteins. Knowledge of these detailed protein structures can now be combined with information from molecular biological and other studies to begin to shed light on the basic mechanisms involved in the movement of visual signals to the brain. Understanding the visual cascade at this detailed level is essential for the design of inhibitors or activators of the cascade, targeted for pharmacological intervention in the diseased retina, such as retinitis pigmentosa and age-related macular degeneration, leading causes of blindness.

Diabetic Retinopathy. The most important causal factor in the development of diabetic retinopathy is increased blood sugar or hyperglycemia. An important question in diabetes research is how hyperglycemia causes its deleterious effects. Recent investigations have focused on protein kinase C (PKC), a family of enzymes that regulate several important functions in the vascular system. PKC activity is increased in the retina and in other tissues of diabetic animals. One particular form of PKC is preferentially increased. An orally-administered inhibitor of this form of PKC has been developed and is effective in improving retinal blood circulation and in improving several other vascular abnormalities in diabetic rats.

Oral Administration of Retinal Antigens. NEI investigators recently developed a new treatment for uveitis, an ocular inflammatory process responsible for approximately 10percent of all the cases of legal blindness in the U.S. This treatment alters the immune response to antigen that stimulates the initial response. In a recently completed clinical trial, patients with sight-threatening uveitis who required long-term steroid therapy were fed retinal S-antigen, a protein extracted from the retina, while being weaned from their immunosuppressive medications. This initial trial demonstrated the safety of this therapy and the potential of this therapeutic approach. A new trial of recombinant S-antigen will attempt to confirm the use of oral tolerance as an alternative to steroids in managing autoimmune ocular disease.

Age-Related Macular Degeneration. Macular degeneration is the generic name given to a number of eye diseases in which the central portion of the retina is destroyed. Age-related macular degeneration (AMD) is the most common cause of severe visual impairment in older persons in the U.S. Approximately 1.7 million Americans have decreased vision from AMD, and 100,000 are blind from the disease. The prevalence of decreased vision from AMD is expected to rise to 6.3 million by the year 2030, when an even greater percentage of our population will enter their retirement years.

The Age-Related Eye Diseases Study (AREDS) is currently underway and is designed to collect natural history data of 4,600 patients of ages 55 to 80 years with the early signs of AMD in both eyes or with advanced AMD in one eye. Through its 11 clinical centers (including one at the NEI Clinical Center), the AREDS will evaluate the rates of development and progression of AMD, the rates of visual loss due to retinal lesions of AMD, and the risk factors associated with the development and progression of AMD over a 10-year study period. In addition, a clinical trial is being conducted to determine whether antioxidants (vitamin C, E, and beta-carotene) and zinc can prevent the development or retard the progression of AMD.

Cigarette smoking has been shown to increase the risk of development of AMD. Two large prospective studies, The Nurses Health Study, conducted among 31,843 registered female nurses followed for 12 years, and the Physicians' Health Study, conducted among 21,157 male physicians followed for seven years, both support previous reports of an association between smoking and AMD. The adjusted risk of developing AMD was increased approximately 2.5 times among current smokers, smoking a pack of cigarettes or more per day, as compared to nonsmokers. Past smokers, smoking over a pack of cigarettes per day, compared to those who never smoked also had approximately a 2 fold increased risk of developing AMD. The risk of developing AMD increased as the number of pack-years smoked increased. Cigarette smoking is an avoidable risk for AMD, which is a major cause of visual disability and blindness in the U.S. elderly and a disease for which no effective treatment exists.

Neurotrophic Survival Factor. A protein (PEDF) isolated from cells that lie behind the retina has been shown to have widespread biological activity that: 1) encourages neuronal differentiation; 2) encourages neuron survival; and 3) inhibits the growth of glial cells (neuron-supporting cells). Research is underway to explore the therapeutic potential of this protein in the treatment of stroke and other traumatic injuries to the brain that cause neural cells to die. Further, PEDF may be found useful as a treatment for Parkinson's disease, where it is necessary to keep neurons alive

and maintain their special function. In addition, most forms of cancer that strike the central nervous system (CNS) involve the neuron-support cells. Because of its inhibitory effect, PEDF may be used to inhibit the cells that support the spread or reoccurrence of cancers affecting the CNS. PEDF may also aid survival and prevent the rejection of transplanted retinal cells, thus offering the prospect of restoring vision lost by degenerative disease or injury.

Corneal Diseases

Diseases and injury to the cornea are the leading cause of visits to clinicians for eye care in the U.S. and rank among the most painful of eye conditions. NEI-supported research on corneal diseases includes studies of ocular infections and inflammation, problems with tears and the ocular surface, refractive errors, corneal transplantation, and corneal wound healing.

Dry Eye. Tears are necessary to maintain the health and comfort of the eye. A lack of sufficient tear fluid is a very common and frequently debilitating condition. Dry eye can result from insufficient secretion of fluid by the lacrimal glands, or from defects in the surface of the eye, mucin or mucous production, or the lipid or fatty components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders, e.g., in Sjögren's syndrome, but also occurs in association with aging, nerve dysfunction, radiation therapy, and with anti-depressant and anti-psychotic drug therapy.

Immune-mediated lacrimal insufficiencies affect roughly two million Americans, particularly post-menopausal women. NEI-supported researchers are investigating the hypothesis that lacrimal insufficiency is triggered by loss of hormonal support for the lacrimal gland's secretory capacity. Much of the dry eye disease that afflicts women after menopause, during oral contraceptive use, pregnancy, lactation, and the late luteal phase of the menstrual cycle appears to be attributable to lacrimal gland atrophy following decreases in available androgen levels. A clinical trial of low-dose androgen supplementation of hormone replacement therapy for post-menopausal women is currently being designed.

The NEI has recently funded a pilot study to develop population-based data on the prevalence of various forms of dry eye. This effort will also include case-control and longitudinal studies to develop risk factor, quality of life, clinical course, and prognosis data. This badly needed information will aid in the development of a series of major research initiatives and lead to new strategies for managing dry eye.

Ocular Herpes Simplex Virus. Herpes simplex virus (HSV) is a ubiquitous pathogen that causes skin lesions upon primary infection. The virus frequently establishes a latent infection in nearby sensory nerve cells, and can later be reactivated to cause recurrent disease in the skin and/or eyes. Ocular herpetic infections are painful, difficult to treat, and potentially blinding. Ocular inoculation with HSV results in both productive and latent pathways of viral gene expression in the sensory neurons. Recent NEI-sponsored research has focused on the role of host cell factors, as well as the host immune system and cytokines on viral latency/reactivation.

Tumor Necrosis Factor (TNF), a potent pro-inflammatory and mitogenic signaling molecule, appears to exert an important inhibitory effect on HSV replication. The many conflicting observations in the literature appear to have been resolved by the discovery that TNF's effects on HSV replication are site- and tissue-dependent, determined by the underlying cell-specific expression of TNF receptor subtypes. This information may be important in the development of therapeutic agents that will inhibit replication of the virus.

Molecular Control of Corneal Transparency. The corneal endothelium is a single layer of cells that lines the inner surface of the cornea. When functioning properly, the corneal endothelium regulates corneal hydration and transparency. If the corneal endothelium is damaged by disease or mechanical injury, fluid and ion transport is disrupted. This leads to swelling of the cornea, disorganization of the collagen matrix within the cornea, and loss of transparency.

A major recent advance in the study of fluid transport in the cornea has come from the discovery of the aquaporin family of water channel proteins (AQP). Currently, scientists are working to identify, clone and sequence, and localize individual transporters and to determine their function. One of these proteins, AQP 1, is expressed in the cornea and may contribute to corneal transparency, while another, AQP 5, has been identified in the lacrimal gland and is implicated in secretion of the aqueous component of tears. Knowledge of the basic molecular mechanisms and biophysical properties of corneal fluid and ion transport is fundamental for understanding how corneal transparency is maintained.

Lens and Cataract

Cataract is an opacity of the lens of the eye that interferes with vision. Cataract is a major public health problem. More than 1.5 million cataract surgical procedures are performed each year at a cost of more than $5 billion. Reimbursements for this surgery account for approximately 12 percent of the entire Medicare Part B budget. The enormous economic burden of cataract will worsen significantly in coming decades as the American population ages. The NEI supports and conducts a number of research activities designed to determine the causes and mechanisms of cataract formation, to search for ways to slow or prevent the progression of cataract, and to develop and evaluate new diagnostic and therapeutic techniques in cataract management.

Cell Cycle Controls in the Lens. Many individuals who undergo cataract surgery develop secondary cataracts, a complication that increases the cost of cataract treatment because a second surgical procedure is required. Research has shown that secondary cataract formation is the result of a normal response of the residual lens epithelial cells that often remain after surgery. In the normal adult lens, cell division and differentiation are precisely regulated as to limit epithelial cell division. However after cataract surgery, the residual cells appear to be relieved of these controls and begin dividing in an attempt to form a new lens. Current research is directed towards understanding the control of cell division in the lens with the goal of using the control points as targets for new drug therapies in order to inhibit cell division, and thus, prevent secondary cataract.

Over the last few years, increasing evidence has pointed to the retinoblastoma gene (Rb) as the gatekeeper that restricts the lens epithelial cells from entering into the cell cycle and hence, begin dividing. As with other systems, the regulation of Rb in the lens involves protein kinases and accessory regulatory proteins. The key players in the inactivation of Rb have been identified. Activation of Rb requires yet another set of proteins. New technologies are being applied to the study of how these proteins coordinately control inactivation and activation of the Rb protein. promising for these studies.

Lens Development. Late in the last century, it was observed that the lens formed as a result of the interaction between generic embryonic tissue, ectoderm, and the developing retina. This led to a series of classical experiments that suggested that lens formation was a simple process involving inductive signals sent from the presumptive retina, the optic vesicle, to the ectoderm. A number of experiments supported the idea that these signals were sufficient to confer lens competency on the ectodermal tissue. With the discovery that the genetic disease aniridia (a disease in which the iris or colored part of the eye is almost entirely missing) is the result of mutations in a key regulatory gene, *Pax-6*, lens biologists have taken a fresh look at early developmental events using molecular techniques and markers. Recent studies now suggest that ectoderm acquires lens competency before the formation of the optic vesicle. At the time of contact between the optic vesicle and ectoderm, regions of the ectoderm have already been committed to forming lens. Thus, rather than a simple induction of lens by primordial retinal tissue, these findings suggest that lens formation is a complex process requiring a number of tissue interactions and the hierarchical expression of a number of genes.

Glaucoma

Glaucoma is a group of eye disorders which share a distinct type of optic nerve damage which can lead to blindness Elevated intraocular pressure is frequently, but not always, associated with glaucoma. Glaucoma is a major public health problem and the number one cause of blindness in African Americans. Approximately 3 million Americans have glaucoma, and as many as 120,000 are now blind from this disease; at least half of all those who have glaucoma are unaware of their condition. Blindness from glaucoma is estimated to cost the U.S. in excess of $1.5 billion annually in Social Security benefits, lost tax revenues, and health care expenditures. The NEI is supporting a number of studies directed toward understanding the mechanisms of the disease through basic research, identifying risk factors, and preventing blindness.

Advanced Diagnostic Instruments for Glaucoma. A number of new instruments are being developed to measure changes in optic nerve structure and function in glaucoma. Glaucoma is characterized by a distinct type of damage to the optic nerve fibers as they travel from the retina of the eye through the optic nerve head to make their connections in the brain. Automated perimetry, which is routinely used to diagnose glaucoma, assesses the visual field loss that results from this damage. A modification has been made in the instrument used to measure the visual field that vastly improves the predictive power of this instrument. The modification called short-wavelength perimetry or SWAP capitalizes on reduced perception of color in glaucoma patients by measuring an individual's ability to detect blue light flashed on a yellow background. The test is proving valuable in the examination of individuals with ocular hypertension, who have high

intraocular pressure but no signs of optic nerve damage. Early indications are that SWAP may be superior to the standard perimetric tests now in use. SWAP detects vision loss 3-5 years earlier and is a better indicator of who is at risk for glaucoma. The instrument's predictive value is being assessed as part of the NEI's ongoing multi-center clinical trial, the Ocular Hypertension Treatment Study.

New Drugs for Treating Glaucoma. Elevated intraocular pressure is believed to be an important factor in the majority of cases of glaucoma. Elevated intraocular pressure results from an imbalance in the inflow and outflow of aqueous humor, the fluid that circulates in the front part of the eye. NEI-sponsored basic research has provided a better understanding of the basic pharmacology and physiology of aqueous humor dynamics. This basic research has led to the direct development of two important new drugs, Trusopt and Latanoprost, for treating glaucoma by lowering intraocular pressure. Both drugs have received FDA approval within the last year. Trusopt, a topical sulfonamide carbonic anhydrase inhibitor, acts by inhibiting carbonic acid synthesis, and thus, aqueous humor secretion into the front chamber of the eye. Latanoprost, a prostaglandin analog, acts by increasing aqueous humor outflow from the eye via a secondary pathway.

Strabismus, Amblyopia, and Visual Processing

Developmental disorders such as strabismus, misalignment of the eyes, and amblyopia, commonly known as "lazy eye", affect 2-4 percent of the U.S. population. The correction of strabismus is one of the most frequently performed of all surgical procedures. In addition to research relevant to strabismus and amblyopia, the NEI supports investigations of the age-related inability of the lens to focus on nearby objects, irregular eye movements, and refractive errors. Three million Americans now have chronic visual conditions that are not correctable by eye glasses or contact lenses. Therefore, the NEI also supports research on improving the quality of life of persons with visual impairments by helping them maximize the use of remaining vision and by devising aids to assist those without useful vision.

Regeneration in the Central Nervous System. Nerve cells in the peripheral nervous system (PNS) survive and regenerate their axons after being severed, but most central nervous system (CNS) nerve cells do not. For years researchers have been trying to determine the basis for this difference, so that damage to either system could be repaired. Recent work on the development of the visual system indicates that the signals that promote the survival and growth of CNS and PNS neurons may differ significantly. Although PNS neurons may require only a single chemical factor to be more responsive to growth factors in the cellular environment, CNS neurons require a combination of factors and external signals. Studies have demonstrated that specialized nerve cells in the retina that are similar to brain cells do not survive in a serum-free culture medium. However, these cells do survive in culture when the medium contains the required combination of factors and signals. Related experiments in animals show that the survival of these specialized retinal cells after damage is significantly increased by injection of these factors into the eye. These findings demonstrate that these retinal nerve cells have similar survival requirements in the living organism and in the test tube, suggesting CNS neurons can be regenerated by activating the appropriate signaling pathways.

Navigating Neurons in the Visual System. Research on the visual system has provided information on how we maintain our sense of direction, as we move through our environment. When we move forward, what we see appears to expand, and the center point of this expansion informs us of the direction, or heading of our motion. However, our eyes also move to track various objects as we move about, and the center point of expansion does not stay fixed upon the same location of the retina of the eye. Somehow the brain is able to compensate for these eye movements, allowing us to keep a clear sense of heading. Psychophysical studies on humans have led a team of vision researchers to look for nerve cells in the brains of monkeys that respond both to expanding images made on the retina by movement through space (optic flow), and to non-vision cues generated by smooth pursuit eye movements. Nerve cells coding both these inputs have been found in a part of the visual brain called the medial superior temporal (MST) area in the parietal cortex of the monkey. Many nerve cells in the dorsal region of MST respond selectively when the animal observes an expanding visual stimulus in a particular part of the visual field, and only when this stimulus shifts, as it would if disrupted by pursuit eye movements. Similar observations have been made in psychophysical studies on humans. These experiments show how the brain accounts for the effects of eye movements as we navigate through our environment, and provides insight on how the brain carries out other complex functions not only in the visual but other systems as well.

Rhythm and Recognition in the Visual System. The visual identification of objects seems so automatic and effortless that we take this highly complex process for granted. Most visual scenes are a rich collection of features varying in shape, color, brightness, texture, etc. To identify an object in a scene, the features of that object must be segregated from those of other objects. We know that in the initial stages of vision these features are transformed into neural signals that are transmitted from the retina to the other parts of the brain, and are then widely disseminated to as many as 30 areas. No one area signals the identity of an object. Rather, it appears that objects are represented through the coordinated signaling of many neurons covering wide areas of the visual centers of the brain. How then is the information relevant to the recognition of an object brought together to produce a unified perception? One theory proposes that this "binding" occurs when neurons in different parts of the brain, responding to the same object, synchronize their firing patterns. Recent work in the visual system of animals reveals this very pattern of synchronization in response to visual stimuli. A newly discovered class of cortical neurons, called chattering cells, appear to act as pacemakers in controlling this synchrony. Other sensory, motor, and association areas also exhibit synchronous activity. By studying the cellular mechanisms and the functional significance of synchronization in the visual cortex, we may gain general insight into the integrative functions of the brain and be able to determine whether this synchronization is involved in perception.

Goals to be Accomplished and Priority Setting Process

For more than 20 years the NEI, in collaboration with the National Advisory Eye Council (NAEC) and the research community, has used its long range planning process to establish goals and objectives, to identify the opportunities for achieving significant progress, and to set priorities within the field of vision research.

The current plan, Vision Research--A National Plan: 1994-1998, has served as a guide to the attainment of these goals and objectives and to seizing the opportunities at hand.

The NEI and NAEC are in the early stages of development of the next strategic plan for vision research. This plan will be for the years 1999 to 2003. Panels of experts representing the various fields of vision research are being assembled with the mandate to set realistic research goals and objectives, determine research needs and opportunities, and develop research strategies for achieving those goals and objectives. The strategic plan should be completed in the fall of 1997.

In addition to the areas of research already identified, where progress is anticipated within the next year, the NEI has identified the following research opportunities within the NIH Areas of Emphasis that it will pursue with the additional funding requested for FY 1998.

Biology of the Brain Disorders. Research on the visual system is providing key insights into development of the nervous system and the mechanisms of neuronal maintenance, cell death, and repair in the central nervous system. Recent work in the retina, for example, has suggested that peripheral and central nervous system neurons may have different survival requirements. The survival of retinal ganglion cells, unlike neuronal cells derived form the peripheral nervous system, is not promoted by extracellular (survival promoting) trophic factors unless the intracellular cAMP level is elevated. In another area, photoreceptor degeneration in several animal models of retinitis pigmentosa is now known to occur through apoptosis. Neurotrophic factors and other regulators of programed cell death are being explored in this system. Other visual system examples include studies examining factors that perturb the guidance of axons in damaged optic nerve and other central visual tracts, and seminal work on factors involved in visual cortex plasticity. These examples demonstrate some of the many opportunities that the visual system offers for research into mechanisms that underlie degenerative and repair processes in the central nervous system.

New Approaches to Pathogenesis. Opportunities exist for expansion of research on the role of vascular endothelial growth factor in retinal neovascularization in diabetic retinopathy, as well as investigation of the role of protein kinase C in the development of diabetic retinopathy. Additionally, further pursuit is warranted of the finding that AQP5, a member of the aquaporin family, is involved in secretion of the aqueous component of tears and may play a rode in dry eye, an important women's health problem.

Genetic Medicine. Although many mutations that result in retinitis pigmentosa have already been identified in genes for key photoreceptor proteins, including the genes for a digenic form of the disease, opportunities still exist for identifying additional genes involved in and serving as the basis for the heterogeneous expression of retinitis pigmentosa. Expansion of genetic research on Leber's hereditary Optic Neuropathy (first human disease conclusively linked to a maternally-inherited mutation in mitochondrial DNA), aniridia (Pax-6), juvenile and primary open angle glaucoma, and juvenile and age-related macular degeneration is also warranted.

New Preventive Strategies Against Disease. Recent experimental results have provided significant insights into the development of myopia or nearsightedness (a condition affecting

approximately 25 percent of American adults). These results justify an expansion of basic research on the development of myopia and other refractive errors, and the initiation of full-scale myopia prevention trials.

Advanced Instrumentation and Computers in Medicine and Research. Opportunities for significant progress exist in the following advanced instrumentation initiatives: the extension of functional magnetic resonance imaging and intrinsic optical imaging techniques to measure activity within very small patches of cerebral cortex provide new opportunities for investigating the computational properties of well-localized cortical areas; the development of laser-targeted dye delivery systems that could revolutionize the visualization of blood vessels in the retina; optical coherence tomography and confocal scanning laser polarimetry for quantitative measurements of the retinal nerve fiber layer; and, the development and testing of very-high frequency ultrasound signal processing techniques to improve B-mode and spectral resolution by more than an order of magnitude.

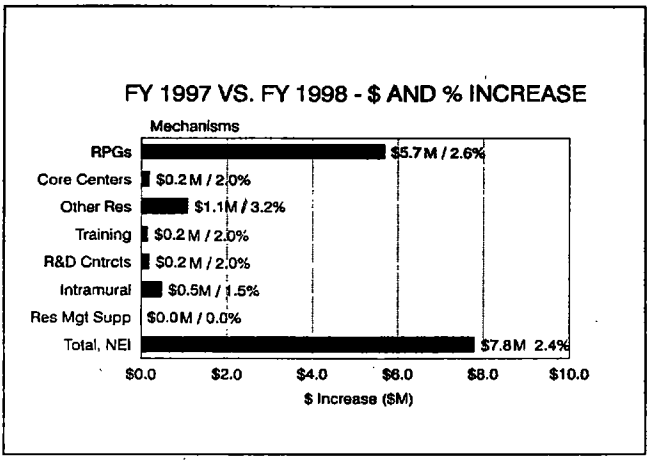
Other Areas of Interest

The NEI is supporting the development and evaluation of an instrument (questionnaire) to assess visual functioning and its impact on health-related quality of life, as self-reported by the patient. This instrument labeled the NEI-VFQ will be a useful complement to traditional clinical measures of vision, not only for use in clinical trials as an outcome measure, but also in medical practice. Intramurally, the NEI is undertaking a pilot study to assess "utility" loss associated with vision impairment as experienced by patients. Utility assessment provides a formal mechanism to assist in the allocation of medical service resources across diseases and conditions.

The NEI has taken a lead role in the establishment and functioning of the Eye Care Technology Forum (ECTF). The ECTF provides a communication mechanism, whereby stakeholders from industry, academia, FDA, NEI, other government agencies, along with eye care provider organizations, can address in a no-fault setting issues related to reducing the time and cost of bringing research findings to the eye care service and product market place.

Budget Policy

The NEI is requesting a total of $330.9 million, an increase of 2.4 percent or $7.8 million over the FY 1997 level. The dollar and percentage increases are highlighted below. Within the $7.8 million increase, $2.0 million would be used for the Special Emphasis Area, "Biology of Brain Disorders." The funds would be used for research project grants in the area of visual neuroscience, visual central nervous system regeneration, mechanisms of neurodegeneration and development of the nervous system. Three additional Special Emphasis Areas are proposed for funding of $1.0 million each. They are: "New Approaches to Pathogenesis," "Genetics of Medicine," and "Developmental and Advanced Instrumentation." At the same time, intramural research in these emphasis areas would continue within existing funding.

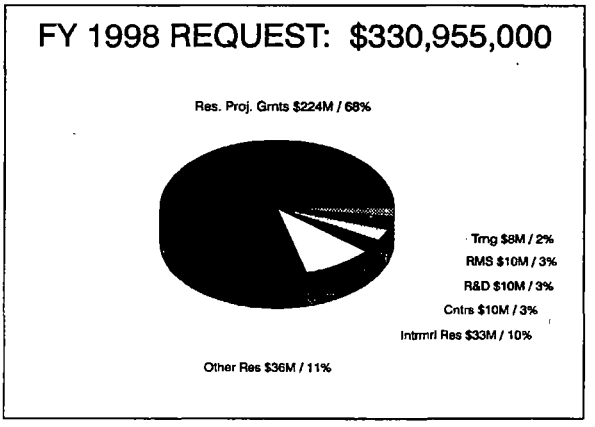


At the FY 1998 level of funding, the NEI would also continue its process in age-related macular degeneration research, specifically in the areas of cell and molecular biology, and genetics research and growth factors for furthering knowledge on new treatments for the disease. Also, the NEI intends to extend its progress in the development of measurements of vision function and quality of life, into areas of refractive error in order to measure the effectiveness of interventions in this area from the patient's perspective.

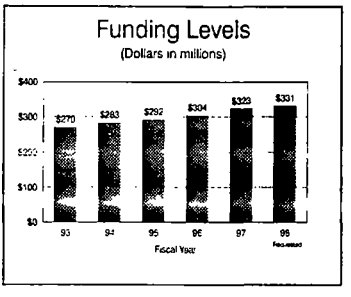
NIH policy links research project grant (RPG) average cost increases to total program budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for RPGs. In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs will increase by up to two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP).

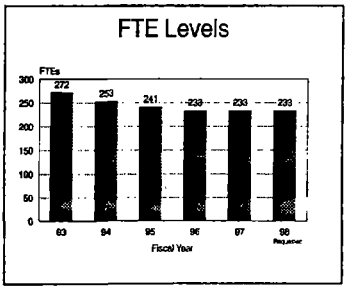
In FY 1998 and FY1997, the NEI FTE ceiling is proposed to remain at the FY 1996 level.

The FY 1998 budget request is illustrated below, showing each mechanism's request level and its percent of the total NEI budget request.



Total funding and FTE levels for the NEI during the last five years are highlighted below.





NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	701	$149,478,000	690	$150,586,000	725	$162,330,000
Administrative supplementals	(22)	1,028,000	(30)	2,154,000	(30)	2,197,000
Competing.						
Renewal	144	34,728,000	169	41,844,000	146	37,058,000
New	92	16,373,000	91	16,567,000	82	15,144,000
Supplemental	0	0	0	0	0	0
Subtotal, competing	236	51,101,000	260	58,411,000	228	52,202,000
SBIR/STTR	37	5,652,000	49	7,509,000	50	7,622,000
Subtotal, RPGs	974	207,259,000	999	218,660,000	1,003	224,351,000
Research Centers						
Specialized/comprehensive	31	8,954,000	31	9,812,000	31	10,008,000
Clinical reseach	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research centers in minority institutio	0	0	0	0	0	0
Subtotal, Centers	31	8,954,000	31	9,812,000	31	10,008,000
Other Research						
Research careers	26	2,740,000	30	3,000,000	30	3,060,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	136	26,886,000	188	30,619,000	188	31,629,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	367,000	0	390,000	0	398,000
Other	3	574,000	3	483,000	3	493,000
Subtotal, Other Research	165	30,567,000	221	34,492,000	221	35,580,000
Total, Research Grants	1,170	246,780,000	1,251	262,964,000	1,255	269,939,000
Training	FTTPs		FTTPs		FTTPs	
Individual	120	3,285,000	95	2,866,000	95	2,923,000
Institutional	168	4,429,000	175	4,998,000	175	5,098,000
Total, Training	288	7,714,000	270	7,864,000	270	8,021,000
Research & development contracts	26	8,917,000	27	9,613,000	27	9,805,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	165	30,227,000	165	32,294,000	165	32,778,000
Research management and support	68	10,396,000	68	10,412,000	68	10,412,000
Cancer prevention & control	0	0	0	0	0	0
Construction	0	0	0	0	0	0
Total, ICD	233	304,034,000	233	323,147,000	233	330,955,000
(Clinical Trials)		(23,236,000)		(25,603,000)		(26,571,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Vision Research		263,310		280,441		287,765		7,324
Subtotal, Extramural research		263,310		280,441		287,765		7,324
Intramural research	165	30,227	165	32,294	165	32,778	0	484
Research management and support	68	10,396	68	10,412	68	10,412	0	0
Total obligations	233	303,933	233	323,147	233	330,955	0	7,808
Unobligated balance lapsing		101		0		0		0
Total, Budget Authority	233	304,034	233	323,147	233	330,955	0	7,808

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Summary of Changes

1997 Estimated budget authority				$323,147,000
1998 Estimated budget authority				330,955,000
Net change				7,808,000
	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$13,442,000		200,000
b. Annualization of January 1997 pay increase		13,442,000		113,000
c. January 1998 pay increase		13,442,000		289,000
d. Legislative proposal, l.51% increase in the CSRS rate		13,442,000		58,000
e. Service and supply fund		2,838,000		74,000
f. Increased cost of laboratory supplies, materials, and other expenses		8,204,000		213,000
Subtotal				947,000
2. Research Management and Support:				
a. Within grade increase		4,500,000		67,000
b Annualization of January 1997 pay increase		4,500,000		38,000
c. January 1998 pay increase		4,500,000		97,000
d. Legislative proposal, l.51% increase in the CSRS rate		4,500,000		37,000
e. Service and supply fund		662,000		17,000
f. Increased cost of laboratory supplies, materials and other expenses		2,617,000		68,000
Subtotal				324,000
Subtotal, built-in				1,271,000

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE
Summary of Changes--continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	690	152,740,000	35	11,787,000
b. Competing	260	58,411,000	(32)	(6,209,000)
c. SBIR/STTR	49	7,509,000	1	113,000
Total	999	218,660,000	4	5,691,000
2. Centers		9,812,000		196,000
3. Other research		34,492,000		1,088,000
4. Research training		7,864,000		157,000
5. Research and development contracts		9,613,000		192,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes		32,294,000		(463,000)
Subtotal, intramural		32,294,000		(463,000)
7. Research management and support		10,412,000		(324,000)
Subtotal, program		323,147,000		6,537,000
Total changes				7,808,000

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Budget Authority by Object

		FY 1997 Estimate	FY 1996 Estimate	Increase or Decrease
Total compensable workyears:				
Full-time employment		233	233	0
Full-time equivalent of overtime and holiday hours		0	0	0
Average ES salary		$121,200	$123,900	$2,700
Average GM/GS grade		10.7	10.7	0.0
Average GM/GS salary		$53,300	$54,400	$1,100
Average salary, grades established by act of of July 1, 1944 (42 U.S.C. 207)		$49,200	$50,700	$1,500
Average salary of ungraded positions		$49,000	$50,500	$1,500
	Personnel Compensation:			
11.1	Full-Time Permanent	9,727,000	10,116,000	$389,000
11.3	Other than Full-Time Permanent	3,044,000	3,166,000	122,000
11.5	Other Personnel Compensation	547,000	569,000	22,000
11.8	Special Personnel Services Payments	1,750,000	1,820,000	70,000
11.9	**Total Personnel Compensation**	**15,068,000**	**15,671,000**	**603,000**
12.0	Personnel Benefits	2,863,000	2,977,000	114,000
13.0	Benefits for Former Personnel	11,000	11,000	0
	Subtotal, Pay Costs	**17,942,000**	**18,659,000**	**717,000**
21.0	Travel & Transportation of Persons	490,000	494,000	4,000
22.0	Transportation of Things	65,000	66,000	1,000
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	0	0	0
23.3	Communications, Utilities & Miscellaneous Charges	619,000	620,000	1,000
24.0	Printing & Reproduction	298,000	298,000	0
25.1	Consulting Services	327,000	329,000	2,000
25.2	Other Services	1,590,000	1,518,000	(72,000)
25.3	Purchase of Goods & Services from Government Accounts	17,148,000	17,196,000	48,000
25.4	Operation & Maintenance of Facilities	942,000	942,000	0
25.5	Research & Development Contracts	7,541,000	7,733,000	192,000
25.6	Medical Care	42,000	45,000	3,000
26.7	Operation & Maintenance of Equipment	600,000	600,000	0
25.8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**28,190,000**	**28,363,000**	**173,000**
26.0	Supplies & Materials	2,828,000	2,734,000	(94,000)
31.0	Equipment	1,820,000	1,694,000	(126,000)
32.0	Land and Structures	0	0	0
33 0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	270,828,000	277,960,000	7,132,000
42.0	Insurance Claims & Indemnities	65,000	65,000	0
43.0	Interest & Dividends	2,000	2,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**305,205,000**	**312,296,000**	**7,091,000**
				0
	Budget Authority by Object	**323,147,000**	**330,955,000**	**7,808,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$9,727,000	$10,116,000	$389,000
Other Than Full-Time Permanent (11.3)	3,044,000	3,166,000	122,000
Other Personnel Compensation (11.5)	547,000	569,000	22,000
Special Personnel Services Payments (11.8)	1,750,000	1,820,000	70,000
Total Personnel Compensation (11.9)	**15,068,000**	**15,671,000**	**603,000**
Civilian Personnel Benefits (12.0)	2,863,000	2,977,000	114,000
Benefits to Former Personnel (13.0)	11,000	11,000	0
Subtotal, Pay Costs	**17,942,000**	**18,659,000**	**717,000**
Travel (21 0)	490,000	494,000	4,000
Transportation of Things (22.0)	65,000	66,000	1,000
Rental Payments to Others (23.2)	0	0	0
Communications, Utilities and Miscellaneous Charges (23.3)	619,000	620,000	1,000
Printing and Reproduction (24.0)	296,000	298,000	0
Other Contractual Services:			
Advisory and Assistance Services (25.1)	327,000	329,000	2,000
Other Services (25.2)	1,590,000	1,518,000	(72,000)
Purchases from Govt. Accounts (25.3)	14,258,000	14,306,000	48,000
Operation & Maintenance of Facililties (25.4)	942,000	942,000	0
Operation & Maintenance of Equipment (25.7	600,000	600,000	0
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**17,717,000**	**17,695,000**	**(22,000)**
Supplies and Materials (26.0)	2,794,000	2,694,000	(100,000)
Subtotal, Non-Pay Costs	21,983,000	21,867,000	(116,000)
Total, Administrative Costs	**39,925,000**	**40,526,000**	**601,000**

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

1997 House Appropriations Committee Report Language

Item

Macular degeneration - The Committee states: Age-related macular degeneration is the leading cause of severe visual impairment and blindness in the U.S. The Institute has made great progress in this area through advances in cell and molecular biology. Additionally, genetics research and advances in the development of growth factors hold great promise for new treatments for this disease. The Institute is urged to encourage research in this area, and to be prepared to discuss the status of research in age-related macular degeneration and prospects for the future in next year's appropriations hearings.

Action Taken or to be Taken

The National Eye Institute (NEI) is conducting and supporting a number of studies on age-related macular degeneration (AMD). Research in this area is a high priority of the Institute; in fiscal year 1997, the NEI is funding approximately $75 million of research in areas generally related to age-related macular degeneration. Of this amount, approximately $16 million is directly related to AMD. One major study involves 11 clinics nationwide at which 4700 patients are being followed to identify risk factors for AMD. Another study is examining families with AMD to assess the role genetic and environmental factors may play in this complex chronic disease. Clinical trials are also investigating the effects certain combinations of vitamins and minerals may have in preventing or slowing the progress of AMD.

In addition to clinical research on AMD, the NEI is actively supporting a broad array of studies in the laboratory. NEI scientists are continuing laboratory efforts to identify genes that cause AMD. These studies may allow us to determine who is at greatest risk of developing the disease and design treatments that will prevent it or delay its onset.

Additionally, NEI-supported scientists are utilizing a variety of approaches to develop retinal transplantation treatments for age-related macular degeneration. Recently NEI investigators have successfully transplanted healthy retinal pigment cells into diseased retinas of laboratory animals. Follow-up on studies in animals are planned for the coming year.

The NEI will continue to support clinical and laboratory research aimed towards learning more about this debilitating disease and using this knowledge to develop treatments to prevent the disease or slow its progression.

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$315,283,000	Indefinite	$322,934,000
National Eye Institute	Title IV, Part C, Subpart 9 Sections 455-456	42§285i et seq.	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288(d)	a/	7,864,000	b/	8,021,000
Total, Budget Authority			0	323,147,000	0	330,955,000

a/ Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208).

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1989	229,021,000 2/	223,288,000 3/	229,271,000	234,218,000
1990	223,777,000 4/	240,636,000	241,774,000	239,889,000 5/
1990 Sequester				(3,356,000)
1991	247,392,000	254,887,000 6/	258,324,000	253,241,000 7/
1991 Sequester				(3,000)
1992	272,260,000	272,260,000	267,229,000	269,300,000 8/
1993	285,133,000	279,102,000	279,102,000	276,188,000 9/
1994	272,201,000	290,260,000	290,260,000	290,260,000
1995 10/	292,022,000	290,199,000	291,886,000	291,340,000 11/
1995 Rescission				(245,000)
1996	300,693,000 10/	314,185,000	297,489,000 10/	314,185,000
1996 Rescission				(202,000)
1997	310,072,000 10/	333,131,000	315,948,000 10/	332,597,000 12/
1998	330,955,000 10/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ The 1989 request excludes funds for AIDS research and education [$4,947,000] proposed for consolidation in the Office of the Assistant Secretary for Health.
3/ Excludes $5,620,000 in NRSA training programs not considered.
4/ The 1990 request excludes funds for the National HIV program [$5,697,000] proposed for consolidation in the Office of the Assistant Secretary for Health
5/ Excludes enacted administrative reductions of $1,316,000.
6/ Excludes $7,105,000 in NRSA training programs not considered.
7/ Excludes enacted administrative reductions of $6,918,000.
8/ Excludes enacted administrative reductions of $1,702,000.
9/ Excludes enacted administrative reductions of $2,914,000.
10/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
11/ Excludes enacted administrative reductions of $138,000, $7,000, and $115,000.
12/ Reflects enacted administrative reductions of $138,000.

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	42	42	42
Intramural Research Program	165	165	165
Extramural Vision Research	26	26	26
Total, NEI	233	233	233
	Average GS/GM Grade		
1993	10.5		
1994	10.6		
1995	10.6		
1996	10.7		
1997	10.7		
1998	10.7		

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
NATIONAL EYE INSTITUTE

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	1	1	1
ES-5	1	1	1
ES-4	2	2	2
ES-3	0	0	0
ES-2	0	0	0
Subtotal	4	4	4
Total - ES Salary	$475,900	$484,800	$495,500
GS/GM-15	22	22	22
GS/GM-14	23	23	23
GS/GM-13	13	13	13
GS-12	27	27	27
GS-11	28	28	28
GS-10	2	2	2
GS-9	10	10	10
GS-8	16	16	16
GS-7	15	15	15
GS-6	5	5	5
GS-5	2	2	2
GS-4	6	6	6
GS-3	2	2	2
GS-2	1	1	1
GS-1	0	0	0
Subtotal	172	172	172
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	2	2	2
Senior Grade	4	4	4
Full Grade	2	2	2
Senior Assistant Grade	0	0	0
Subtotal	8	8	8
Ungraded	56	56	56
Total permanent positions	179	179	179
Total positions, end of year	240	240	240
Total full-time equivalent (FTE) employment,end of year	233	233	233
Average ES level	4.8	4.8	4.8
Average ES salary	$118,400	$121,200	$123,900
Average GS/GM grade	10.7	10.7	10.7
Average GS/GM salary	$52,000	$53,300	$54,400

THURSDAY, FEBRUARY 27, 1997.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE

WITNESSES

FRANCIS S. COLLINS, M.D., Ph.D., DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE
ELKE JORDAN, Ph.D., DEPUTY DIRECTOR
KATHY HUDSON, Ph.D., ASSISTANT DIRECTOR FOR POLICY COORDINATION
JAMES C. VENNETTI, EXECUTIVE OFFICER
ERIN S. BURGESS, BUDGET OFFICER
HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We begin our hearings this morning with the National Human Genome Research Institute and Dr. Francis Collins. Dr. Collins, welcome. Nice to have you here as an institute now. Why don't you introduce the people who are with you and then proceed?

INTRODUCTION OF WITNESSES

Dr. COLLINS. Thank you very much, Mr. Porter.

Sitting at the table, beginning at my left, Mr. James C. Vennetti, who's the Executive Officer; Dr. Kathy Hudson, who is the Assistant Director for Policy Coordination; Ms. Erin Burgess, Budget Officer; Dr. Elke Jordan, the Deputy Director; Dr. Harold Varmus you are familiar with, and Mr. Dennis Williams from the Department.

OPENING STATEMENTS

It is indeed an honor to testify for the fourth time in front of this committee, but the first time as the Director of the National Human Genome Research Institute. I have to keep thinking before I say those words, or I tend to get them wrong.

In reality, the former NCHGR, the National Center for Human Genome Research, is now the NIH's newest research Institute. On January 14, after consultation with you and other Congressional leaders, Secretary Shalala signed documents that gave the National Center for Human Genome Research a new name and new status. We are proud the NCHGR has been recognized for its successful leadership of the Human Genome Project, the accomplishments of its cutting-edge intramural laboratories, and its active policy research programs. As an Institute, NHGRI looks ahead to completing the Human Genome Project and to playing a leading role in 21st century health science based on understanding the instructions encoded in our DNA.

In my statement, I could enumerate milestones and accomplishments of this grand adventure called the Human Genome Project over the last year and project some of the future ones, and don't worry, I will. But I also thought it would be appropriate to put this into the context of human health. Because as a physician, clearly my excitement about this project is what it will do to benefit human beings, to alleviate suffering, and to avoid illnesses which currently plague so many.

PROSTATE CANCER

So I would like to tell the committee about an individual named Robert. Robert is currently 64 years old. At the age of 54, he was diagnosed with prostate cancer. This was for him in some ways a surprise, and in other ways not. Both his father and his paternal uncle had previously been diagnosed with prostate cancer and they had both died of it. So finding his own diagnosis at age 54 was perhaps less surprising than it would have been to others, although certainly a very young age to have that diagnosis.

Now, Robert was treated at the Johns Hopkins University surgically and is currently doing well some 10 years later. However, his son was recently diagnosed at the age of 42 with prostate cancer.

Families of this sort are not rare, although they are uncommon. In a collaborative effort between Johns Hopkins and the National Human Genome Research Institute, an intense effort was made to try to figure out what is at the basis of this inherited predisposition to prostate cancer. There had been indirect evidence for three or four years, based on studies of large families, that there was something going on in the way of a hereditary factor.

Last November, we published in the journal *Science* that in fact there is a specific gene on chromosome 1 named HPC–1, for hereditary prostate cancer gene number 1, which if misspelled, or mutated, carries an estimated 80 percent likelihood of conferring prostate cancer on an individual by age 80. And the age of onset for such individuals is skewed towards a considerably earlier age than the general risk of prostate cancer.

Now, prostate cancer is a terribly common disorder. Three hundred and forty thousand men will be diagnosed with that disease this year and more than 40,000 will die from it. It is this early onset type that is particularly of concern. It is estimated that some quarter of a million men have mutations in this gene called HPC–1, and that identifying those individuals might potentially be of great value by warning them of their high risk.

Now, let me hasten to say, we have not yet identified the precise gene involved. We know its neighborhood. We know the company that it keeps. And an intense effort is underway now to identify the gene itself.

This same strategy that mapped this gene in Robert's family was applied this past year to also map a gene for Parkinson's disease in a large Italian family to chromosome 4. A great advance, I think, in terms of understanding a disorder which has been very frustrating and puzzling. And up until recently, there had not been much evidence that genes played a role. And now it's very clear that at least in that family, they do.

INHERITED DISEASE RESEARCH

Similar advances have been made in mapping genes for diabetes and multiple sclerosis. And in fact, in collaboration with the Johns Hopkins University, the NIH has now set up a Center for Inherited Disease Research with the National Human Genome Research Institute acting as the lead agency within NIH to facilitate this kind of mapping of genes for complex disorders. The NIH recognized that this is at the forefront of what we need to accomplish, and that many investigators don't have the technology in their own local institutions to do this, but would like to be able to. And we're looking forward to this being a very important addition to NIH's powerful set of tools to further the business of identifying genes that contribute to disease.

I might also say, we have a new initiative within NHGRI partnering up with Howard University and with the Office of Research on Minority Health to specifically look at the genetic underpinnings of diabetes and prostate cancer in African-Americans. Requests for proposals have been issued for both of those and one of those studies on diabetes is now getting underway. And I have personally been very pleased to play a role in getting those efforts underway, given that those are both disorders which disproportionately affect African-Americans. And clearly, there may be genetic causes for that.

FINDING THE GENES

In order to take the situation that Robert's family is now in, where we know the general neighborhood of a prostate cancer gene, and go to the gene itself, one needs the next step. And here is where the Human Genome Project's tools, which are already available, and happily you didn't have to wait until the project was done, have played a major role. So the area around HPC–1, which normally would have taken a matter of a couple of years to develop a map of, already has a very detailed map, because the Human Genome Project has now mapped 96 percent of the human chromosomes to a level of specificity that we thought would take us until 1998.

Furthermore, once you have the neighborhood, you not only want to know where the milestones are, you want to know where the genes are. Because each one of those genes is a potential candidate for a gene that's involved in prostate cancer.

A major step forward occurred last October with the publication in *Science* magazine of the first gene map of human DNA. Associated with the article is a very useful Web site with 16,334 of the estimated 80,000 genes placed in rather precise intervals on human chromosomes. So that for the gene hunter, there was about a 20 percent chance, as of last October, that the gene you're looking for has already been placed in the spot you're searching, and that saves you a huge amount of time.

I think positional cloning, this business of finding genes that are responsible for disease, continues to accelerate as a consequence of this. Last year some 21 disease genes were identified, the best year yet. And I think that number will continue to grow in a very gratifying way.

COMPLETE DNA SEQUENCE

But the sequence, all of the DNA, is what we now really want. And of course, that is the ultimate goal of the Human Genome Project. And I'd like to tell you also that this is coming along quite well. This past year saw the completion of the complete DNA sequence of yeast, and the completion about a month ago of E coli, the bacterial organism which has served as the work horse for a very large amount of microbiology research over the course of many decades. That particular sequence was accomplished by a grantee of the Human Genome Project, is already in high demand, and is available on the public data base run by the National Library of Medicine.

Our partnership with the National Library of Medicine in all of these databases, including the World Wide Web page I cited a moment ago, has been critical to the availability of this genomic information. NLM is also, I think very appropriately, being sensitive to the possibility of using these databases as educational tools. The gene map Web page that I mentioned had 500,000 hits on it in the first two months. And the estimates are that more than half of those were from high school students who were looking to learn something about human genetics. And this Web page is set up in a fashion that makes it very accessible to them, and a very useful educational tool.

I might add, as the DNA sequencing is now ramping up, and we have initiated six pilot projects around the country, which by the end of next year should have produced something like 100 million base pairs of sequence. A great deal of enthusiasm is coming forward for this effort from private industry. For instance, I was gratified to see that the CEOs of the biotechnology industry organization last year chose the maps from the Human Genome Project as the thing that they most wanted to celebrate as having done the most for their industry, an unusual step, because they usually choose some more defined effort that's come from a particular company.

BEYOND THE FIRST SEQUENCE

Furthermore, we are very much now in the process of thinking about what shall we do when this sequence is in hand in 2005, or maybe if all goes well, a little sooner than that. Many people have compared the determination of the human genome sequence as something analogous to deriving the periodic table of the elements for chemistry. The periodic table for biology might have 80,000 entries, one for each of the human genes, instead of the 100 or so elements of the chemical table.

But the parallel is a useful one to consider, because it sort of puts into context what a table of genes does for you. It provides you with that basic chart of the elements of the human organism, and then a great deal of exciting activity can follow in terms of figuring out how these genes talk to each other, interact to make a cell or a tissue or a whole organism.

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS

So back to Robert. I have tried to sort of outline here briefly some of the accomplishments of the last year. What about Robert? Well, Robert has another son. I told you he has one who has been diagnosed with prostate cancer at 42. He also has another son who's just turned 40. And of course, that individual is anxious, as is Robert, about the future. I think it's fairly likely that in the course of the next year or two, the HPC–1 gene will be found and Robert's son will have the chance, if he desires to know the information, to learn whether he is at similarly high risk or not. And he might not be, of course, the transmission of this disease is not 100 percent. It's probably in the neighborhood of 50 percent that this son would have the same risk as his father.

But of course that then raises the question, is that a good piece of information to know? And this again raises all of the ethical, legal and social issues which come out of genome research. I ran across a quote recently from Winston Churchill, which I'm fond of, because I think some people have argued that the ethical considerations are so severe that we should really slow down this research. And I completely disagree with that logic, because I think this research holds within it the promise of curing so many human ills. Churchill said: "My faith is in the high progressive destiny of man. I do not believe we are to be flung back into abysmal darkness by those fearsome discoveries which human genius has made. Let us make sure that they are our servants, but not our masters."

Well, our effort to make sure these discoveries are our servants, not our masters, is the ethical, legal and social implications program, the ELSI program of the Human Genome Project. And in the past year, a number of important things have happened. The Task Force on Genetic Testing, which has been meeting for almost two years, has produced its principles and very recently published in the Federal Register a set of implementation recommendations, which are being submitted for public comment. These recommendations involve a number of new initiatives to look at the issue of testing, to make sure that it's done accurately, that the results can be trusted, and also that there is some oversight about when a test is ready to leave research and move into clinical practice.

In the area of health insurance discrimination, I think we all should celebrate the Kassebaum-Kennedy bill, which does on its list of issues which health insurers should not use to take away coverage or to set exorbitant premiums, list genetic information. Just the same, there are areas that are not covered by that legislation, particularly for individual policy holders. And we are very interested in providing information to the degree that we can to assist the process of closing those loopholes.

In the area of employment discrimination, there is some optimism that employers would not be at the present time able to use genetic information to discriminate. And I think that is something to be hoped for, because clearly, your DNA is not something you get to choose. And to have your DNA used to deny you a job seems inherently unfair. But to really prevent that, a legislative approach is needed. And we held a conference last October, out of which came a series of very specific guidelines which have been submitted

for publication, which we hope will be looked at. That was a conference organized by the National Action Plan on Breast Cancer in collaboration with the ELSI working group, and I think produced a very useful document.

Finally, the area of education, particularly of health professionals, continues to be one that we have enormous interest in catalyzing. Increasingly, individuals are going to their doctors with the latest copy of *Time* or *Newsweek,* saying, does this refer to me? Should I have this test for breast cancer? And soon it will be questions about testing for prostate cancer. And most physicians are not well prepared to answer those questions.

In collaboration with the American Medical Association and the American Nursing Association, a coalition for health professional education in genetics has been started, and will have its first full meeting in about 10 days. We're very optimistic that that will be an effective way to pull together a whole host of primary care provider disciplines, allowing them to work together to achieve better literacy for health care professionals and genetics on a short turnaround.

So Mr. Chairman, even without this week's revelations about Dolly, we live in exciting times. The Human Genome Project is proud to be at the center of a revolution in biomedical research. The promise for better health that the Human Genome Project provides is beginning to be realized in some quarters, although most of that promise lies ahead, and most of what I've been talking about are more in the area of inspirations than culminations.

But I'm glad once again to be able to tell you that we are ahead of schedule and under budget. The request for the National Human Genome Research Institute is $202,197,000. And I'd be happy to answer your questions.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Human Genome Research Institute

Mr. Chairman, it is truly an exciting opportunity to testify before you today, for the first time, as director of the NIH's newest research Institute, the National Human Genome Research Institute (NHGRI). On January 14, after consultation with Congressional leaders, Secretary Shalala signed documents that gave the National Center for Human Genome Research (NCHGR) a new name and new status. We are proud the NCHGR has been recognized for its successful leadership of the Human Genome Project, the accomplishments of its cutting-edge intramural laboratories, and its active policy research programs. As an Institute, NHGRI looks ahead to completing the Human Genome Project and to playing a leading role in 21st-century health science based on understanding the instructions encoded in our DNA.

As in the past, we continue to make remarkable strides toward our goals, and in the process, spin off new ways to approach the study of genetic disease. The genetic maps are complete, the physical maps nearly so, and both are in wide use by the scientific community. The slowest part of a disease-gene hunt nowadays is sorting through all the genes in the target region on a chromosome and determining which one is responsible for the disease. To help solve this, scientists at NHGRI-supported research centers, the National Library of Medicine, and genome centers in England and France, created an on-line map that pinpoints the locations of over 16,000 human genes--about one-fifth of the estimated 80,000 total. With it, the number of mapped human genes has tripled in less than two years; that number will likely double again over the coming year. Taking full advantage of cutting-edge information technology, the electronic map is a mouse click away from on-line references in the medical and research literature, which will aid scientists in linking information about a likely disease gene to its role in cell function.

Human genome maps and technologies are now making the difficult "needle in a haystack" search for genes much easier. As a result, the number of disease genes isolated nearly doubles every year. In 1996, 21 disease genes were isolated using genome maps--almost twice as many as the year before and nearly five times the number isolated the year the genome project began. Among them are genes that contribute significantly to human diseases, including polycystic kidney disease, an adult form of diabetes, and hereditary hemochromatosis (HH).

HH is a common disorder of iron metabolism, affecting about 1 in 400 individuals of Northern European descent. It occurs when both parents contribute a mutated HH gene to their child. About 1 in 10 individuals carries a single mutated HH gene. The major symptoms of HH--liver cirrhosis, heart deterioration, and other organ failures--don't occur until mid-life, and untreated, the disease causes early death. But treatment by simple blood letting allows people with HH to live a normal lifespan. Because HH is so common and easily treatable, it provides an excellent example for offering genetic testing on a large scale to identify people at risk for a disease and

enabling them to avoid becoming ill. NHGRI and the Centers for Disease Control and Prevention are planning a workshop this spring to examine the scientific, ethical, social, and medical implications of widespread testing for HH.

The ultimate map of the human genome will spell out all 3 billion letters that make up human DNA. Ongoing projects to sequence the DNA of non-human organisms have provided an opportunity for scientists to practice sequencing genomes much smaller than that of the human, but bigger than anything sequenced before. This past year, an international consortium of scientists finished spelling out the entire genetic code of a species of yeast valuable to biologists and commonly used by bakers and brewers. At 12,057,500 bases, the yeast genome is the largest to be completely deciphered so far and is the most advanced organism yet to be sequenced. Having the entire yeast DNA sequence now paves the way for scientists to study how all the genes in a complex cell similar to human cells function as a system.

With progress in sequencing moving so rapidly, NHGRI has launched pilot studies at six U.S. research centers to explore the feasibility of large-scale sequencing of human DNA--the most technologically challenging phase of the Human Genome Project. This initiative is projected to produce the sequence of about 3 percent of human DNA in the first two years and will help to streamline and cut the cost of DNA sequencing in order to finish the entire human genome by the year 2005.

Using current mapping technology to understand the inheritance of single-gene disorders--the so-called "Mendelian" disorders--is usually relatively straightforward. Current genetic maps are now dense enough to place a disease gene within reach in a matter of weeks. This past year, these maps led NHGRI scientists to a gene associated with Parkinson's disease in a large Italian-American family and to a gene associated with prostate cancer in another study of 91 American and Swedish families. Although these genes have not yet been isolated, "linking" them to specific chromosomes gives scientists the first direct evidence that genes play an important role in these disorders.

But most diseases of modern life--cancer, heart disease, diabetes, arthritis, and a host of neuro-psychiatric disorders--seem to result from the activities of several genes and the interplay between a human body and its environment. NHGRI is supporting several initiatives to make the complex genetic and environmental components of these disorders easier to decipher and understand, and thereby easier to prevent or treat.

In a creative government-university partnership, eight components of the NIH, led by NHGRI, and the Johns Hopkins University School of Medicine, have established a new research center to facilitate analysis of the complex genetics of these common disorders. The new Center for Inherited Disease Research (CIDR) is located on the Johns Hopkins Bayview Medical Center in Baltimore and is expected to be fully operational this spring. Under full capacity, CIDR researchers expect to study six to nine complex disorders per year.

In other studies of complex disorders, NHGRI and the NIH Office of Research on Minority Health are collaborating with scientists at Howard University to study why people of African descent seem to develop adult-onset diabetes and prostate cancer more frequently than do many other population groups. Understanding the genetic basis of an increased risk for these diseases could lead to better strategies to prevent them from causing serious health problems.

Tracking down all the genetic components of a complex disorder requires analysis of the entire genomes of hundreds and perhaps thousands of individuals. For this to be possible, genome maps must be easily adapted to highly automated strategies. In the coming years, NHGRI will begin improvements on the existing maps, which have been so useful in finding single-gene disorders, to increase their usefulness in ferreting out the multiple genes that contribute to so many of today's common disorders.

The impact on the future of biology of knowing the order of all 3 billion human DNA bases has been compared to Mendeleev's establishment of the Periodic Table of the Elements in the 19th century and the advances in chemistry that followed. The complete DNA sequence of the human--the biologic periodic table--will make it possible to define a unique 'signature' for every gene. Rapidly evolving technologies, comparable to those used in the semi-conductor industry, will allow scientists to build detectors that trace hundreds or thousands of these gene signatures in a single experiment. Scientists will use the powerful new tools to reveal the secrets of disease susceptibility, create broad new opportunities for preventive medicine, and provide unprecedented information about the origin and migration of human populations.

One example of this kind of experiment was recently carried out by NHGRI-supported scientists who developed an automated method for determining differences as small as one base pair in comparisons of the entire 16,000 base-pair mitochondrial genome among 10 human volunteers. The scaled-up technique could potentially be used to analyze the entire 3 billion base-pair nuclear genome of the human in a single experiment. NHGRI scientists are using similar technologies to identify the broad range of genes possibly activated during cancer development.

While scientists are discerning the secrets once buried in the human genome, concerns about how the information will be used outside the laboratory call for new public policies about privacy and discrimination. An NHGRI-supported study showed that individuals from families with genetic disorders experience frequent discrimination in health insurance. Some do not even apply because they believe they will be turned down because of their condition.

NHGRI has established productive partnerships among consumers, scientists, and policy makers to help reduce the possibility that genetic information will be used to harm an individual or family members. The Ethical, Legal, and Social Implications (ELSI) Working Group in collaboration with the National Action Plan on Breast Cancer (NAPBC), has created a successful model for policy development through a series of workshops on genetics issues. The first of these resulted in recommendations

on genetic information and health insurance that were later incorporated in part into the Health Insurance Portability and Accountability Act of 1996. A second ELSI-NAPBC workshop developed recommendations relating to genetic discrimination in employment. The ELSI-NAPBC team is also interested in addressing privacy issues.

The Task Force on Genetic Testing (TFGT) of the ELSI Working Group has been examining the strengths and weaknesses of current practices and policies for development and delivery of safe and effective genetic tests in the United States and the quality of laboratories providing the tests. Last March, the TFGT released a set of interim principles for public comment. The final principles and recommendations of the task force have just been published in the Federal Register for public comment and will be reported to the Working Group this spring.

In another ELSI project on genetic testing, NHGRI is co-sponsoring a consensus development conference this spring to look at issues related to testing for cystic fibrosis mutations and to determine whether such testing should be a standard part of medical care.

The broad range and critical importance of ELSI issues prompted NHGRI last spring to establish an outside group to evaluate the role of the ELSI Working Group in these functions. To provide the best attention to these important issues, the evaluation committee recommended dividing the Working Group's responsibilities among different committees and at various levels within the government, including a newly established ELSI Research Evaluation Committee to oversee the ELSI grant portfolios at NHGRI and DOE, an NIH-wide process to coordinate the ELSI activities of the various institutes engaged in genetics research, and a federally chartered committee at the DHHS level to formulate public policy resulting from advances in genetics.

As the demand for genetic tests moves from the medical genetics specialty into general practice, it is imperative that health care professionals across disciplines understand the technology and its potential benefits and risks. NHGRI has played a leading role, along with the American Medical Association and the American Nurses Association, in forming the National Coalition for Health Care Professional Education in Genetics. This Coalition brings together leaders in medical professional organizations, consumer groups, government agencies, and industry to develop and implement a national genetics education program for health care professionals. An organizational meeting was held last July, and the first meeting of the full Coalition will be held this spring.

Mr. Chairman, I am rewarded and astounded by the strides human genome research has made and the unprecedented opportunities it offers biomedical science to improve the lives of people in this country and around the world. The President's request for FY1998 for the National Human Genome Research Institute is $202,197,000. I am happy to answer your questions.

Mr. PORTER. Dr. Collins, thank you for that wonderful statement.

The average person reading the newspaper and let's say they read about HPC–1 and that you've found it, probably thinks to themselves, we now can cure or prevent prostate cancer. And I wonder if you could carry the concept of finding HPC–1 further and tell us what is required or may be required to get to the actual point of being able to change the gene or to cure the disease from what you have found.

Dr. COLLINS. Thank you for the question. I think there is a great concern that many of us have that media reports of gene discoveries may sound like cures for disease, when in fact it is only a step down that path. Finding the gene is sort of the end of the beginning. Without the gene in hand, one is often really feeling in the dark, to try to understand the disorder.

So for HPC–1, when the gene is identified, hopefully in a year or two, it will almost immediately, if it seems to be a good thing, allow the possibility of diagnostic testing to identify the men at highest risk. And that kind of testing would not ordinarily be done except for individuals with a strong family history of the disease, because applying it across the board might pick up many false positives. Basically, finding the HPC–1 gene would put prostate cancer in the circumstance where breast cancer is now, with BRCA–1 and BRCA–2 being a few years ahead of HPC–1.

That testing alone for prostate cancer could be quite a valuable advance. This is a disease where early detection is the mainstay of cure. And we have a blood test, the PSA test, which detects early evidence of tumors. But it's almost too sensitive, in that it finds things that you're not quite sure what to do about. If you could combine that test with a genetic susceptibility test, you might have a more valuable predictor about who really needs an intervention.

But I will not be satisfied, nor should anybody else be, by simply having the ability to do diagnosis. The discovery of the gene should tell us something fundamental about how is it that a prostate epithelial cell becomes malignant. That same gene, one would expect, may turn out to be involved in the more common variety of sporadic prostate cancers. One can't be sure until you get there, but that's a likely outcome. That's certainly been the case for many other cancers.

Learning about how that gene functions, what its biological niche is, should provide new insights into therapies. And that's where you really want to go, and I think that's the nature of your question. Those therapies might come in the form of a gene therapy, although that is probably going to be quite difficult for an organ like the prostate, and especially if it turns out that this is one of those genes where if you don't correct it in every single cell, the cells you miss will go on and form the cancer anyway.

On the other hand, understanding how the gene works might give you much better ideas about drug therapy, as protease inhibitors have arisen out of understanding the HIV genome. That sort of designer drug pathway is a very appealing one. But it is a pathway whose timetable can never be predicted.

And so I can tell you these views of what's coming in the future, but the one thing I can't tell you is how many years between where we are now and where we really want to be. And anybody who sort of tries to make those predictions I think is speaking beyond the information that they have. There are so many things that are unpredictable about this. But it is the way to get there. And we're on the road.

BUDGET INCREASE

Mr. PORTER. You said, and we applaud the fact that you are ahead of schedule and under budget. That's the best news that appropriators can hear.

How would you respond to a question that said, well, if you're under budget and if NIH as a whole is only getting a 2.6 percent increase, why is your Institute scheduled for an 8.3 percent increase?

Dr. COLLINS. One of the reasons I guess is that ramp-up of the Human Genome Project to full funding has never quite been achieved. And I understand the reasons for that. Starting a new program at a time of fiscal restraint has been quite a challenge. I think the Congress has been very generous in their enthusiasm for this project in appropriating what has come our way so far. And we understand those restraints.

I do think that we are now in a circumstance, having succeeded at the mapping phases for the most part of this project and now beginning to ramp up the sequencing component, where we in many ways are significantly budget limited. We know what to do, we know pretty much how to do it. How soon we get there will be a function of how much budget we have available. We could go faster at this point, in fact, if it were possible for the budget to ramp up more than it has.

In the current proposal, in the President's budget, I think we have done well on the basis of the NIH initiatives. Some $14 million, which is almost all of our increase, comes out of those specific initiatives, particularly in the area of genetic medicine, which Dr. Varmus and the rest of the NIH leadership have identified as being the highest priorities for payoff in fiscal year 1998.

So I think the answer to the question would be, if we're going to basically deliver the products that the Congress wants, that the public seems to want, we could actually do better if this budget continues to ramp up. If we're truncated, we can continue to sort of do what we've been doing. But it will take us longer to get there.

Another part of this is we are beginning to spend a small fraction of our effort looking at what happens after the human genome sequence is done. It would be very unfortunate to sort of get there and then realize we should have been planning for the next step. So we are doing that planning, and we've issued a couple of requests for applications this year for people to begin to look at whole genome technology and for developing a "genome attitude" towards biology on a larger scale. And I think that's a very important part, but a small one at the present time, of our portfolio.

FINISHING FASTER—FINDING A CURE

Mr. PORTER. Is the real answer then that there is a certainty that more money will get more results with respect to the mapping project, and that therefore, the likelihood of bringing real progress to prevention and curing of disease is more likely with the money spent at a higher rate earlier than in other places?

Dr. COLLINS. You could argue that every year that goes by that we don't have the complete human genome sequence we are missing out on opportunities to cure disease. You could certainly argue that every year that goes by, people are wasting a lot of money getting bits of sequence that wasn't already available for them. And people have tried to add up what that amounts to, and especially if you include the private sector, that may be as much as a half a billion dollars every year that's spent on activities that won't be necessary when the Human Genome Project is done.

CLONING—SCIENTIFIC OPPORTUNITIES

Mr. PORTER. Dr. Collins, you were present yesterday when Dr. Varmus addressed the Dolly question.

Dr. COLLINS. Yes.

Mr. PORTER. I wonder if you would like to expand on that answer, or add your own viewpoint to it, and see what you think about cloning.

Dr. COLLINS. Sure. When I came to this job as Director of the National Center for Human Genome Research, which is what we were called then, I did so with some trepidation. But after I had been here a year or so, it occurred to me that many of the aspects of my own training had actually prepared me pretty well for this position in terms of having a background in physical science, being a physician trained in genetics. Only this week did I realize another part of my background was appropriate, and that is that I grew up on a sheep farm. [Laughter.]

So from that particular context, and mindful of Mark Twain's remarks: "There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of facts." That seems to be happening rather broadly this week in the press.

Nonetheless, I think what was reported and I guess is being reported in *Nature* today, but has already been talked about very broadly, is a fundamentally exciting scientific achievement. And I completely agree with Dr. Varmus' analysis of some of the scientific opportunities that this offers in terms of understanding development.

For me as a geneticist, this notion that the DNA sequence of a differentiated cell could be convinced to sort of go back and start over again as a fully undifferentiated embryonic state is remarkable. I think most of us would not have guessed that would happen. It sort of says that the whole array of genes are like an orchestra, and in a particular cell maybe only some parts of the orchestra are playing. But the whole orchestra is there. And if you can figure out how to sort of shut off the playing for a little while and then start it back up again, you can get the whole orchestra to perform. And that is fundamentally really interesting. I think the possibilities,

some of which Harold mentioned yesterday, about being able to use this kind of de-differentiating process medically are very intriguing ones. I would also say that in terms of the ethical issues, we should make it very clear that the use of this technology to clone human beings is unacceptable. Repugnant is the word that Dr. Varmus used yesterday and I agree with that.

On the other hand, to rush in and criminalize a certain aspect of scientific research without careful thought would be unfortunate. And I applaud the President's decision to involve the National Bioethics Advisory Commission, a group that I think is very well positioned to look at this issue over the next 90 days and come back with some observations about possible options of what might be done.

So I think although in many instances, when you have a media event around science, you worry a little bit that it's going to scare the public off. This observation has engaged the public in conversations that we might not otherwise have had. And I think the reverberations of this observation, provided it can be duplicated, of course, we will all be interested to see the first confirmation of this report. But provided that is so, I think something has really changed in science, in the way we view biology. And that is something to be welcomed.

Mr. PORTER. So you're expressing some scientific skepticism that this is actually good science, or you want to at least have it proved that it can be done repetitively?

Dr. COLLINS. I think any new observation that is as fundamentally revolutionary and unexpected as this ought to be confirmed by another investigator. I have read the paper reporting this. It looks very solid. I don't see anything wrong with it. It seems quite well founded, and I suspect it will be possible to reproduce. Although it is clear that this was a very difficult thing to do with only 1 lamb actually being born out of almost 300 that were attempted. So there must be some enormous inefficiency in the process.

One of the things I'll be very interested in is to see whether Dolly ages prematurely. There is a history of arguments about the molecular basis of aging and is it in fact something that is acquired as a cell divides over and over again and acquires mistakes in the DNA? Is that what eventually causes the process to run down and the cell to die?

Now, Dolly's single original cell, typically in the one cell stage, had already gone through six years of life. Is it going to be the case, therefore, that her longevity is affected? That will be a very interesting thing to follow.

Mr. PORTER. With your background on a sheep farm, maybe this is where you can——

Dr. COLLINS. Go back to my roots here. [Laughter.]

Mr. PORTER [continuing.] Add something to the research.

Mrs. Lowey.

GENETIC TESTING—BREAST CANCER

Mrs. LOWEY. Thank you, Mr. Chairman.

And thank you, Dr. Collins. The possibilities of the work of your institute are certainly overwhelming. And it is certainly a privilege

for us to play some small role in helping advance the important research you're doing, and I want to thank you.

And I look forward to working with you on the whole area of employment discrimination, and I am delighted that those findings will be published. As you know, I have been working on that whole issue, and I'm looking forward to your presentations on the legislative remedies.

Because I have to participate in another hearing immediately, I just want to, and I know what we'll be discussing the areas of employment discrimination with regard to genetic testing, etc., I would like to just ask you, since we gathered last and you reported to us on your BRCA–1 and BRCA–2 findings, have there been any additional findings in that regard, any other additional research that you'd like to share with us?

Dr. COLLINS. I appreciate the question, and I very much appreciate your leadership in the area of genetic discrimination and legislative initiatives to do something about that. I appreciate what you're doing about employment this year. I think the opportunities are quite good to solve this problem at the Federal level.

BRCA–1 and 2 research is in sort of an incredible flurry of activity, now that the genes have been in hand for a year or two, some of the best labs in the country have turned their attention to trying to figure out what they do. Mouse models have been made for both of those, where the BRCA–1 and BRACA–2 genes have been knocked out to see what happens. At the present time, it's not clear that the mouse models show the same risk of cancer, at least not in the first few months. But still, those models are likely to be quite useful in understanding the mechanisms and how these genes contribute to cancer of the breast and ovary.

In terms of understanding how the protein products of these genes work, there have been at least two, and one hears rumors of a third, experiments that show other proteins in the cell that interact with the BRCA–1 protein and therefore probably work together with it to do whatever its normal function is. And that is one of those clues that starts you into a pathway which might be very useful in understanding how these genes do their work and how they don't succeed when they need to in somebody who has an alteration.

In terms of understanding the clinical consequences of alterations in this gene, the Washington Area Ashkenazi Jewish study has now been going on for a year, and the results of that study have been submitted for publication. I'm not at liberty to describe them. But this particular study looked at 5,300 men and women, collected their family history and obtained a blood sample to find out whether or not they are carrying one of these genetic alterations. One in 40 of those individuals was carrying a mutation in either BRCA–1 or BRCA–2, about the expected number, based on previous studies.

And obviously, the main payoff that we are waiting for from that study is to find out what really is the risk to such an individual? Is it as high as the 85 percent that has been proposed in other studies? This study I think gives a better window on that, because it's less likely to be a biased estimate, and hopefully those results will come forward very soon.

Mrs. LOWEY. I appreciate that. Because I believe you shared with us two facts, among many other facts, but number one, it's still a very small percent of the cancers.

Dr. COLLINS. Yes.

Mrs. LOWEY. And number two, or perhaps I should ask you this in the form of a question, when you're saying 1 in 40, are you determining at what age that cancer appears, so after a certain age, the incidence of cancer increases in every population?

Dr. COLLINS. Sure.

Mrs. LOWEY. So that if you're identifying that gene to be 1 in 40, you're not making determinations at this point whether that person will get that cancer at the age of 40, 50, 70 or 80. Or are you?

Dr. COLLINS. I may not have been completely clear. The 1 in 40 is the frequency of finding an alteration in BRCA–1 or 2 in a Jewish individual, regardless of their cancer history. What the study is trying to determine for those individuals who do have those alterations, what is their likelihood of getting cancer and at what age. Is it an early age of onset, which some of the other studies have suggested, and if so, by how much. We don't have the answer, but in the coming months, that should come forward.

GENETIC TESTING—COUNSELING AND CONTROL

Mrs. LOWEY. And has there been any progress made on counseling and control of these tests? Because many of us are concerned, and we talked about that last year, about the commercialization of these tests and what goes with it, and what kind of consistency is there in the counseling with those tests.

Dr. COLLINS. Well, there are a number of answers to that question, certainly a number of centers are looking at counseling, trying to figure out what is an effective way to deliver these services. There is a Cancer Genetics Studies Consortium which is funded jointly by the National Human Genome Research Institute, the National Cancer Institute, the National Institute for Nursing Research and the National Institute of Mental Health that has banded together about 11 researchers to share their experiences doing genetic counseling for both breast cancer and colon cancer. And a lot of useful information has come out of that consortium with at least four publications in prominent journals to guide the rest of the world in terms of how to present this information so that it is absorbed and understood and put into practice.

The other thing you're referring to, though, is really sort of the marketing of the tests themselves. There has been, since we last met in this room, the marketing announcement of a company in Utah of a test for BRCA–1 and 2. It cost $2,400 to have a particular sample analyzed to see if there is a mutation present. And it is available to individuals outside of research protocols, which up until fairly recently was where most of this testing was being done.

So that's raising questions about whether this is premature or not. Various statements have been made on that topic, and they don't all agree with each other. The National Action Plan on Breast Cancer has a published statement saying that it's unfortunate to have such testing done outside of research protocols when we're not sure yet what the clinical utility is.

But at present, there is no Federal oversight to prevent that. The Task Force on Genetic Testing, which I mentioned in my opening statement, has very much been looking at this issue. And they have actually made the recommendation that the Secretary of Health and Human Services establish an Advisory Council on Genetics and Public Policy to review such tests and to make such judgments about whether or not they are appropriate for taking up a role as part of general clinical medicine. It will be very interesting to see how that's received.

Mrs. LOWEY. Well, thank you, and I look forward to continue working with you in this area. And I thank you, Mr. Chairman. And I do apologize.

Dr. COLLINS. Thank you, Mrs. Lowey.

Mr. PORTER. Thank you, Mrs. Lowey.

Mr. Miller.

CLONING—INTERNATIONAL COOPERATION

Mr. MILLER. Thank you, Mr. Chairman.

Dr. Collins, I always look forward to your presentation, you're so excited about it. A couple of questions. The Dolly question. Were you caught off guard by that? Was that unexpected, or is that type of research being done here in the United States?

Dr. COLLINS. I was totally caught off guard. This was a result that I think was not expected to succeed. There were preliminary experiments by the same group published a year or so ago, where they were able to take sheep embryo cells and take out the nucleus and then put it back into an oocyte and produce a lamb. But that was less surprising. An embryo cell is sort of programmed to be an embryo cell. The idea that you could take a mammary epithelial cell from the udder of a sheep and convince it to behave that way, that is the profoundly surprising part of this. And I think most people would not have expected that to work.

Clearly, the group that did this work kept it very tightly under wraps. A strong effort was made not to have this leak out prematurely. So no rumors had been circulating.

This kind of research is certainly done in this country, although it is in sort of the animal husbandry area, which is a separate discipline from the folks that are looking at, say, mouse models of human disease using molecular biology. But it has certainly electrified the community. You cannot walk down the hallways of a research building in any university in this country, I don't think, without being engaged in a conversation about Dolly this week.

Mr. MILLER. Was that in an animal husbandry department?

Dr. COLLINS. It's animal science, I guess, it's in an institute in Scotland which is privately funded, and involves a biotechnology company as well.

Mr. MILLER. Is that an embarrassment, to have this—[Laughter.]

Dr. COLLINS. Oh, I can't be embarrassed. I guess as a scientist, I've always been sort of a fan of the notion that science is an international activity. Certainly the Human Genome Project is. And we tend to celebrate exciting advances wherever they come from.

FUTURE HEALTH CARE DELIVERY

Mr. MILLER. When I get a chance to speak to young people, one thing I say is, there are two areas that are so exciting, what the future holds. And it's hard to comprehend what it's going to hold. One is the whole area of telecommunications and computers, which is mind-boggling how far we've come in the past 10 years. I'm not sure where we're going.

But the other area is the area you're in. And it's hard to comprehend what medicine is going to be like. I was speaking to a group, I was even relating that to a group of employees at a hospital last week, health care delivery is going to be very different 10, 20 years from now. How could you describe the potential of the way health care is being delivered 10 years from now? We're on the verge of so much that's happening. People will still grow old, parts will wear out, but the ideas of cancer and all that, how could you describe what a health care delivery system will be like 10 years from now?

Dr. COLLINS. I'll give it a shot. As my old professor of medicine kept reminding me, the death rate will still be one per person. [Laughter.]

We have to have realistic expectations, but I do think there will be stunning advances in the next 20 or 30 years in understanding the basis of the common diseases that so frequently cut people down prematurely, things like cancer and diabetes, hypertension, schizophrenia. This very long list of disorders which we currently can describe the symptoms of and often treat the symptoms of, but whose underpinnings have not really made themselves known.

Obviously, as the geneticist, I will tell you that a significant route to getting to those underpinnings will be our understanding of the genetic contribution to those disorders. We all are walking around, it's estimated, with 5 to 20 genes that are misspelled and that are sort of lurking there, waiting to potentially cause us trouble. You may have a different set than I do, but we all have some. There are no perfect genetic specimens, not even in these hallowed halls of the Congress, I'm afraid.

So the possibility of uncovering those misspellings becomes quite real over the course of the next 10 or 15 years, with the Human Genome Project producing all of these tools. And with that will come the ability to make individualized predictions about risk.

Now, if I knew I was at risk for colon cancer more than the average person, that would be something I'd like to find out about, as long as I was sure it wasn't going to be the end of my health insurance, because I know that colon cancer can be cured if it's detected early, while it's still a small, benign polyp. So you will see, in I would say the next 10 years, you wouldn't have to wait longer than that, the emergence of individualized programs of preventive medicine based on this kind of genetic susceptibility testing, to allow people to design programs for themselves, focused on staying well.

And not just one size fits all, everybody should do the same thing, which is what we often do, but individualized programs based on your own susceptibility. Obviously, that depends on the kind of testing. It has to be voluntary, and I would hasten to say this is the sort of thing that some people maybe won't want to

know, and shouldn't have to know. But I suspect for disorders where interventions are available, a lot of people will be interested.

Now, the therapeutic side of medicine is also going to be going through remarkable changes in the next 20 or 30 years. Whether those come from gene therapy, a field which is still in its infancy and therefore it's hard to tell what kind of kid it's going to be when it grows up, or comes from drug therapies that are really designed to target the precise problem. We were talking about therapies for HPC–1 a minute ago, I'm not sure which therapy will develop and I don't care, as long as it works. And I think there's a good likelihood that you will see many of those things, not tomorrow, not next year, but in the next 20 or 30 years.

Furthermore, medicine will probably become very much influenced by the computer revolution that you mentioned. Things like telemedicine will become much more familiar parts of everyday medical care. I think that's good. I think we have to be cautious about how we oversee that, so that we don't lose the human touch. As a physician, I will argue very strongly that a very important part of medicine is that human touch. And if everything we do ends up being robotized, we've lost something really important and we should resist that.

DESIGNER DRUG STRATEGIES

Mr. MILLER. You mentioned, one area that you mentioned is protease and how the Genome Project had a relationship to that. I see Dr. Fauci is coming up next right behind you.

Dr. COLLINS. Yes, he might disagree with that. [Laughter.]

Mr. MILLER. But what areas have we already seen a relationship to bring out that's available, the relationship for example of protease? What areas are we farthest along as far as providing treatments available on diseases? Is protease a good illustration of that?

Dr. COLLINS. I used it as an example of a designer drug strategy, whereby understanding the genome of HIV, and that was not the Human Genome Project, but that was AIDS researchers working very hard to try to understand this very frustrating, difficult virus, learning that it did make this particular enzyme, this protease, and then figuring out what kind of small molecule could be designed to effect that activity. Then you see this revolution that seems to be happening over the course of the last year, where potentially the course of the illness has been significantly altered. And I'm sure Dr. Fauci will talk more about that. That's the model, the designer drug strategy.

Another example that I guess I would give is in the area of cholesterol management. We have learned a lot about why it is that some individuals have early heart attacks by understanding this disease called familial hypercholesterolemia, which turns out to be rather common, and it's an alteration in a receptor that normally binds to LDL, which is one of the molecules that carries lots of cholesterol. Understanding that genetic alteration led to insights by the Nobel laureates, Brown and Goldstein, which have now put in our hands a whole generation of cholesterol controlling drugs, which are actually very effective. In situations where individuals in the past really didn't have many options other than diet control, which didn't work well, these are now very treatable conditions. It's

another model where gene understanding led to insight about pharmacological therapy and then to the control of a disease which had really been quite resistant. There are others, but that's a particularly attractive one.

I might say, another area of future medicine will be the business of predicting what kind of drug should this person get for this disorder, based on their genetic endowment, pharmacogenetics, as it's sometimes called. It may be that some drugs work particularly well for some people and less well for others. It may be that the toxicity of drugs is determined to some degree by the genes of the host. If we understood that better, and there's a great effort to do so in many pharmaceutical companies, then we could individualize therapies, to avoid the toxic side effects and maximize the benefit.

Mr. PORTER. Thank you, Mr. Miller.

Mr. Wicker.

Mr. WICKER. Thank you, Mr. Chairman.

Dr. Collins, let me ask a question about cloning. And let me just observe, Mr. Chairman, that you have figured out a way to get the television cameras here, just tell people, as you did yesterday, that we're going to talk about cloning, and CNN will show up. And I saw Dr. Varmus last night on Headline News talking about cloning.

Mr. Dickey and I have been whispering about these technical terms that Mr. Miller's been using. We're very impressed.

[Laughter.]

CLONING—POTENTIAL FOR HOAX

Mr. WICKER. I want to try to ask a real layman's question. The Chairman, asked a question about skepticism. And I believe Dr. Varmus used the word science fiction yesterday in talking about this very serious subject. First of all, do you think there's a chance this Dolly experiment might be a hoax? Are you convinced beyond a doubt that it is real?

Dr. COLLINS. I think it's unlikely that it's a hoax, looking at the data and seeing that this is a paper produced by several authors, not just one, certainly the data as presented does indicate that Dolly's genes appear to be identical to the genes of the sheep that donated that mammary epithelial cell, so there wasn't a mix-up of some sort.

I guess I would say it is never possible to sort of look at a published paper and say absolutely for sure this could not be a hoax, but it doesn't seem to have that flavor. I guess what I was saying a moment ago was that science always should be confirmatory. When you have a new result, particularly a surprising one, other people should—and believe me will—be going out to see whether they can reproduce that result. So I think it's very unlikely that it is a hoax.

Mr. WICKER. I have an article about you from the Chicago Tribune. It describes you as a lanky, laconic physician, chemist, geneticist, country music singer, and motorcycle buff. And we should now add former sheep farmer. [Laughter.]

CLONING—WHY A SHEEP

Mr. WICKER. Is there anything about a sheep, and you wouldn't know this from having been a farmer, but as a scientist and geneticist, something about that particular mammal that you think made it an easier candidate for this type of experiment?

Dr. COLLINS. I don't know if there's something unique about it. Certainly one of the motivations for using sheep for this experiment is there's a great deal of interest in using sheep, particularly the ability to put genes into the mammary glands in order to make proteins in sheep milk, which could then be purified and used as pharmaceuticals. So there was a drive from the point of view of the biotechnology industry to try to achieve this in a sheep and not in, say, a horse.

There are a couple of interesting things about sheep. You can operate on the sheep uterus without inducing labor. You can't do that in most other mammals. So there's been a long experience of doing fetal surgery with sheep, which may in some way have played into this. There's a lot of veterinary experience dealing with the sheep reproductive system, because it seems to be more tolerant of interventions during gestation.

Outside of that, I'm not sure that this could not somehow have been done in some other large mammal. It just happened that this group that was doing it was most interested in that particular mammal.

Mr. WICKER. Well, you mentioned a horse. And I was thinking a race horse, you know. [Laughter.]

Dr. COLLINS. Well, you can be sure people in Kentucky are talking about that this week.

Mr. WICKER. Undoubtedly. I appreciate what you and Dr. Varmus have said about the ethical considerations. There are very profound considerations that go into this. But the human is a mammal. And I just want to hear your comments, if you can clone a sheep, and if somebody had the money to pour into the project, is it totally science fiction to assume that a human being could not be cloned?

CLONING HUMANS

Dr. COLLINS. Harold, do you want to jump in?

Dr. VARMUS. I just want to clarify my reference to the term science fiction yesterday. I did not use that term to say that it would not be possible to do similar experiments in humans. What I was pointing out was that there was a lot of science fiction composed around this idea. And that from the point of view of most scientists, this is not where the interesting component of the current experiment lies. The interest lies in the use of animal models, the or understanding of how genes are turned off and on, and the possible exploitation of that for benefit.

Mr. WICKER. Okay, but I really am interested, though, in the answer to the question.

Dr. VARMUS. We acknowledge the possibility that it is possible. I made that clear yesterday. And with not very expensive equipment. However, your question about sheep is right on the mark. We don't really know whether this is a special case. It's impossible

to evaluate how easy it was in the sheep, because remember, starting with an adult cell, it was only 1 case out of almost 300. Now, in someone else's hands, that might have been 1 out of 5,000, in which case it probably wouldn't have happened, because it's too difficult to do. Perhaps in other species, it will prove to be more efficient or less efficient. I think we don't know.

And when Dr. Collins referred to the importance of confirmation of the observation, one of the things that will be interesting is not simply confirming the observation with sheep, but looking in other agricultural animals or for that matter in the mouse. Dr. Collins referred to some interesting notions about aging that could come from these experiments. And it will be very important to try to do this kind of experiment in the mouse.

I point out to you that what is called a clone is not strictly speaking a clone—in fact, less identical than identical twins. The reason for that is that when this experiment is done, you are putting the cell into an environment where there are mitochondria, the small DNA-containing organelles that exist in the cytoplasm—I'm sorry to use the terminology, but——

Mr. WICKER. I'll get Mr. Miller to explain that later.

[Laughter.]

Dr. VARMUS. So there is other DNA, there is DNA outside of the nucleus, in the cytoplasm of our cells, which is in Dolly, but was not in the donor. That's important. So it's not truly a clone.

Moreover, as Dr. Collins mentions, the cells that came from the donor have been through many, many duplications. In the course of those duplications, there were almost certainly mutations introduced into the DNA. We don't know the effect of those mutations. But it makes Dolly different from the fertilized egg that gave rise to the donor.

HUMAN EMBRYO RESEARCH

Mr. WICKER. Okay. Let me just ask a quick question, for either one of you. The case of Dr. Mark Hughes. I wonder if you could comment on that. He was forced to leave NIH because it turned out he was using Government equipment to conduct human embryo research in violation of the so-called Dickey–Wicker amendment.

In that case, I understand it was disputed who alerted NIH. And I just wonder, how confident we can be that other situations like this don't exist and what steps are being taken to make sure of this?

Dr. VARMUS. Perhaps I should answer that, Mr. Wicker. Obviously, as in the case of any law, all we can do is look for offenders and be sure that people understand the law. There is no doubt that Dr. Hughes understood the law. It was explained to him by many people, including myself. The intramural NIH research program was fully aware of the law. Anyone who had applied to the NIH for grants to do work that could involve human embryo research not only was informed, but had signed a statement saying that they knew that in receiving money from the NIH, they were not to use any of that money to do that kind of work.

We have put reminders in light of the evidence about Dr. Hughes on our Web site. The Department of HHS has sent to all institutions that receive our grants reminders about your amendment as

well as other restrictions on the use of our money. We've made every effort to be sure that our grantee institutions and our grantee scientists understand what the law is, and we expect them to follow it.

Mr. PORTER. Mr. Dickey.

Mr. DICKEY. Thank you, Mr. Chairman.

I apologize for not being here yesterday. It wasn't because the cameras were here. I know I'm kind of a shy guy and I'm sometimes afraid of the cameras, but it wasn't for that reason.

I'm concerned overall, and I've expressed to you my concern about the Dickey-Wicker amendment. And I think I've settled that. But I'm concerned overall that we might not be progressing toward cures, and we might be distracted by giving appropriations to more areas. Can you help me with that? Is that question clear?

Dr. VARMUS. No.

Mr. DICKEY. What I'm concerned about, as I look at the expenditures, we're taking money away from heart disease, and cancer and so forth. Or stated another way, we have money that we're sending to other areas of responsibility like diabetes, for example; we could be taking that money and bearing down more toward a cure.

Tell me how I'm wrong in that perception.

Dr. VARMUS. Again, I'm not quite sure where you get this idea that we're taking money away from those areas. All areas of research could be aided by additional funds. There are various ways to evaluate whether the amount we're spending in different areas is appropriate; it may seem appropriate to some and not to others.

We believe that the money that we spend is all directed toward alleviation of human suffering, and that the calculus that one uses to determine what is correct may vary from calculator to calculator. But it's not the case that there is money being taken away from the areas you've mentioned. Every area you've mentioned is an area that has received increases over the last several years. Not always equal to the increases that are received by every component of NIH for example, as we discussed earlier, the Genome Center, now Institute, has been "ramping up," in Francis Collins' words, more rapidly, because it began from a very low level. A very similar argument could be made for the funding of AIDS research, which for a time "ramped up" quickly. Now it receives the same increase as every other area of NIH. Breast cancer research was "ramped up" some years ago as were Alzheimer's, and tuberculosis research, in response to specific needs. We've been funding research on diabetes and heart disease and cancer for many years, at quite generous levels. We believe that we respond to the scientific opportunities and that great progress is being made in all the areas that you mentioned.

So I would take issue with the general contention that we are taking money away from these areas of serious medical concern, and I'm not quite sure where you think the money is going where it's not deserved. Maybe you could be more explicit about that for me.

Mr. DICKEY. I just got the impression, and I just watched it, diabetes is one particular thing that I've gotten concerned about because of a friend of mine's loss of his daughter, 32 year old daugh-

ter. I think it was heart complications of diabetes that caused her to lose her heart functions.

Now, I get this idea (and I don't think I can support it factually) that we are, that some things are old hat and we're making progress; however we're not really going to war in certain areas. Heart disease, for instance, let's see, $28 billion was spent out of Medicare for heart disease, covering some 17 million, 18 million patients. Now, I don't see an intensity of that going at the heart disease, and saying, we're closer, we're closer, we're closer. Is that an accurate observation?

Dr. VARMUS. I don't believe it is, sir. And I say that for a number of reasons. One is that we've made tremendous strides in the treatment of heart disease and prevention of heart disease over the last 20 or 30 years. So the mortality rates have fallen by about 50 percent. That doesn't mean that we're there. There's still a very high burden of disease, especially with the aging of the population. We have a number of very important initiatives, and you'll hear about them next week. We spend over $1 billion a year on a variety of research on the heart and the vessels. As you know, much of the heart disease that we have in our society is due to diseases of the vessels. You could read yesterday's testimony about the intensity of research on the process we call angiogenesis. That's a word, Mr. Miller, that refers to our understanding of how blood vessels are generated. [Laughter.]

It is a very, very important new field of research, because if blood supply to an organ like the heart or the brain is impaired, obviously what we would like is a way to replenish the blood supply by making new blood vessels. And we've learned largely from research in cancer new ways to do that.

Mr. DICKEY. Let me interrupt you, because I'm afraid my time's run out. From what I understand, NIH over the last 10 years appropriation has increased 98 percent. Diabetes, from that appropriation, diabetes has increased only 32 percent. Maybe that is a way of describing what I'm trying to say. In other words, just taking diabetes, it hasn't increased, as we increased your appropriation, diabetes has gotten a lesser——

Dr. VARMUS. Well, I don't know, I'd have to look at the source of those numbers. It probably is the case that if you look at the numbers over that long a period, you may see a lower than average increase because a number of things have expanded in a very major way because of the growth of the genetic enterprise or because of the growth of our expenses to respond to the AIDS epidemic or in response to Alzheimer's, which has become an increasing problem.

But I think if you look at diabetes research broadly and analyze the way in which diabetes research is being affected by other disciplines, you will get a different picture. Let me give you one very pertinent example. The kind of work that Dr. Collins and the Genome Institute have done has allowed in the last year the isolation of two genes that have been studied for totally different reasons that are responsible for two inherited forms of diabetes called maturity onset diabetes of the young. These are remarkable opportunities, inspirations, if you will, for understanding diabetes at the fundamental level.

I will also point out to you that we have made tremendous progress in diabetes. You can read the transcript of Dr. Kupfer's performance yesterday, and you'll see that we now have the means to treat diabetic retinopathy very effectively. One of the problems in caring for diabetics at the moment is persuading patients and physicians to respond to the new information that we've accrued over the last several years by studying the long-term complications of diabetes. As the death of your friend's daughter illustrates, we know that diabetes affects blood vessels and nerves and kidneys and eyes. We also have learned that careful control of diabetes, which is difficult to achieve and requires patience and hard work, has a major effect in reducing the morbidity of the complications of diabetes. So a large part of the problem in diabetic morbidity has to do with taking the discoveries that have been made with NIH research and getting them applied in the clinic.

Mr. DICKEY. I really believe that my support of what you're doing has a lot to do with the intensity of the commitment. And I just don't want you all to let up. I mean, you all are scientists and I'm where I am. But I'm just saying, it's the intensity, and it's just pushing forward. It's the cure that we need to go after. Diabetes is only an example.

Dr. VARMUS. I appreciate your comments. And I hope you'll come to hear from Dr. Gordon and Dr. Lenfant, who will address some of these issues.

Mr. DICKEY. As long as there aren't any cameras. [Laughter.]

Thank you, Dr. Varmus.

Mr. PORTER. Thank you, Mr. Dickey.

Before I call on Ms. DeLauro, I want to say that the situation is a very unfortunate one that we are running out of time. And we have asked Dr. Fauci if he might stay a little bit later. The Chair intends to go until 12:30 with Dr. Fauci. And Dr. Varmus, I am feeling that we are not allowing sufficient time in some instances. And I would ask that we consider perhaps bringing back yourself and certain institute directors later in the year, if we feel we really haven't had a thorough opportunity to look at the situation in each of those institutes.

Dr. VARMUS. We would be delighted to do that.

Mr. PORTER. I know how valuable your time is, and I don't want to burden you, but I also don't want members of the subcommittee to feel they haven't had a real opportunity to discuss things that are on their minds with you.

Ms. DeLauro.

GENETIC DISCRIMINATION AND PRIVACY

Ms. DELAURO. I'm very supportive of what this project and this institute is about, in terms of what it means to our ability to identify therapies or cures in the long-term. I think it's one of the most important efforts that we have taken.

One of the concerns that I have is there are about 40 million people today who are not covered by health insurance in this country. We've got tremendous advances in medical technology like the human genome map. What concerns me is that in the future you may have someone who tests positive for a mutated gene that could yield breast cancer at some point in their lifetime, and they will

not be able to get any kind of preventive care in order to avoid that disease.

You have a landscape with insurance coverage today that potentially may make it very difficult, once we've got this wonderful discovery, she may be left without any recourse, unable to deal with it. I mean, the question is, and I'm struggling with the question here myself, with what you are doing and what you are able to uncover in the Human Genome Project, will it help or hurt individuals with little or no health care coverage in the future? That may not be specifically what you are about, but we're dealing with what science is uncovering and what is happening to the people at the other end of the process.

Dr. COLLINS. It's a very serious matter. We are, among all Westernized, civilized countries, the one that seems most willing to let the largest fraction of our own population be in a circumstance where they can't get access to health care. And you really do look at that and wonder, how did this happen.

I don't think that the genetic aspect of medical care is particularly different from the rest of medical care. If you're not covered, you're not covered, and that's a serious tragedy, and one which I think this Congress seems interested in addressing, albeit maybe not in the overarching way that was discussed a couple or three years ago.

Ms. DELAURO. I get scared about pre-existing conditions.

Dr. COLLINS. Well, sure. There are two areas that we can and should start to fix, even within our existing flawed health care system. And I sort of think of these as the two pillars of a building. And one of them is privacy and the other is avoiding discrimination. The avoiding discrimination pillar, in order to really be robustly protective, requires Federal legislation to make it illegal for health insurers to use genetic information to deny coverage or to set exorbitant premiums. And Kassebaum-Kennedy moves in that direction in a very gratifying way, if you're in a group policy. For individual policies, it's much less protective. Efforts are underway in the current Congress to do something about that as for instance, Congresswoman Slaughter announced yesterday legislation that I think highly appropriate.

Discrimination comes in other flavors besides health insurance. Employment issues need to be addressed as well.

The other pillar is privacy and confidentiality. Not only should third parties not be able to use this genetic information against you, they really shouldn't be able to see it unless you tell them it's okay. And if you have one of those pillars without the other, the building still falls down.

We really need a way to protect medical records in this country. Right now, it's ridiculous. If you start counting up the number of people that can look at your medical records, you sort of get tired after 100, because it just keeps getting bigger and bigger. And there is no meaningful control of that process. Clearly that is an area of great concern amongst the public and in the Congress. There are at least three bills this year that are being introduced or will be shortly.

My own view is that you can't take the genetics part of the medical record and set it in a separate category and say we're going to

apply protections to that and not worry about the rest. Because which part is the genetic part? Every disease has a genetic component. Everything in your medical chart, if you want to look at it with really a hard, cold eye, you could say there is some familial contribution. It's not possible to separate the information.

So to solve the privacy issue for genetics, we have to solve it for the whole medical record. And I certainly think that ought to be a very high priority, especially as more and more of this information becomes electronic, and maybe it gets easier therefore to eavesdrop in places that the patient would not allow had they known.

So I think every possible effort ought to be made. I must say, I'm very gratified, after four or five years of bringing up these topics and not receiving much enthusiasm, now one sees in many areas on both sides of the aisle in both houses of the Congress, a good deal of interest in doing something about this. And in the case of Kassebaum-Kennedy, an actual piece of legislation has been passed and signed.

Ms. DELAURO. Well, I think it's important to have your voice engaged in this discussion, because I think it's a very important road we're going down.

Dr. COLLINS. I couldn't agree more.

Ms. DELAURO. These are uncharted areas in a whole variety of these cases. And we truly do need to make sure we're going to continue with discovery part of it, and then how do we ensure, that we can protect the individual.

Dr. COLLINS. The greatest tragedy would be if this project is scientifically successful but socially unacceptable. And you have this wonderfully powerful new brand of medicine which has promise to save many lives, but nobody wants to have anything to do with it, because they're fearful that the information will get used against them. What a terrible stillbirth that would be. Yet, we can prevent that if we act now.

Ms. DELAURO. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. DeLauro.

Mr. Hoyer.

Mr. HOYER. No questions, Mr. Chairman.

Mr. PORTER. Dr. Collins, thank you for the marvelous work that you do at your new institute, and for your always fascinating testimony. We very much appreciate that.

I suspect that the subcommittee may want to ask you to come back, perhaps for another hour, sometime later in the year.

Dr. COLLINS. I'd be delighted.

Mr. PORTER. If we do, I hope that you would be able to respond. We do respect your very, very busy schedule and Dr. Varmus'. Sometimes these hearings are just too short to get really deeply into this. I have pages of questions I haven't been able to ask and I really want to ask them.

So again, we appreciate your testimony today, and hope you remain ready to come back. If we ask you, would you?

Dr. COLLINS. I am most ready at your wish, by all means.

Mr. PORTER. Thank you very much.

The subcommittee will stand in recess briefly.

[The following questions were submitted to be answered for the record.]

INSTITUTE DESIGNATION

Mr. Porter: What statutory authority permits the Secretary to redesignate your Center an Institute through administrative action? Does elevation to Institute status change any aspect of the day-to-day functioning of your organization or generate additional administrative expense?

Dr. Collins: The National Center for Human Genome Research (NCHGR) was created as an Office within the Office of the Director, NIH, on October 1, 1988. One year later, the Secretary, Department of Health and Human Services elevated the Office to the status of Center. As a Center, NCHGR had a separate appropriation and authority to award research grants. It was not appropriate to designate NCHGR as an Institute at that time, because it had a small budget of only $59,538,000, a ceiling of only 30 FTEs and did not have an Intramural Program.

By FY 1996, the NCHGR had developed to the point where its size, functions, responsibilities and organizational structure were comparable in virtually every way to the NIH research Institutes. The FY 1996 budget was $170,041,000 with an FTE ceiling of 192, and most importantly, the Center had developed a substantial and highly productive Intramural Program. The Center was the NIH focal point for, and the major player in the worldwide Human Genome Project. The advent of the Intramural Program had greatly expanded the Center's mission in the advancement of research in human genetic disease and the development of better diagnostics, animal models, and gene therapy.

The Secretary of the Department of Health and Human Services may establish "national institutes" at the NIH after providing Congress with a 180 day notice, as stated in Title IV, Section 401(c)(1)(B) of the Public Health Service Act. Letters were sent to the Chairmen and Ranking Members of the Senate Committee on Labor and Human Resources and the House Committee on Commerce, on July 17, 1996. On January 14, 1997, Secretary Shalala conferred Institute status on the NCHGR.

Designating the Center as a research Institute provided recognition of its expanded mission and acknowledges the Center's role as an NIH focal point for human genome research and an important contributor to research in gene identification, disease gene biology, diagnostics, and gene therapy. It also provided the new Institute with appropriate status for Federal inter-agency coordination, collaboration with industry, academia and international organizations in the field of genomic research and medical genetics. Institute status gave the Director equal standing with other Institute Directors and will facilitate collaboration with other Institutes on numerous scientific activities. Further, Institute status enhances the Center's ability to attract and retain outstanding scientists in the Intramural Program.

It is important to note that becoming an Institute **was budget neutral** and did not require an increase of funds or of FTEs. Further, Institute status did not result in any reorganization or affect employee grades or pay, since the NCHGR was already organized in the same way as the NIH Institutes.

There were certain legislative reasons for designating NCHGR as an Institute. Section 401 of the PHS Act describes the NIH as being composed of two types of "agencies": the "national research institutes" and four "entities" (NCRR, FIC, NCHGR and NLM). Section 405 of the Act provides authorities to each national research institute, but not to the "entities." Examples of the authorities that the Center lacked were the ability to make awards ($50,000 or less) without Advisory Council approval and flexibility to publish materials more efficiently and in a more timely fashion, without the need for extensive and time-consuming clearances.

FINISHING FASTER - ADDITIONAL FUNDS NEEDED

Mr. Bonilla: Dr. Collins, your Institute has grown at a faster rate than any other in recent years and the results have been quite gratifying. For example, your success with identifying the existence and probable location of the Parkinson's and prostate cancer genes in the past year has been a significant step forward. If you had a year to plan for it - if the administration were to request it and Congress were to approve it - how much additional money could your Institute responsibly spend, in FY 99, and to what degree would spending that money now shorten the amount of time it would take to complete this first phase of sequencing the human genome?

Dr. Collins: NHGRI appreciates the enthusiam the Administration and the Congress has shown for the Human Genome Project, and is grateful for the budget increases provided in FY 1997 and proposed by the President for FY 1998. We currently have 6 pilot projects underway, testing various approaches to large scale human DNA sequencing. These projects will undergo a thorough evaluation this fall and we expect that a number of them will then be ready to start scaling up substantially the amount of sequence they can produce. Within the President's FY 1998 budget, we have allocated $60 million for this effort. We have estimated that, assuming a more or less level budget with only inflationary increases, we can finish the first human sequence by 2005. With a higher level of funding it may be possible to finish one or two years earlier.

Mr. Bonilla: Alternatively, if your budget growth were slowed - to the overall NIH rate - what would be the impact on the kind of discoveries that are made and what would be the impact on the anticipated completion date of the project?

Dr. Collins: If our budget increases are kept equal to those of NIH, we are still hopeful that we can finish the human DNA sequence on schedule. This would be our first priority; however, we would then be limited in our ability to support related research that would be needed to interpret the DNA sequence. For example, most scientists believe it is critical to study the mouse genome side by side with the human genome in order to understand the meaning of the DNA sequence. With level funding our support for the sequencing of mouse DNA would be constrained. Other efforts at interpreting the DNA sequence would also be slowed.

GENETIC TESTING GUIDANCE

Mr. Wicker: In a recent article in the Chicago Tribune, you were quoted as saying that your worries about gene testing were, "That we will not be careful enough. That the public will get turned off by a few examples where genetics seems to have harmed somebody. Then this wonderful new technology with so much promise, would essentially be stillborn." What guidance is the Institute following to insure that fears don't become a reality?

Dr. Collins: When the Human Genome Project was being established, concerns were raised about how the new genetic information would be used and how individuals and society could be protected from possible harm. The Ethical, Legal, and Social Implications (ELSI) Research Program was developed at NHGRI (and at the Department of Energy) to examine these issues and assist in the development of policy recommendations and guidelines to ensure that genetic information is used appropriately. To accomplish this, the ELSI program was charged with (1) developing a program to help understand the implications of the Human Genome Project and (2) identifying and defining the major issues of concern and developing initial policy options to address them.

To accomplish these goals, the NHGRI ELSI Program has established a number of functional components to address specific areas. The ELSI Research Program, which funds extramural researchers, has funded 126 research and education projects in more than 30 states, that have resulted in increased understanding of ELSI issues, the development of education programs for health professionals and the general public, and the establishment of policy recommendations regarding topics such as the use of genetic tests and prevention of discrimination based on genetic information. This research provides the basic knowledge from which policy recommendations and guidance can proceed. The common theme in all of these projects has been the desire to identify and address ethical, legal, and social issues before they become problems for society, a model that has been subsequently adopted by other nations involved in the Human Genome Project. Four high priority areas have emerged: privacy and fairness in the use and interpretation of genetic information; clinical integration of new technologies; issues surrounding genetics research; and public and professional education.

In addition to the extramural ELSI Research program, three other functional components of the NHGRI have been established to address specific areas. An NIH/DOE ELSI Working Group on Ethical, Legal, and Social Issues in Human Genome Research (The ELSI Working Group) was established to provide guidance on policy issues arising from the Human Genome Project. A variety of specific and important products could be cited. In 1993, the ELSI Working Group created a Task Force on Genetic Information and Health Insurance. In 1995, the ELSI Working Group and the National Action Plan on Breast Cancer developed and published recommendations for state and federal policy makers to protect against genetic discrimination in health insurance (*Science*, vol. 270, Oct. 20, 1995). Several state and federal legislatures have proposed and passed legislation based on these recommendations.

Following the success of the 1995 collaboration, in October 1996, the National Action Plan on Breast Cancer held a workshop with the ELSI Working Group to address issues surrounding genetic information and the workplace. Recommendations from this workshop are now in press in *Science*.

In 1995, the ELSI Working Group established a Task Force on Genetic Testing, to examine the development and delivery of safe and effective genetic tests and the quality of the laboratories providing the tests. The Task Force includes representatives from the biotechnology industry, professional medical and genetics societies, the insurance industry, consumers, and federal agencies. In light of the rapid pace of disease-gene discovery and genetic test development, the findings of the Task Force will be crucial to the development of sound policies and practices for the introduction of new genetic tests. The group has published its initial recommendations in the *Federal Register* and will reconvene later this spring to consider the comments received from this notice and to prepare its final recommendations.

The NHGRI has created two other components of the ELSI program to provide detailed guidance on research and policy issues. In 1995 the Office of Policy Coordination was created in the Office of the NHGRI Director to address specific policy questions raised by the Human Genome Project. In 1996, an intramural component of the ELSI Program, the Office of Genome Ethics, was created to provide specific advice to NHGRI research in the intramural program.

Taken together, these components of the ELSI program provide NHGRI with constructive guidance on the issues that are of most pressing concern.

LARGE SCALE SEQUENCING

Ms. Northup: Your pilot program for large scale sequencing is located at six U.S. research centers. Where are these centers located?

Dr. Collins: The pilot projects are being carried out in laboratories at Washington University (St. Louis, MO), Baylor College of Medicine (Houston, TX), Stanford University (Palo Alto, CA), the University of Washington (Seattle, WA), the Whitehead Institute for Biomedical Research (Cambridge, MA), and The Institute for Genomic Research (Rockville, MD).

Ms. Northup: How would the initiative that you mentioned in your testimony streamline and cut the cost of DNA sequencing?

Dr. Collins: The purpose of the pilot project initiative is to develop and test technologies and strategies for full-scale production sequencing of human DNA. The goal is to obtain the first complete, accurate, finished human DNA sequence by the year 2005. When the pilot projects were initiated in 1995, it was evident that considerable improvement would still be necessary if this goal was to be met. Progress has been made in the first year of the pilot project program, but more is still needed.

Through the efforts of the investigators presently engaged in large-scale DNA sequencing, the process is being increasingly automated (which has the effect of reducing labor costs), the capacity of the instruments is being significantly increased (making those instruments much more efficient), the amount of material needed in the sequencing process is being reduced (lowering the materials cost for sequencing), and the systems for data analysis are being improved (speeding and simplifying the finishing component, which is always the most expensive). We are confident that all of these improvements will allow us to finish the human sequence on time and within the projected budget.

Ms. Northup: How expensive is DNA sequencing?

Dr. Collins: Because DNA sequencing at the scale that is necessary to accomplish the goals of the Human Genome Project is still undergoing considerable experimental development, the current costs are hard to estimate. It is, for example, difficult to distinguish the costs of technology development from sequencing costs when the sequencing is being done in order to test process improvements, which is the stage that most of the pilot projects are in. However, as best as can be estimated, sequencing costs appear to be steadily decreasing and the most advanced efforts are reporting costs in the range of $0.40 to $0.60 per base.

CENTER FOR INHERITED DISEASE RESEARCH

Ms. Northup: How much funding are you going to allocate for the Center for Inherited Disease Research?

Dr. Collins: The Center for Inherited Disease Research (CIDR) is funded through an NIH inter-Institute agreement with NHGRI as the lead agency and participation by seven other Institutes. The 5-year contract to operate the CIDR facility is for $21,790,411. Additional infrastructure support is provided directly by the intramural program of the NHGRI.

Ms. Northup: How will priorities be set within the Center, regarding which diseases to research?

Dr. Collins: All applications requesting access to the Center for Inherited Disease Research (CIDR) will be reviewed for scientific and technical merit by panels of outside experts. Factors that will be weighed by these peer review groups include, but are not limited to, the scientific or medical significance of the proposed research project, the applicant's experimental design, the qualifications and experience of the investigators, and the resources available to them.

Only applications deemed to be of high scientific merit will be potential candidates for access to the CIDR facility. The final decision about which projects may use the CIDR facility will be made by the CIDR Access Committee, a chartered committee of outstanding scientists, expert in the analysis of complex diseases, and the Board of Governors, the governing body of CIDR. The Board is comprised of the eight Institute directors that are contributing funds to the contract, as well as two non-voting members: the CIDR Director and a representative of Johns Hopkins University, the contractor for this facility.

PRIVACY AND DISCRIMINATION

Ms. Northup: You briefly mentioned your concerns about how information about a person's genetic makeup could affect public policies regarding insurance coverage. Could you provide for the record the recommendations referred to you relating to genetic discrimination in employment. Also could you be more specific on what the ELSI-NAPBC team is doing to address privacy issues.

Dr. Collins: The NAPBC and ELSI Working Group have developed the following recommendations to offer guidance for state and federal policy makers to protect against genetic discrimination and to promote privacy in the workplace. These recommendations were published in Science magazine on March 21, 1997.

- Employment organizations should be prohibited from using genetic information to affect the hiring of an individual or to affect the terms, conditions, privileges, benefits, or termination of employment unless the employment organization can

prove this information is directly job related and consistent with business necessity.

- Employment organizations should be prohibited from requesting or requiring collection or disclosure of genetic information prior to a conditional offer of employment and, under all other circumstances, employment organizations should be prohibited from requesting or requiring collection or disclosure of genetic information unless the employment organization can prove this information is directly job related and consistent with business necessity or otherwise mandated by law. Written and informed consent should be required for each request, collection, or disclosure.

- Employment organizations should be restricted from access to genetic information contained in medical records released by individuals as a condition of employment, in claims filed for reimbursement of health care costs, and other sources.

- Employment organizations should be prohibited from releasing genetic information without prior written authorization of the individual. Written authorization should be required for each disclosure and include to whom the disclosure will be made.

- Violators of these provisions should be subject to strong enforcement mechanisms, including a private right of action.

Recommendations to help ensure the privacy of genetic information were included in both the NAPBC-ELSI Working Group recommendations on health insurance and the recommendations on employment. The NAPBC is continuing consideration of this important topic.

Ms. Northup: In regard to genetic testing, who will be involved in the conference that NHGRI is cosponsoring this spring?

Dr. Collins: The NHGRI Spring 1997 consensus development conference will bring together researchers, health care providers, epidemiologists, geneticists, ethicists and other experts, as well as representatives of the public, to present and discuss the latest data on the use of genetic testing for Cystic Fibrosis. After 1 ½ days of presentations of research data and audience discussion, an independent, non-Federal consensus panel will weigh the scientific evidence and write a draft statement that it will present to the audience on the third day. This statement will provide recommendations on the appropriate uses of genetic testing for CF in specific populations and in the general population.

Ms. Northup: Are you including insurers?

Dr. Collins: The meeting is open to the public and can be attended by anyone with an interest in the topic. However, given the NIH Consensus Development

Conference conflict of interest policies, individuals or companies with a vested interest in the outcome of the conference are not asked to serve on the panel. The speakers at the conference are selected for their expertise in the topic area and their ability to present and discuss their latest research findings. While none of the conference speakers represent insurance companies, two of the speakers are employed by managed care organizations.

BUREAUCRATIC

Ms. Northup: In reading and listening to your testimony, I can't help but feel that your agency is quite bureaucratic in relation to the number of Working Groups and Task Forces involved in certain issues. Do you believe that this is a fair assessment and, if not, why not?

Dr. Collins: No, I do not believe that it is a fair assessment. The Human Genome Project has, since its inception, been a tightly planned project, with clearly articulated, well-defined goals and implementation strategies. These plans and strategies have been developed by NHGRI staff working with a large number of members of the scientific, scholarly, consumer, and public communities who have participated in a number of meetings, committees, working groups, and task forces. Both the overall success of the Human Genome Project to date, as well as the success in addressing individual issues, are due to the sophisticated planning and continuous evaluation that has taken place. However, in almost every case, the bodies that have been assembled to provide us with advice and guidance have been short-lived; as soon as they have accomplished their task, they have been disbanded. Thus, I believe that rather than being bureaucratic, the Human Genome Project has made creative and effective use of these committees to involve various communities in the planning, carrying out, and evaluation of the Human Genome Project.

NEWEST RESEARCH INSTITUTE

Mr. Stokes: As you have indicated in your opening statement, the "National Human Genome Research Center" has recently become the newest "Research Institute" of the National Institutes of Health. What impact will this new designation have on the way the Institute does business: What new opportunities will be made available to you that did not exist for you as a Center? What new opportunities will now be exploited?

Dr. Collins: The National Center for Human Genome Research (NCHGR) was created as an Office within the Office of the Director, NIH, on October 1, 1988. One year later, the Secretary, Department of Health and Human Services (DHHS) elevated the Office to the status of Center. As a Center, NCHGR had a separate appropriation and authority to award research grants. By FY 1996, the NCHGR had developed to the point where its size, functions, responsibilities and organizational structure were comparable to the NIH research Institutes. The FY 1996 budget was $170,041,000 with an FTE ceiling of 192, and most importantly, the Center had developed a substantial and highly productive Intramural Program. The advent of the Intramural Program had greatly expanded the Center's mission in the advancement of research in human genetic disease and the development of better diagnostics, animal models, and gene therapy. Thus, on January 14, 1997, Secretary Shalala conferred Institute status on the NCHGR.

Designating the Center as a research Institute provided recognition of its expanded mission and acknowledged the Center's role as an NIH focal point for human genome research and an important contributor to research in gene identification, disease gene biology, diagnostics, and gene therapy. Institute status gave the Director equal standing with other Institute Directors and will facilitate collaboration with other Institutes on numerous scientific activities. Further, Institute status enhances the Center's ability to attract and retain outstanding scientists in the Intramural Program.

It is important to note that becoming an Institute **was budget neutral** and did not require an increase of funds or of FTEs. Further, Institute status did not change the mission of the organization nor result in any reorganization or affect employee grades or pay.

There were certain legislative reasons for designating NCHGR as an Institute. Section 401 of the PHS Act describes the NIH as being composed of two types of "agencies": the "national research institutes" and four "entities" (NCRR, FIC, NCHGR, and NLM). Section 405 of the Act provides authorities to each national research institute, but not to the "entities." Examples of the authorities that the Center lacked were the ability to make awards ($50,000 or less) without Advisory Council approval, and flexibility and efficiency to publish materials in a more timely fashion, without the need for the extensive and time-consuming clearances.

MINORITIES AND WOMEN

Mr. Stokes: As you are aware, African Americans and other minorities are disproportionately impacted by a number of diseases from cardiovascular diseases to diabetes to cancer to AIDS. To what extent is the institute investigating diseases that disproportionately affect minorities?

Dr. Collins: NHGRI intramural scientists have worked closely with the NIH Office of Research on Minority Health to initiate several programs in partnership with Howard University. The first of these projects, a study of the West African origins of genetic susceptibility to non-insulin dependent diabetes mellitus in African-Americans, has resulted in the issuance of a Request for Proposals, funded by the Office of Research on Minority Health. Proposals for this study, which will be coordinated by scientists at Howard University, have been reviewed and five chosen for funding. All five principal investigators are from West Africa: two from Ghana and three from Nigeria. A meeting of the principal investigators took place in early February 1997 and work has now begun.

The second of these projects, also in collaboration with Howard University, is a proposal to study the genetics and epidemiology of prostate cancer in African-Americans. Prostate cancer is a major cause of morbidity and mortality among African-American men. The identification of genes predisposing African-Americans to prostate cancer should contribute to earlier diagnosis and more effective interventions. The Office of Research on Minority Health provided support for the planning phase of such a prostate cancer study, and Howard University and NHGRI intramural scientists have begun to develop the scientific objectives for this project, with the intent to issue a Request for Proposals in the next two months.

The NHGRI, in collaboration with the Office of Research on Minority Health, plans to expand its array of research projects on genetic susceptibility to diseases that disproportionately cause disease or death in African-Americans, including breast cancer and hypertension. Consideration of the ethical, legal, and social issues raised by the research in these studies will be a significant component of these efforts as well.

Mr. Stokes: It is thought that the increased participation of minorities and women in the conduct of research and research training, in research decision making, and in clinical trials would help tremendously to further advances in such disease categories. What activities are underway and planned at the institute to increase the participation of women and minorities both as investigators and as subjects?

Dr. Collins: We are fortunate in genetics, in that the participation of women as investigators is relatively high. The same is true for participation as research subjects, as genetics research requires the study of both males and females, indeed of whole families. The situation with respect to minorities is more difficult. We have taken a number of steps to increase the number of minority investigators in genetics research. In the intramural program, in addition to the collaboration with Howard University described above, we run a number of training programs for minority students and faculty.

Extramurally, we have funded a substantial number of pre-doctoral fellowships for minority students. In the ELSI program we are funding several projects that are studying the psycho-social impact of genetic testing in minority populations. The initiative mentioned above specifically aims to enroll minorities in studies of the genetics of diabetes and prostate cancer. We are committed to continuing these efforts and to initiating new ones as the opportunities arise.

PROGRESS

Mr. Stokes: According to the opening statement, the genetic maps are complete, the physical maps are nearly so, and both are in wide use by the scientific community. What are the primary implications of this accelerated success -- as it relates to expediting improvements in the health of the American people.

Dr. Collins: Mr. Stokes, the completion of the genetic maps and the near completion of the physical maps of the human genome have already had a dramatic effect on health research. The effect has been both direct and indirect. Directly, these maps have expedited the discovery of disease genes. For example, genes that when mutated can predispose to breast cancer or prostate cancer have recently been mapped. Such a discovery can very quickly lead to the availability of a genetic test for the mutated gene, so that individuals who are at high risk can be identified. More importantly, in the long run, the discovery of a gene involved in a disease provides a tremendous stimulus for research on the disease and opens up many avenues for new discoveries about the mechanism of the disease. Eventually this research will lead to new preventive and therapeutic interventions.

The availability of genetic and physical maps of the human genome has also indirectly stimulated research on the basic understanding of cellular function. Such knowledge is fundamental to understanding the mechanism of all diseases as well as to the development of treatments.

Mr. Stokes: The budget submission speaks about an online map that pinpoints the locations of over 16 thousand human genes. How useful is access to this information in its current form?

Dr. Collins: The map is accessible to both the scientific community and the general public through the Internet (http://www.ncbi.nlm.nih.gov/SCIENCE96/). The map, which is the product of an international consortium of five laboratories and over 100 scientists, was converted into a Web Site by investigators in the National Library of Medicine and is useful both as a research tool for the scientific community and as an educational tool for the general public. For example, it provides information about a number of genes associated with important diseases in a readily understandable format. The Human Transcript Map Web site has been visited many thousands of times since it was opened up and many of the users have been students.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS WORKING GROUP

Mr. Stokes: According to the opening statement, in 1996, 21 disease genes were isolated using genome maps--almost twice as many as the year before and nearly five times the number isolated the year the genome project began. This speed of success is amazing. While we can be encouraged by this rate of success, we have to be concerned and work hard to ensure that the ethical, legal, and social implications do not lag seriously behind or worse fall through the cracks and go unaddressed. We have been hearing a great deal about the activities of the Ethical, Legal, and Social Implications Working Group sponsored Task Force on Genetic Testing. To what extent can you comment at this time on the Task Force recommendations which are expected to be released this Spring?

Dr. Collins: Genetic testing is a new medical intervention for which the regulatory and legal controls are unclear. In general, predictive genetic testing should not be offered without knowing the reliability and validity of the tests in high-risk families and in the general population, as well as the safety and effectiveness of medical interventions for people who are found to carry inherited alterations that put them at high risk for disease. Recognizing the need for public policy in this area, the ELSI Working Group established, in early 1995, the Task Force on Genetic Testing. The Task Force has examined the strengths and weaknesses of current practices and policies relating to the development and delivery of safe and effective genetic tests and the quality of laboratories providing the tests.

The Task Force has approached its work in two stages. The first stage was the development of the framework for its recommendations, known as the Interim Principles. These Principles were released for public comment in March 1996. The second stage, which is now nearly complete, is the formulation of recommendations to implement these principles. These recommendations will address the scientific and clinical validity of genetic tests, the quality of laboratories performing genetic tests, and appropriate education and counseling that should accompany the delivery of genetic tests. Draft recommendations were published for public comment in mid-January 1997 and final recommendations will be reported to the National Advisory Council for Human Genome Research in Spring 1997. Some of the key recommendations in the current draft are:

- The Task Force calls for a Secretarial level Advisory Committee on Genetics and Public Policy. Until such a committee is established, they urge the Secretary to use existing agencies and policies to protect the public in the area of predictive genetic testing to the extent possible.

- Criteria are proposed for ranking tests according to the level of scrutiny needed before a test can be used. The characteristics of the disease, the characteristics of the test, and the intended predictive uses will determine the level, or stringency, of scrutiny needed.

- A National Genetics Board (NGB) should be established by the Secretarial Advisory Committee to ensure protection of human subjects in the development of genetic tests. The Board would review protocols requiring stringent scrutiny referred to them by IRBs.

- Laboratory proficiency testing and quality assurance should be accomplished by establishing a genetics advisory board to the Clinical Laboratory Improvement Amendments (CLIA) Advisory Committee and by adopting the accreditation program established by the College of American Pathologists - American College of Medical Genetics with some modifications.

- A "Genetic Test Devices Panel" should be established as part of the Medical Devices Advisory Committee to advise the FDA.

An internal working group has been established by the DHHS to review the Task Force recommendations once they are presented to the Secretary, and to develop a strategy for addressing these important, complex issues.

Mr. Stokes: Upon completion, how will the Institute work to help ensure that these recommendations are widely distributed? Elaborate.

Dr. Collins: On completion the Task Force recommendations will be widely distributed within the Executive Branch, to the U.S. Congress and the public, including posting on the World Wide Web.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists' cloning of adult sheep. These articles expressed excitement with regard to opportunities for advances in medical treatments, and concern with regard to misuse of the technology and the possibility of human cloning. This is another area where we must now be certain to examine and address the ethical, legal, and social issues of research on the front-end. As a leading researcher and as an institute director, what is your professional opinion of this technology and what are your most serious concerns. With regard to your institute's activities, what impact does this technology have on your research?

Dr. Collins: The recent announcement that researchers in Scotland had successfully "cloned" a sheep by introducing the nucleus from an adult, terminally differentiated cell into an enucleated oocyte is of widespread scientific and social interest. Developmental biologists have long believed that the genetic material in the nucleus of a cell undergoes irreversible changes throughout development and differentiation so that it is no longer totipotent but rather, is capable only of expressing those genes necessary to be, for example, a mammary gland cell. The cloning experiment demonstrates that this process of differentiation is, at least under specific experimental conditions, reversible.

If applied successfully to other non-human mammals, this technology could have significant implications for agriculture and medicine. Dr. Varmus, in his testimony, described some of the potential medical applications of this new technology.

One of the advantages this technology brings is to allow fairly rapid creation of genetically identical animals for research. The ability to create genetically identical animals means that variability from "genetic background" can be eliminated, thus allowing for careful dissection of the genetic and environmental contributions to disease. The availability of genetically identical research animals would greatly decrease the number of experimental animals needed to get valid data. Another advantage of the technology is that it will allow the production of custom designed animals that have medically useful properties, such as production of therapeutic compounds in their milk.

Certainly the notion that this technology would be used to clone a human is morally unacceptable. However, the technology may have useful medical applications short of cloning a particular person. As you know, the president has issued a directive prohibiting the use of federal funds for such research and calling for voluntary compliance by non-federal entities and has asked the National Bioethics Advisory Commission to evaluate this technology and make recommendations in 90 days.

HEATH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996

Mr. Stokes: Last year, the health insurance portability and accountability act was enacted into law. A number of individuals and organizations have expressed serious concern with regard to the provisions pertaining to protection of patient information. In your professional judgment, does the legislation provide adequate protection against genetic discrimination? Elaborate.

Dr. Collins: The Health Insurance Portability and Accountability Act of 1996, P.L. 104-191, addresses a number of concerns regarding genetic discrimination in health insurance. It does:

- Prohibit excluding an individual from group coverage because of past or present medical problems, including genetic information.
- Prohibit charging a higher premium to an individual than to others in the group.
- Limit exclusions for preexisting conditions to 12 months, and prohibit such exclusions if the individual has been previously covered for that condition for 12 months or more.
- State explicitly that genetic information in the absence of a current diagnosis of illness shall not be considered a preexisting condition.

Mr. Stokes: Specifically, what other provisions need to be instituted to ensure adequate protections? To what extent is the Ethical, Legal, and Social Implications Working Group providing guidance in this area?

Dr. Collins: The Act still does not guarantee coverage for uninsured individuals seeking individual health insurance policies, offer protections against exorbitant premiums in the individual market, or provide privacy/confidentiality protections.

The Ethical, Legal, and Social Implications (ELSI) Working Group has been working to provide policy analysis and recommendations for decision makers to use in crafting legislation that deals with genetic information. In 1992, the ELSI Working Group established a Task Force on Genetic Information and Health Insurance. This Task Force made a number of recommendations regarding genetic information and health insurance. In 1995, the National Action Plan on Breast Cancer and the ELSI working group joined forces to re-examine the issues and proposed a series of recommendations for legislation. Many, but not all, of these latter recommendations were incorporated in the Health Insurance Portability and Accountability Act of 1996. Enacting the remainder, to fill the gaps still remaining after passage of P.L. 104-191, would be a worthy goal for the 105th Congress.

Mr. Stokes: How much is included in the budget for examining such, and how does this compare with the FY 1998 budget request, and is it sufficient to do the job?

Dr. Collins: The NHGRI provides 5 percent of its budget for research activities that address the ethical, legal, and social implications of genetics research. These funds have been used effectively and have had an enormous impact on the field.

PROTECTION OF PATIENT MEDICAL INFORMATION

Mr. Stokes: In community after community across the nation, and here in the Congress, the protection of patient information has become a serious problem that must be appropriately addressed. The issues of privacy and discrimination are critical. In the wrong hands, the availability of such information has major negative implications in all areas of our lives and can adversely impact each of us individually and collectively. To what extent has the agency invested resources in addressing the potential for misuse of genetic information in the workplace?

Dr. Collins: Within the past few years, scientific research has dramatically increased the ability to identify mutations within genes. Yet, increased ease of access to this potentially powerful information by employers raises concerns that this information will be used to discriminate against individuals. Employers that cover health care costs for employees and their dependents have economic incentives to deny employment to individuals they perceive as more likely to consume health care resources. Many individuals may choose not to be tested out of fear the information will be used to deny them employment, and consequently, access to health insurance. The National Action Plan on Breast Cancer (NAPBC) recently joined with the NIH-DOE Joint Working Group on the Ethical, Legal, and Social Implications of Human Genome Research (ELSI Working Group) to address the issue of genetic information and the workplace. The following NAPBC/ELSI Working Group recommendations were designed to offer guidance for state and federal policy makers to protect against genetic discrimination and to promote privacy in the workplace.

- Employment organizations should be prohibited from using genetic information to affect the hiring of an individual or to affect the terms, conditions, privileges, benefits, or termination of employment unless the employment organization can prove this information is directly job related and consistent with business necessity.

- Employment organizations should be prohibited from requesting or requiring collection or disclosure of genetic information prior to a conditional offer of employment and, under all other circumstances, employment organizations should be prohibited from requesting or requiring collection or disclosure of genetic information unless the employment organization can prove this information is directly job related and consistent with business necessity or otherwise mandated by law. Written and informed consent should be required for each request, collection, or disclosure.

- Employment organizations should be restricted from access to genetic information contained in medical records released by individuals as a condition of employment, in claims filed for reimbursement of health care costs, and other sources.

- Employment organizations should be prohibited from releasing genetic information without prior written authorization of the individual. Written authorization should be required for each disclosure and include to whom the disclosure will be made.

- Violators of these provisions should be subject to strong enforcement mechanisms, including a private right of action.

These recommendations were published in *Science* in March 1997 and will be made widely available to interested parties and Congressional staff.

Mr. Stokes: I am concerned about not only the misuse of genetic information but medical information in general. Information that should be left in the privacy of a patient and his or her health provider. Is it possible to protect genetic information without protecting all medical information?

Dr. Collins: Genetic information cannot reasonably be maintained separately from the rest of the medical record because virtually every disorder has a genetic component. Segregation would create a system of incomplete medical information and would interfere with optimal health care. Genetic information is increasingly becoming valuable in the diagnosis, treatment and prevention of human diseases. It may be present in the medical record in the form of the results of a molecular genetic test (e.g., BRCA1 or BRCA2 testing), a gene product test (e.g., hemoglobin electrophoresis for the detection of sickle cell trait), or a physical examination or family history. Consequently, in order to protect the privacy of genetic information, it will be necessary to protect the privacy of all medical information.

INTRAMURAL PROGRAM

Mr. Stokes: A few years ago, the committee provided the Center resources to implement an intramural research program. We often hear from the Directors of the various Institutes about how critical it is to have and adequately maintain their intramural programs. Would you bring the committee up-to-date on the Institute's recently implemented intramural program, and explain how it differs from the rest of the NIH Institutes?

Dr. Collins: In less than four years, the Division of Intramural Research at NHGRI has constructed an outstanding program of research in human genetic diseases. The establishment of NHGRI's, Division of Intramural Research has enabled the study of a broad range of common and rare disorders and has provided a focus at the NIH for expertise in medical genetics and human genomics. The Division of Intramural Research applies the fruits of the Human Genome Project to the study of specific diseases. Intramural researchers provide a resource of expertise and genomic technology for the entire NIH campus.

In addition to its own research activities, the Division of Intramural Research provides a focus for human genetics research on the NIH campus. The Division of Intramural Research plays a role far beyond its numbers in providing advice in faculty searches, recruitment, and new program initiatives. To date, the Division of Intramural Research has successfully developed a presence on campus as a highly collaborative and interactive group of scientists. Most notable recent achievements are the formation of the Center for Inherited Disease Research and a proposed NIH Intramural DNA Sequencing Center.

In 1996 alone, collaborative efforts between Division of Intramural Research researchers and others identified the location of the first major gene that predisposes men to prostate cancer, and pinpointed the location of a gene responsible for some cases of Parkinson's disease -- a disease where research had languished for nearly 20 years.

Mr. Stokes: What has the intramural program allowed the Institute to accomplish that it would not have been able to without an intramural program?

Dr. Collins: The NHGRI extramural program focusses on building maps, technologies, and DNA sequence needed for the Human Genome Project, as well as the ethical, legal, and social implications. The NHGRI intramural program operates on a different philosophy--the application of genome approaches to an understanding of disease. While most NIH centers and institutes are primarily disease-specific, the NHGRI intramural program serves as a focal point for studying the genetic components of a variety of human diseases. Many NIH intramural programs have genetic research components through which researchers now collaborate with the NHGRI Division of Intramural Research. It is, however, the NHGRI intramural program that has taken the lead role at NIH in implementing widespread genetic studies and strategies in concert with the mission of the Human Genome Project.

The Division of Intramural Research has several programs/offices unique to the NHGRI: the Genetic Counseling Training Program, the Medical Genetics Fellowship, and The Office of Genome Ethics.

The genetic counseling training program, developed in collaboration with the School of Hygiene and Public Health at Johns Hopkins University, is a program to train both practitioners and investigators in the field of genetic counseling. This is an important development because there is a real need for counselors who have the experience and training to perform research into the methodology and impact of the field.

The Medical Genetics Fellowship program has been reorganized under NHGRI leadership, while maintaining the vital contributions of our inter-institute colleagues in the area of medical genetics. The program is now accredited as a tri-partite training program, involving the NIH, Children's National Medical Center and Georgetown University Medical Center.

The Office of Genome Ethics (OGE) was established to assist intramural researchers at the NHGRI to identify and to address ethical issues arising from genome research. These include issues that must be addressed in order to pursue research ethically in this area, as well as issues arising for society as a whole as a result of new research findings and discoveries in genetics. Of long-term interest, the OGE seeks to bring the results of research sponsored by the NHGRI extramural program in the Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project into the work of intramural NHGRI researchers.

CREATION OF THE GENOME PROGRAM

Mr. Stokes: As you may recall, when the NIH and the committee started to envision the human genome center, subjects discussed included how long will it take to complete the project. The genome project was envisioned to take 15 years to complete. Would you bring the committee up-to-date on how well we are progressing on this time table? After the sequencing is completed, what is the next step?

Dr. Collins: The Human Genome Project was formally initiated in 1990 and has established a number of specific goals as well as a timetable for achieving them. These goals, developed as a joint effort between the National Institutes of Health and the Department of Energy genome programs, include the construction of detailed genetic and physical maps of the human genome, the determination of the sequence of the three billion base pairs in human DNA, and the identification and location of all the genes. The goals also include the characterization of the genomes of several other organisms that are extensively used in biological research as model systems for human disease.

Several of the goals have already been met ahead of the projected schedule. The genetic map is complete, the physical map is nearing completion, and sequencing of the human DNA has begun in earnest. A human gene map was published last year, showing the location of about 20 percent of the anticipated genes. More than 70 disease genes

have been identified by taking advantage of these powerful tools, including genes for breast cancer, diabetes, and Alzheimer's disease. Completing the DNA sequence remains a challenge, but the path toward this goal is now clear and there is optimism that it will be achieved on target by the year 2005. The work on model organisms is also proceeding rapidly: the genomes of yeast and E. coli have been sequenced, the roundworm genome is expected to be completed in 1998 and the Drosophila genome in 2000. An excellent genetic map of the mouse is available and some sequencing of mouse DNA is beginning.

From the inception of the Human Genome Project, it was clearly recognized that acquisition and use of genetic knowledge would have momentous implications for both individuals and society and would have a number of consequences requiring both public and professional deliberations. As a result, the analysis of the ethical, legal and social implications of genome research has been an integral part of the Human Genome Project since the beginning. Four priority areas have been identified for immediate attention: privacy and fairness in the use of genetic information, safe clinical integration of new genetic technologies, ethical issues surrounding the conduct of genetics research, and public and professional education in genetics. Influential recommendations on genetic testing and health insurance have been produced and similar recommendations relating to workplace discrimination will be published soon. A Task Force on Genetic Testing will be finalizing its recommendations this spring relating to the safe and effective integration of genetic testing into mainstream medical practice. (See above)

In view of the tremendous progress and the confidence that all the original goals can be achieved in the near future, planning has now begun for the next phase of human genome research. While having the sequence of human DNA will be a tremendous boon to biological research, much remains to be done to understand the meaning of the genetic instructions contained in that DNA. There are many opportunities for facilitating research in this next stage using the approaches that have worked so well for the Human Genome Project thus far: namely the development of technology for large-scale analysis and the production of widely needed resources and data. For example, we need to know how DNA sequence varies between individuals and between species. Much more efficient technology for sequencing will be required to obtain the massive amounts of data that will be needed. Technology will be needed for systematic approaches to studying how genes are expressed and how they interact in the normal or diseased cell and at various stages of development. We look forward to a time when the cell can be studied as a system rather than one gene at a time, but much research is needed to get to that stage. The Human Genome Project is well positioned to provide the infrastructure for this kind of research, including the continued examination of the ethical, legal and social implications of new discoveries in genetics.

Mr. Stokes: As the opening statement indicates, most diseases of modern life – cancer, heart disease, diabetes, arthritis and a host of neuro-psychiatric disorders seem to result from the activities of several genes and the interplay between a human body and its environment. To what extent have we, and are we learning how to effectively unravel the two?

Dr. Collins: As you note, most of the major health problems of this country are of the sort known to geneticists as "complex" diseases. They result from a complex set of genetic and non-genetic factors. Distinguishing the genetic factors from the non-genetic factors, will be a key to developing effective control measures for these terrible problems. Understanding the genetic components to complex disease will also allow us to identify those individuals at highest risk and focus prevention measures on them, and perhaps to identify previously unsuspected environmental influences.

To date, the maps and other research products of the Human Genome Project have proven to be enormously useful in helping us to understand the genetic bases of diseases which are predominantly genetic in origin, in which non-genetic, environmental factors play a relatively small role. Our attention is now turning to the more difficult scientific problems involved in the analysis of complex diseases. Some progress has already been made. Improved genetic maps, new statistical tools and approaches, as well as more efficient genotyping technologies are now available and more are under development for studying the genetic components of such diseases.

Recently, the NHGRI established the Center for Inherited Disease Research as a facility that will provide rapid and efficient genotyping for investigators studying the genetics of complex diseases.

CENTER FOR INHERITED DISEASE RESEARCH

Mr. Stokes: The opening statement speaks about the new Center for Inherited Disease Research at Johns Hopkins, in Baltimore, and also about how the Center's researchers are expected to study six to nine complex disorders per year. How will you identify which diseases should be targeted for study?

Dr. Collins: All applications requesting access to the Center for Inherited Disease Research (CIDR) will be reviewed for scientific and technical merit by panels of outside experts. Factors that will be weighed by these peer review groups include the medical significance of the proposed research project.

Only applications deemed to be of high scientific merit will be candidates for access to the CIDR facility. The final decision about which projects use the CIDR facility will be made by the CIDR Access Committee, a chartered committee of outstanding scientists, expert in the analysis of complex diseases, and the Board of Governors, the governing body of CIDR. The Board is comprised of the eight institute directors that are contributing funds to the contract, as well as two non-voting members: the CIDR Director and a representative of Johns Hopkins University, the contractor for this facility.

HOWARD UNIVERSITY CENTER

Mr. Stokes: I was pleased to see that the Institute and the NIH Office of Research on Minority Health are collaborating with scientists at Howard University to study why people of African descent seem to develop adult-onset diabetes and prostate

cancer more frequently than do many other population groups. I concur with your statement that understanding the genetic basis of an increased risk for adult-onset diabetes and prostate cancer could lead to better strategies to prevent them from causing serious health problems. How soon is this effort expected to get underway?

Dr. Collins: The National Human Genome Research Institute and Howard University plan to establish a Center for Collaborative Research on Genomic Analysis of Diseases that Disproportionately Affect African-Americans. This Center will build on the fruits of seed money supplied by the NIH Office for Research on Minority Health to study the genetics of such diseases while at the same time strengthening the scientific expertise in human genome research at Howard University. The initial objectives of the proposed center are to recruit appropriate African-American families for collaborative genomic research; develop standardized protocols for collection of genetic, clinical, and epidemiologic data on the study population; and establish core facilities for the isolation, characterization, and storage of cells and DNA for genomic and biological studies, and for training. This will be achieved through completion of a pilot study of the genetics of non-insulin dependent diabetes mellitus in West Africans, initiation of a major study of hereditary prostate cancer in African-Americans, continuance of breast cancer genetics research, and laying the groundwork for training of African-American graduate students and postdoctoral fellows in human genome research. A blue ribbon panel of lay and scientific experts is also proposed to help guide Howard University and the NHGRI in this historic undertaking.

The first meeting of Principal Investigators for the diabetes studies, African-American Diabetes Mellitus (AADM), was held last month. Data collection is expected to start at the five West African sites this month. The first shipment of specimens for genotyping should arrive within 3 months (shipments will be on a quarterly basis for the first year of AADM). The entire pilot study is expected to last one year, during which time it will be evaluated and decisions made on further funding of an expanded, full-scale study.

In collaboration with Howard University, NHGRI plans to issue a Request for Proposals for hereditary prostate cancer (HPC) this month. We expect that the study itself should get underway in late summer.

DIVERSITY

Mr. Stokes: According to the budget submission, the institute has played a leading role, along with the American Medical Association and the American Nurses Association, in forming the National Coalition for Health Care Professional Education in genetics. I understand that the coalition brings together leaders in medical professional organizations, consumer groups, government agencies and industry for the purpose of developing and implementing a national genetics education program for health care professionals. I would expect that concerns discussed and addressed by this coalition greatly impact all segments of the population, and thus impacts each of us individually and collectively. It is against this backdrop that I ask does this coalition's composition reflect the diversity of the United States population and include representatives from

leading African-American, Hispanic, and other minority organizations as key participants and decision makers.

Dr. Collins: Every effort has been and will be made to ensure that the Coalition reflects the diversity of the United States population. Since the first planning meeting of the Coalition, participant organizations have been encouraged to consider the issue of diversity and the overall composition of the Coalition as they choose their representatives. In addition, the following minority organizations have been invited to participate in the Coalition: the Association of Asian Pacific Community Health Organizations, the Association of Minority Health Professions Schools, the Coalition of Hispanic Health Organizations, the Department of Health and Human Services' Office of Minority Health, the National Black Nurses Association, the National Coalition of Hispanic Health and Human Services Organizations, the National Institutes of Health's Office of Minority Health, and the National Medical Association.

OVARIAN, BREAST, AND CERVICAL CANCER

Ms. Delauro: Studies have shown that if ovarian cancer is properly diagnosed and treated early, the survival rate for women is 92 percent. But to date, there is no simple diagnostic test to detect ovarian cancer or clear method of prevention. What kind of research has been done at NHGRI to bring us closer to a cure or prevention for ovarian cancer? Breast cancer? Cervical cancer?

Dr. Collins: In 1994, The National Human Genome Research Institute released a Request for Applications which solicited research projects designed to examine the psychosocial and clinical impact of using gene-based diagnostic tests in families with heritable forms of breast, ovarian, and colon cancer; to assess public knowledge and attitudes about genetic testing for cancer risks; and to gather information needed to establish clinical protocols for the optimum use of these risk assessment technologies in the future.

As a part of this initiative, the NHGRI has formed what is known as the Cancer Genetics Studies Consortium (CGSC). Important co-funding comes from the National Cancer Institute, the National Institute for Nursing Research, and the National Institute of Mental Health. The CGSC was formed to increase communication among investigators, stimulate inter-project synergy, reduce duplication of effort, increase the likelihood of cross-study comparisons, jointly solve unanticipated problems, and encourage investigators to combine study results. At this point, the CGSC has achieved a number of important accomplishments. They include:

- the formation of a task force on informed consent and the development of recommendations for informed consent in cancer genetic testing.

- the formation of a task force on follow up recommendations for those found to have BRCA1 and BRCA2 or HNPCC mutations. Two papers regarding these topics are to be published in the Journal of the American Medical Association in March 1997.

- the identification of major policy issues surrounding cancer genetic testing and the submission of a paper summarizing these findings.

- the formation of a task force to develop a statement on population-based testing for BRCA1 and BRCA2 and HNPCC mutations.

It is hoped that as results from these studies become available, more will be learned about who is at increased risk to develop breast, ovarian, and colon cancer, what care needs to be provided to those found to be at increased risk, and what interventions are useful in order to reduce their risk for developing or dying from cancer. NHGRI is currently not studying the genetics of cervical cancer, however, in the NHGRI intramural program, investigators are studying chromosomal changes that occur in cervical cancer as a model system for understanding how sold tumors are formed.

CLONING AND ETHICS

Ms. Delauro: Monday's Washington Post article on the recent cloning of sheep in Scotland contains a quote from George Annas, a bioethicist and professor of health law at Boston University, on using this cloning technique on humans. He says the "[t]he real question [about cloning] is: How can it be prevented? You can't very well stop a rich person from setting up a lab on some tropical island." I recognize NIH keeps close tabs on the research being done within its purview. But given the highly sensitive nature of the research being done at NHGRI, what types of training do you provide on the ethical implications to non-NIH researchers on this issue [and] the knowledge achieved under the Human Genome Project?

Dr. Collins: The National Human Genome Research Institute (NHGRI) staff is well aware of the potentially sensitive nature of the research it supports. As a result, it has developed guidance in a number of areas for investigators who are carrying out genome or genetics research. For example, the NHGRI developed guidance on human subjects issues for investigators involved in large-scale DNA sequencing. In addition, when the Ethical, Legal, and Social Implications (ELSI) Research Program organized its Cancer Genetics Studies Consortium, it arranged for investigators to consult with experts in the field of human subjects protections as they were designing their informed consent process. The ELSI Program has also supported a number of workshops which have resulted in the publication of recommendations regarding human subjects protections in genetics research. These publications include a chapter on human subjects protections in genetics research in the 1994 Institutional Review Board Guidebook published by the Office for Protection from Research Risks and a 1995 article published in the Journal of the American Medical Association on informed consent for genetics research using stored tissue samples. In addition, the Division of Intramural Research has established an Office of Genome Ethics, which provides guidance, training, and advice to intramural NHGRI investigators on issues of research ethics. This year, the intramural NHGRI program has developed a required course in scientific ethics for all researchers, regardless of level. Since NIH trains researchers who ultimately end up in many different settings, this kind of training has long term and broad consequences.

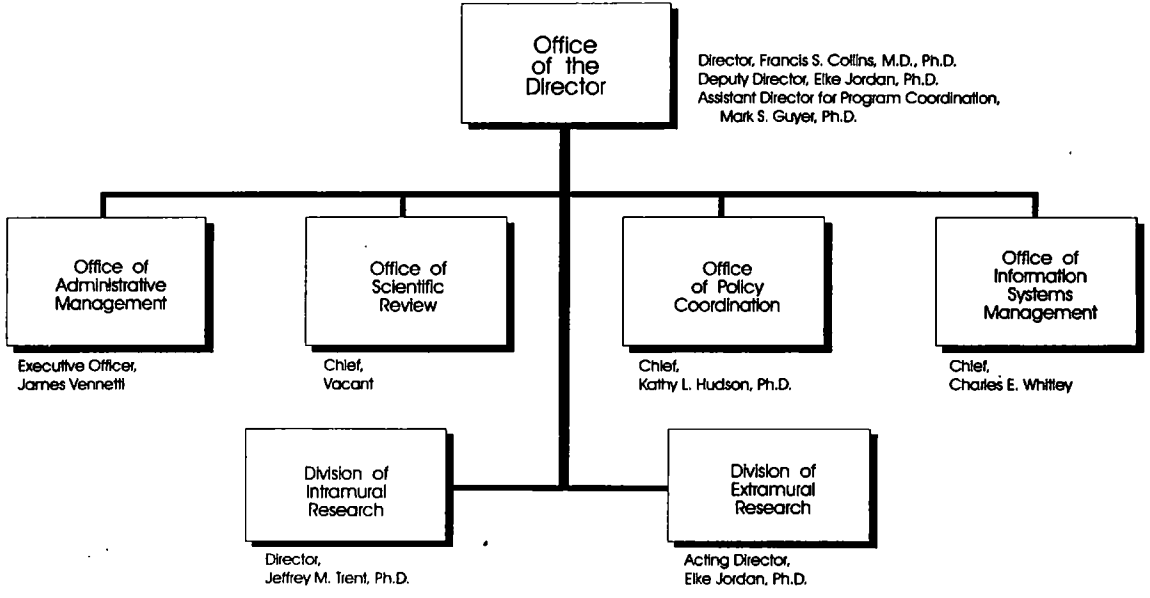
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

FY 1998 Budget	Page No.
Organization chart	2
Appropriation language and language analysis	3
Amounts available for obligation	4
Justification	5
Budget mechanism table	21
Budget authority by activity	22
Summary of changes	23
Budget authority by object	25
Administrative costs	26
Significant Items in House, Senate and Conference Appropriations Committee Reports	27
Authorizing legislation	31
Appropriation history	32
Detail of full-time equivalent employment (FTE)	33
Detail of positions	34

NATIONAL HUMAN GENOME RESEARCH INSTITUTE
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

[National Center for Human Genome Research]
National Human Genome Research Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to human genome research, [$189,657,000] *$202,197,000.*

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1997, P.L. 104-208)

Language Analysis - Effective January 14, 1997, the Secretary signed the authorization retitling the National Center for Human Genome Research to the National Human Genome Research Institute. This decision was prompted by the recent explosion of information about human genetics emerging from the Human Genome Project and the establishment of the Division of Intramural Research within the Center, with far-reaching implications for advancing human genetic disease research. Designation of the Center as a research Institute provides recognition of the expanded mission and acknowledges its prominent role in advancing human genome research as well as contributing to research in gene identification, gene therapy, and human genetic disease.

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$170,041,000	$189,657,000	$202,197,000
Rescission in accordance with P.L. 104-134	($266,000)	---	---
Reduction in accordance with P.L. 104-208	---	(128,000)	---
Subtotal, Adjusted Appropriation	169,775,000	189,529,000	202,197,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority	(457,000)	0	0
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	(1,000,000)	(3,001,000)	0
Subtotal, adjusted budget authority	168,318,000	186,528,000	202,197,000
Unobligated balance, lapsing	(25,000)	0	0
Total obligations	168,293,000	186,528,000	202,197,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1996 - $629,000; FY 1997 - $950,000; FY 1998 - $852,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research:
FY 1998 - $2,990,000

Note: Excludes $4,500 in FY 1996 and $41,500 in FY 1997 for royalties.

Justification

National Human Genome Research Institute

Authorizing Legislation: Section 301, 485B, and 487(d) of the Public Health Service Act, as amended. Reauthorizing legislation will be proposed.

Budget Authority:

FY 1996 Actual		FY 1997 Appropriation		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
187	$168,318,000	187	$186,528,000	187	$202,197,000	---	+$15,669,000

This document provides justification for the the FY 1998 non-AIDS activities of the National Human Genome Research Institute (NHGRI). Formerly the National Center for Human Genome Research, the organization was re-titled the National Human Genome Research Institute effective January 14, 1997. Justification of the NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled "Office of AIDS Research."

Mission

Virtually every disease, except possibly trauma, has a genetic component. The National Human Genome Research Institute (NHGRI), through its extramural and intramural research programs, contributes to the identification of genes involved in human diseases and the study of the function of these genes and their products. The ultimate goal is the development of better preventive medicine strategies, treatments, and cures for the wide array of disorders that affect humankind.

The NCHGR, re-titled the NHGRI effective January 14, 1997, was established in 1989 to lead the National Institutes of Health's role in the Human Genome[1] Project, a worldwide research effort to determine the location of the estimated 100,000 human genes and to read the entire set of genetic instructions encoded in human DNA. Since 1990, NHGRI has been carrying out this task by providing financial support through its extramural program to investigators at universities and other research laboratories throughout the United States. At this time, the Human Genome Project is accomplishing its goals ahead of schedule and with lower levels of funding than originally expected.

In February 1993, the NHGRI expanded its role at the National Institutes of Health (NIH) by establishing the Division of Intramural Research, including in-house laboratories that employ the tools developed by the Human Genome Project to further knowledge about human genetic

[1]The genome of an organism is defined as the complete set of hereditary factors represented in its DNA

disease and its diagnosis and treatment. These laboratories have become the hub of human genetics research at the NIH. In the intramural laboratories, scientists are developing and using the most advanced techniques to study the fundamental mechanisms of inherited and acquired genetic disorders, including planning and conducting clinical trials to test DNA-based methods for their treatment and perhaps cure. Researchers are identifying and studying families in which diseases are inherited--a facet of the Division that provides the nucleus for a physician training program in medical genetics. Researchers also translate basic science advances into effective, reliable, and cost-effective diagnostics for genetic conditions.

Background

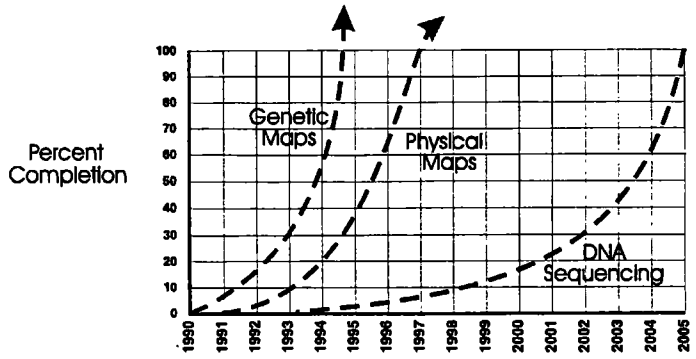
The NHGRI has made a significant contribution toward shaping the foundation for science in the twenty-first century--DNA sequence-based biology. At the heart of this effort is the Human Genome Project, which has led to a phenomenal increase in the understanding of the role of genes in human health and disease, and created expectations for the development of much improved diagnosis, treatment, and prevention for many diseases.

Because of the unique nature of the Human Genome Project, the NHGRI, together with the genome program of the Department of Energy, developed formal plans to guide this program. The first 5-year plan was published in 1990 and due to rapid progress, the second 5-year plan was published in 1993. Both laid out specific scientific goals, priorities, and timetables. The goals included the construction of detailed genetic and physical maps of the human genome, the determination of the complete sequence of human DNA, and the identification and location of the estimated 50,000-100,000 human genes. They also included the characterization of the genomes of several other organisms that are extensively used in biological research laboratories as model systems for human diseases (e.g. the laboratory mouse, the fruit fly, a roundworm, brewer's yeast, and the bacterium, *E. coli*). A final goal was to identify, analyze, and address the ethical, legal, and social implications of human genetics research.

Each of the plans was accompanied by a budget plan that indicated the investment required in the various areas to achieve the goals that had been established. These plans provided the overall framework for priority setting in the extramural program and are regularly re-examined and updated in light of new scientific developments. At each stage of the process, advice is sought from the scientific community and from the National Advisory Council for Human Genome Research. The NHGRI has already started the process for the development of a new 5-year plan which is expected to be published in 1998.

The Human Genome Project has now passed its sixth anniversary with the achievement of several of its goals, advancement of others to within sight of completion, and the creation of a path to the most challenging goal, the determination of a complete reference human DNA sequence. Although only a small percentage of human genomic DNA has been sequenced at this point, NHGRI is confident that the sequence will be completed by 2005. As a result, the NHGRI is already thinking about the ways in which it can contribute to the next stage: un-raveling the complex functional information that is coded in the DNA sequence.

Human Genome Project Progress



Deciphering the human DNA sequence will represent a momentous step in biology. It can be compared to the revolution in chemistry that occurred more than a century ago when the periodic table of the elements was discovered by Mendeleev. This table provided a framework for organizing what was known about all atoms and demonstrated that they could be understood in such a way that the similarities and differences in their properties were related to their structure. Based on this table, chemists knew all the building blocks of matter and could predict many of their chemical properties. The DNA sequence, which represents the complete genetic instructions of an individual, will be a first step in gaining a full understanding of what those instructions mean for human health and disease. This "periodic table" of 50,000-100,000 genes will allow scientists to organize and classify genes and to study their properties, not just one at a time but in interactive combinations.

In order to achieve the goals of the Human Genome Project successfully a variety of new technologies were needed. Advanced means of making the information widely available to scientists, physicians, and others so that the results may be rapidly used for the public good were required. Thus, significantly improved technology and rapid dissemination of information for biomedical research purposes have been other important goals of the Human Genome Project.

Development of Spectral Karyotyping
One new technology, developed in 1996 by scientists in the NHGRI intramural research program and their colleagues, that identifies all 23 pairs of human chromosomes by a different color, is called spectral karyotyping. This method allows scientists to examine the entire group of human chromosomes more easily for changes that could lead to disease (e.g. insertions, deletions, or rearrangements) not visible with conventional karyotyping. Spectral karyotyping can be used effectively to pinpoint chromosomal changes linked to diseases, and is also a valuable technique for comparing genomes from different species.

From the inception of the Human Genome Project, it was clearly recognized that acquisition and use of such genetic knowledge would have momentous implications for both individuals and society, and would have a number of consequences requiring both public and professional deliberations. As a result, the analysis of the ethical, legal, and social implications related to discoveries made as a result of the Human Genome Project and other genetics research have been an integral part of the Human Genome Project since its origin and a number of public policy options and recommendations have been developed.

Accomplishments and Priorities

Finding a single gene among the three billion base pairs of human DNA, requires a set of powerful tools. The Human Genome Project is developing several basic types of tools to make analyzing DNA and finding genes faster, cheaper, and practical for almost any scientist.

Genetic mapping

Genetic mapping is the first step in isolating a gene, providing clues about which chromosome contains the gene and precisely where on that chromosome the gene lies. Genetic maps are used by scientists to study the inheritance patterns of genes in families. If it is determined that the same family members who inherit a certain genetic marker also are the individuals in the family who usually get the disease under study, then the scientist knows that the disease gene must be located near the genetic marker on the chromosome. One of the major goals of the Human Genome Project was to develop dense genetic maps of markers spaced evenly throughout the human genome. This goal was achieved ahead of schedule in 1994. In addition, the Human Genome Project has produced genetic maps for the widely-used laboratory model, the mouse, which will facilitate further analysis of the human genome.

Completion of Human and Mouse Genetic Maps

Detailed genetic maps of the human and mouse genomes have been completed, marking the achievement of the Human Genome Project's genetic mapping goals. An international collaboration of scientists has developed a human genetic map that is now seven times denser in markers than was projected in the original plan. The NHGRI supported the U.S. portion of this project. The mouse genetic map was almost entirely produced at the Whitehead Institute with NHGRI support.

Using current genetic maps, an investigator can rapidly localize a candidate gene to a chromosomal region just a few million base pairs in length. As a result, the numbers of disease genes that are being mapped each year has risen dramatically.

Location of Parkinson's Disease Gene Found on Chromosome 4
Scientists in the NHGRI intramural research program and their colleagues have mapped a gene believed to be responsible for some cases of classical Parkinson's disease. This discovery provides strong evidence that a genetic alteration may, in some cases, cause the disease. The next step will be to find and identify the specific gene involved. Learning what the gene is and how it works may help researchers design better diagnostic tests and treatments for not only inherited cases of Parkinson's disease, but also those with no apparent familial link.

The availability of high-resolution, easy-to-use genetic maps promises to revolutionize genetic and other types of biomedical research. The NHGRI is now turning its attention toward the requirements for mapping genes underlying complex traits, that is, those traits that are specified by several genes or are significantly affected by both genetic and environmental factors. While the current genetic maps have been successfully used to analyze genes that contribute to some complex traits, including the genes involved in some forms of diabetes, multiple sclerosis, and psychiatric illness, improved maps with markers that can be analyzed on a large scale and by automated procedures are needed to tackle the genetic contributions to many other common diseases.

Diseases that disproportionately affect minorities
NHGRI intramural scientists have worked closely with the NIH Office of Research on Minority Health (ORMH) to initiate several programs in partnership with Howard University. The first of these projects, a study of the West African origins of genetic susceptibility to non-insulin dependent diabetes mellitus in African-Americans, has resulted in the issuance of a Request for Proposals, funded by the ORMH. Proposals for this study, which will be coordinated by scientists at Howard University, have been reviewed and five chosen for funding.

The second of these initiatives is a proposal to study the genetics and epidemiology of prostate cancer in African-Americans. Prostate cancer is a major cause of morbidity and mortality among African-American men. The ORMH provided support for the planning phase of a such a prostate study, and Howard University and NHGRI intramural scientists have begun to develop the scientific objectives for this project. The identification of genes predisposing African-Americans to prostate cancer should contribute to earlier diagnosis and more effective interventions. These two initiatives are representative of the growing collaboration between the NHGRI and investigators at Howard University.

Building on these initiatives, the NHGRI, in collaboration with ORMH, plans to expand its array of research projects on genetic susceptibility to diseases that disproportionately cause disease or death in African-Americans, including breast cancer and hypertension. Consideration of the ethical, legal, and social issues raised by the research in these studies will be a significant component of the effort as well.

Intramural researchers as well as researchers throughout the country now have an important new resource for the identification of the genes that play a role in complex traits--the **Center for Inherited Disease Research** (CIDR). The CIDR focuses on mapping genes for common disorders in humans, including cardiovascular and pulmonary disease, cancer, psychiatric disorders, diabetes, and autoimmune diseases. The CIDR will also conduct research to develop improved approaches for: 1) statistical genetics; 2) genetic epidemiology; 3) medical informatics and database management; 4) genotyping; and 5) technology development. The services and facilities of the CIDR are funded through an NIH inter-Institute agreement with the NHGRI as the lead agency. The contract to operate the CIDR facility was recently awarded to The Johns Hopkins University.

Physical Mapping

After scientists use a genetic map to locate a gene to within a relatively small area on a chromosome, they use a physical map to learn more precisely the gene's location. A physical map provides scientists with DNA representing known segments of a chromosome and the raw material for DNA sequencing. Significant progress has been made toward completing the physical map of the human genome. In late 1995, a physical map of the human genome was published that covered about 95 percent of the genome with overlapping cloned pieces of DNA and contained about half the number of markers required by the physical mapping goal. This map is progressing rapidly and should be completed well before the target date of 1998. In addition, detailed maps of roughly half the human chromosomes have been developed by a number of groups and are currently also available in the publicly accessible databases.

The Human Gene Map

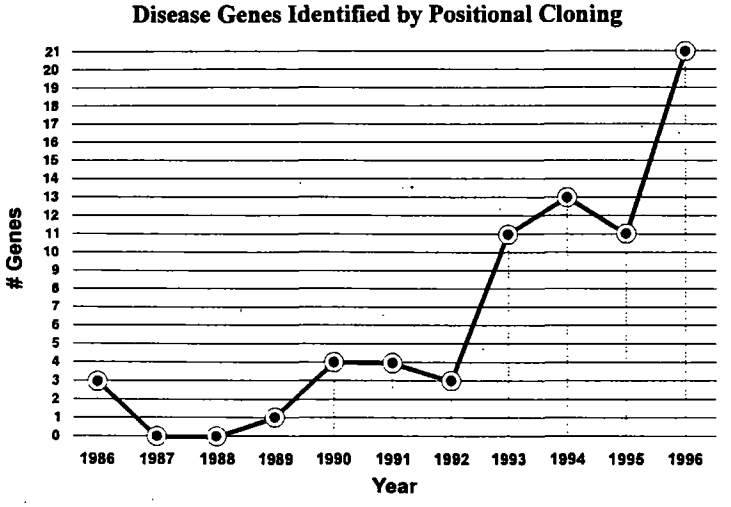
A team of over 100 scientists from government, university, and commercial laboratories around the world have developed a map that pinpoints the locations of over 16,000 genes (or about 20 percent of the total number) in human DNA, thus tripling the number of genes mapped in less than 2 years. This map, in which the National Center for Biotechnology Information of the National Library of Medicine played a major computational role, combines computer technology with biomedical research tools in a powerful, multi-disciplinary approach to biological science and will more rapidly advance the understanding of the genetic basis of many diseases. An electronic version of the map is available via the Internet (www.ncbi.nlm.nih.gov/science96/), with extensive links to supporting data about the DNA structure of the genes and proteins they encode. This electronic version provides students and scientists with an on-line educational and research tool containing the latest information about genes and their function in both health and disease. In 1993, the Human Genome Project set a goal of developing "efficient methods for identifying genes and for placement of known genes on physical maps." With the NHGRI providing a major portion of the U.S. research effort, this first human gene map is a clear indication of the significant progress that has been made toward this goal.

Positional cloning

The genetic and physical maps that have been produced as a result of the Human Genome Project have provided a remarkable advantage to scientists engaged in the search for disease genes by positional cloning. Once scientists have identified the region of a chromosome in which a gene is located, they can apply advanced techniques to determine what genes are located in the region

of interest. Those genes can then be further studied to see if they might be a candidate for the gene that is being sought. Having the various maps available has saved scientists a great deal of time.

The isolation of the gene(s) underlying human diseases and other biological phenomena has become a major experimental paradigm in biology over the past 40 years. One of the key motivations for the Human Genome Project was the development of a scientific infrastructure that would increase the efficiency of finding human disease genes. The accomplishments of the gene finders over the past 2 years have validated that rationale. Below is a chart of the number of disease genes identified by positional cloning from 1986 through 1996.



Finding the Gene for Hereditary Hemochromatosis
One of the genes that was identified in 1996 is the gene that is altered in people with hemochromatosis, a serious and relatively common disease of iron metabolism that is difficult to diagnose but easy to treat if it is diagnosed early. About twenty years ago, the gene was mapped to a region on chromosome 6. However, further progress in isolating the gene was impeded by lack of detailed maps. Last year, a private biotechnology company finally isolated the gene, using detailed maps of the region of chromosome 6 sequencing 250,000 bases of DNA surrounding the gene. The discovery of this gene raises the possibility of population screening. The significant clinical, ethical, legal and social issues (ELSI) that need to be considered are discussed below in the section on ELSI.

A Gene for Skin Cancer is Revealed by Positional Cloning
Using the tools developed by the Human Genome Project, two groups, one of which was supported by the National Cancer Institute, discovered a gene that causes basal cell nevus syndrome (also known as Gorlin disease), which predisposes affected individuals to developmental abnormalities and a variety of cancers, especially skin cancer. This gene was determined to be similar to a well-known gene in the fruitfly, known as *patched*, which plays a key role in early fruitfly development. The similarity of the human and fruitfly genes played a major role in finding this gene and in identifying its chemical function providing an excellent example of how the study of model organisms is helpful to medical research. It has now been found that the same gene is involved in the much more common sporadic forms of skin cancer, where the gene is presumably mutated by exposure to ultraviolet light.

Development of Atm-deficient Mice
Ataxia telangiectasia (A-T) is a complex childhood neurologic disorder caused by a mutation in a single gene that results in health problems throughout the entire body. Scientists in the NHGRI intramural research program contributed to the isolation of the gene in 1995. These researchers and their colleagues have now developed a laboratory mouse with virtually all the characteristics of a person with ataxia telangiectasia, including neurologic problems, cancers of the immune system, slow growth, radiation sensitivity, and abnormal development of sperm and eggs. This new mouse model, developed within a year after the discovery of the Atm gene, gives scientists the first opportunity to study the disease in a controlled way in animals other than humans. Evidence suggests that otherwise healthy "carriers" of the A-T gene, who may make up 1 percent of the general population, may be at a higher-than-average risk for a wide range of cancers. A-T affects between 1 in 40,000 individuals in the U.S. and 1 in 100,000 individuals worldwide; some 500 children in the U.S. have A-T, although many more are probably undiagnosed. People with A-T usually die in their teens or early twenties.

DNA Sequencing
The NHGRI is now facing the most challenging technological undertaking of all: determining the entire sequence of the three billion DNA bases throughout the length of the human DNA. Knowing the order of DNA bases will reveal where all the genes are located, as well as the instructions carried in a particular segment of DNA. Once the sequence has been completed, the organism's entire genetic script becomes known, and investigators will have the opportunity to find and study every genetic element of the organism. This knowledge creates unparalleled opportunities, with far-reaching implications for both research and practical applications.

Completion of DNA Sequence of *Saccharomyces cerevisiae*

Saccharomyces cerevisiae, or brewer's yeast, has the largest genome to be completely deciphered so far. The sequence of its 12 million base pairs of DNA was completed in April 1996. This single-celled organism has many similarities to human cells, including a distinct nucleus and compartmental structures for carrying out specialized processes. The availability of the entire yeast DNA sequence now provides experimental and computational biologists with an incomparable resource for systematic and comprehensive analyses of the genetic basis of cellular function. The yeast sequencing initiative involved both U.S. and European laboratories. The NHGRI supported the U.S. effort. *Science* magazine reported this accomplishment to be among the ten most significant scientific achievements of 1996.

To date, technology development for DNA sequencing has largely been carried out using model organism DNA with genomes smaller than in humans. The NHGRI continues to support the efforts of investigators sequencing the DNA of the roundworm (expected completion in 1998) and the bacterium *E. coli* (expected completion in 1997), and the fruit fly (expected completion in 2000). All of these projects are expected to be completed on or ahead schedule. Scientists are now ready to begin systematically sequencing human DNA with technologies developed using model organisms.

To lay the groundwork for sequencing the human genome, in FY 1996, the NHGRI funded two new research initiatives: "Improved Electrophoretic DNA Sequencing Technology," aimed at developing improved automated sequencing technology suitable for large-scale sequencing of DNA; and "Pilot Projects for Sequencing of the Human Genome," which resulted in the funding of six research projects designed to test a variety of strategies for full-scale production sequencing of human DNA. These projects are scheduled to produce 100 million base pairs of human DNA sequence in the coming 2 years. It is anticipated that the most successful investigators will then be encouraged to expand the projects to full production levels. All of the projects are required to release sequence data rapidly to the scientific community, so that it can be used in other research projects.

As the first complete genomic sequences are made available to the biomedical and biological research communities, and sequence-based approaches come to play a major role in biological research, the demand for more rapid and less expensive methods for DNA sequencing will increase. Thus, the NHGRI will also continue to support the development of a new generation of DNA sequencing technology that is orders of magnitude faster, cheaper and more powerful.

Databases

Given the high rate and volume of data being produced and the need for providing easy and rapid access to the new data, large and sophisticated public databases are the ultimate product of the Human Genome Project. For this reason, NHGRI considers the support of databases an integral part of its programs. Databases are already the major medium through which genome mapping and sequencing data are published and shared with both the genome research and the wider

biomedical research communities. In the past few years, the amount of information deposited into the databases and the level of use have both increased dramatically. For example, in FY 1996 genome database usage continued to increase, with biomedical researchers accessing genome databases thousands of time per day. In September 1996, GDB (Genome Data Base) was accessed an average of 8,852 times per day, while SGD (Saccharomyces Genome Database) was accessed 4,837 time per day, and FlyBase (the Drosophila genome database) was accessed an average of 1,517 times per day. The NHGRI supports and will continue to support a variety of public databases containing information about maps, DNA sequences, model organisms and genetic diseases. In FY 1996, $7.5 million was expended in this area and this commitment is expected to grow in the coming years. These databases have become a crucial and indispensable resource for all biomedical researchers.

Ethical, Legal, and Social Implications of Human Genetics Research

From the inception of the Human Genome Project, it was recognized that mapping and sequencing the human genome would have profound implications for individuals, families, and society. The most immediate and direct effect of the Human Genome Project is the discovery of disease genes. Once a gene has been identified, scientists have an essential key to understanding the origin of a disease. While treatments for such diseases take time to be developed, isolating a gene can quickly lead to the development of a diagnostic test. Such a test can readily be used to determine whether or not an individual carries an alteration in that gene. Thus, within a short time after a gene is isolated, individuals can be told whether or not they have an alteration in their copy of this gene. Often, however, they cannot be told at first what that information means to them in terms of their future health or what strategies might be available to reduce their risk of developing a particular disease.

Recently two genes that cause breast cancer (BRCA1 and BRCA2) were isolated. Much debate has occurred as a result of this discovery and the advisability of offering a test for alterations in these genes to women. While those who test positive have an increased risk of breast and ovarian cancer, the actual risk to develop these diseases outside high-risk families remains unknown. Even in high-risk families the risk is not 100 percent. Those who test negative may still get breast or ovarian cancer due to environmental factors or other, as yet unknown, genes. While increased cancer surveillance and prevention options can be offered to those found to have alterations in their genes, the effectiveness of these interventions remains uncertain. Furthermore, those who test positive are at increased risk of discrimination in insurance or employment. While the discovery of a gene and the development of a genetic test may be viewed as a great scientific advance, it may not result in an immediate benefit to the persons who undergo testing. This interim phase, when testing is possible but interventions are of uncertain benefit, raises questions about the appropriate use of genetic technologies and information.

From the outset, the Human Genome Project has devoted 3-5 percent of its budget to analysis of the ethical, legal, and social implications (ELSI) of human genetics research. The NHGRI has identified four areas which have high priority for the ELSI program. These priority areas, listed below, form the basis of a recently released, revised Program Announcement, which will serve to further focus future program activities.

A. Privacy and fairness in the use and interpretation of genetic information – This area includes studies of the meaning of genetic information and how to minimize or prevent its misinterpretation or misuse. Of particular concern is genetic discrimination in health insurance and employment.

B. Clinical integration of new genetic technologies – This includes an examination of the impact of genetic testing and counseling on individuals, families, and society and the development of policy options related to the clinical use of genetic technologies.

C. Issues surrounding genetics research – Informed consent, privacy, and other ethics issues related to the design, conduct, and reporting of genetics research are included here.

D. Public and professional education – Activities in this area include the development and evaluation of alternative means of providing education about genetics and related ELSI issues to health professionals, policy makers, and the public.

The NHGRI has established four functional components that are responsible for specific areas of ELSI activities. These are: (1) the ELSI research program (in the Division of Extramural Research) responsible for supporting research and education projects addressing ELSI issues through grants and other support mechanisms; (2) the Office of Policy Coordination (in the Office of the Director, NHGRI) to address specific policy concerns raised by the Human Genome Project; (3) the Joint NIH/DOE Working Group on Ethical, Legal, and Social Implications (the ELSI Working Group) to analyze critical issues and provide guidance to the NIH and DOE's ELSI programs; and (4) the Office of Genome Ethics (in the Division of Intramural Research) to perform research, provide advice to the NHGRI intramural research program, and develop ethics curricula for the NHGRI intramural program trainees.

Task Force on Genetic Testing

The ELSI Working Group has formed a Task Force on Genetic Testing which is examining the current state of genetic testing in the U.S. to make recommendations that will ensure the development and delivery of safe and effective genetic tests. Specific issues being addressed are the scientific validation of new genetic tests; laboratory quality assurance; and education, counseling, and delivery of genetic tests. Several federal agencies including the Food and Drug Administration, Health Care Financing Administration, National Centers for Disease Control and Prevention, and Agency for Health Care Policy Research, professional societies, as well as the biotechnology

industry, insurers and consumers are participating in the Task Force. In March 1996, the Task Force released a set of draft Interim Principles for public comment. The final Principles and Recommendations of the Task Force are expected to be released in the Spring of 1997.

ELSI Working Group Evaluation

As an organization, NHGRI has evolved over time to meet new challenges and opportunities presented by the Human Genome Project, a vigorous intramural research program, and the ELSI research program and related policy issues. In view of the many changes that have taken place, it was determined that an independent evaluation of the ELSI Working Group, its structure and its relationship to NHGRI and other activities would be appropriate and timely. An evaluation committee was established and co-chaired by representatives of the DOE and NHGRI's advisory committees. The Committee released its final recommendations in December 1996 and will be presenting them to the NHGRI Advisory Council and the DOE Health and Environmental Research Advisory Committee in early 1997.

National Coalition for Health Professional Education in Genetics

It is imperative that our nation's health care providers have the knowledge, skills, and resources to effectively integrate new genetic knowledge and technologies into the prevention, diagnosis, and treatment of disease. Therefore, the NHGRI has been working with the American Medical Association and the American Nurses Association to establish a National Coalition for Health Professional Education in Genetics (the Coalition). The Coalition will bring together and establish collaboration between leaders in health care professional, consumer, government, genetics, and industry organizations, for the purpose of developing and implementing a comprehensive, national genetics education effort for health care professionals. An organizational meeting of the Steering Committee, which included representatives from consumer organizations, medical professional organizations, nursing professional organizations, and genetics professional organizations, was held in July 1996. The first meeting of the full Coalition will be held in early March 1997.

Policy Development Conferences

On October 4, 1996, the National Action Plan on Breast Cancer and the ELSI Working Group held a workshop on genetic information and employment discrimination. It is anticipated that the recommendations from the workshop will provide meaningful information to policy makers as they discuss the need for additional legislative protections. The recommendations from the workshop will be published and widely disseminated to policy makers, consumer advocates, and other stakeholders.

Hereditary hemochromatosis is a common genetic disease; 1 in 10 Northern Europeans carry the trait, and 1 in 400 have the disease. It is caused by a defect in iron metabolism that results in the accumulation of iron in various organs in the body. Early treatment can

prevent the clinical manifestations of the disease. However, hemochromatosis can masquerade as other diseases and is frequently misdiagnosed, preventing prompt treatment and leading to needless illness and death. The NHGRI is planning a workshop to examine the implications of the discovery of the gene for hereditary hemochromatosis. Workshop participants will discuss the scientific and ethical issues surrounding the possibility of widespread population-based testing for the disease. The meeting is scheduled to be held on March 3, 1997, and will be co-sponsored by the Centers for Disease Control and Prevention.

Cystic Fibrosis Consensus Conference
The NHGRI ELSI research program has supported a number of projects to examine issues raised by genetic testing for cystic fibrosis. The results of these studies, together with other related research results, will be examined at an NIH consensus development conference, "Genetic Testing for Cystic Fibrosis." This conference will be held April 14-16, 1997 and will bring together a panel of health care providers, researchers, ethicist, and consumers to consider the current state of the science of genetic testing for cystic fibrosis; ethical, legal, social and other policy issues related to such testing; and whether such testing should be recommended.

Training Programs and Activities

The extraordinary amount of information emanating from the Human Genome Project will provide scientists and scholars intellectual challenges for many years to come. To ensure that these intellectual challenges are met, the NHGRI supports training programs and activities that will provide scientists and scholars with the fundamental knowledge and skills adequate to the task. The NHGRI is committed to ensuring that women, minorities, and people with disabilities participate in its training programs and activities.

A set of interdisciplinary training grants were awarded in 1995, that embody the type of research experiences that future molecular biologists will require to pursue genomic approaches in the study of biological problems. Opportunities are provided for pre-and post-doctoral students, and short-term fellowships are provided to introduce undergraduate students to problems of genomic analysis. Complementing the institutional training grants are regular and senior postdoctoral fellowships, as well as predoctoral fellowships for minorities and individuals with disabilities.

To encourage individuals with expertise in areas such as engineering, computer science, mathematics, physics, and chemistry to do research in the genome field, the NHGRI has established a special career development program. The purpose of the program is to provide enough training and research experience to allow the individual to develop the interdisciplinary skills necessary for an independent genomic research investigator. In September 1996, one of the awardees, Dr. Deirdre Meldrum, was nationally recognized as a promising young scientist, and received a Presidential Early Career Award for Scientists and Engineers.

In the NHGRI intramural program, a genetic counseling training program has been established in collaboration with the Johns Hopkins School of Hygiene and Public Health. The program focuses on the development of advanced counseling skills, research capabilities in genetic counseling, and competence to provide education for health care providers and the public. Graduates receive a Master's degree from the Johns Hopkins University School of Hygiene and Public Health.

Beyond the Human DNA Sequence

Finding the gene(s) involved in a specific condition is only the first step in the development of diagnostics, preventive and treatment interventions. Once a gene has been discovered, many questions can begin to be addressed – what does the gene do? what is the gene product? how does the gene product function? what happens to the gene product and its function when the gene is altered? Now that the initial goals of the Human Genome Project appear to be attainable, systematic attention can be given to these subsequent questions. Until now, most of this effort has focused on individual genes. With the expectation of having the sequence of all human genes in the coming decade, truly novel approaches to understanding functions and interactions of tens of thousands of genes at any one time become possible to contemplate.

The successes of the Human Genome Project have come in large measure from improved technologies that were developed to be cost-efficient and applicable at large scale. In FY 1996, recognizing the power of such technologies, the NHGRI initiated the development of "genomic-scale" technologies for the study of genomic function and sequence variation by issuing two requests for applications. The first (co-sponsored by the National Cancer Institute), "Large Scale Functional Analysis of the Yeast Genome," called for research projects that will take advantage of the complete yeast DNA sequence to study biological phenomena important for human health and disease, in rapid, comprehensive and efficient ways. The second, "Technologies for Genome Analysis," is intended to stimulate the development of improved technologies that will facilitate systematic and comprehensive study of genomic function and sequence variation in complex organisms, including humans. Applications resulting from both solicitations will be funded in FY 1997.

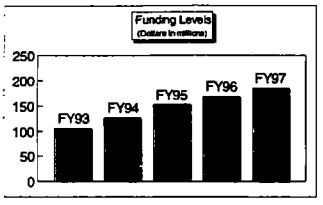
The NHGRI has now begun the process of planning for the period beyond the current 5-year plan and indeed beyond the year 2005, the time when the first reference human DNA sequence is expected to be completed. In December 1995, the NHGRI sponsored a symposium, entitled "Visions of Sequence-Based Biology and Medicine," to initiate this process. In September 1996, the NHGRI and the Howard Hughes Medical Institute held a meeting to continue these discussions. Further planning activities will take place over the next one to two years. Already it is clear that there are many opportunities and many scientific needs that can be addressed by the NHGRI in the future. Returning to the analogy with the discovery of the periodic table in the field of chemistry, the completion of the human DNA sequence will usher in an era of unprecedented productivity for biomedical science. The NHGRI will continue to play a key role in these developments.

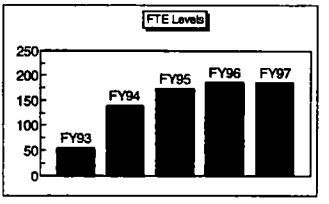
Purpose and Method of Operation

The NHGRI carries out its mission through the support of research project grants, research center grants, research career awards, other research grants, training grants and fellowships, and intra/inter-agency agreements within NIH and with other Federal agencies. In addition, the NHGRI supports an intramural research program which conducts research on genes and their function in disease and the eventual prevention, treatment, or cure of human diseases. The scientific and administrative management and other overhead items are funded through the research management and support budget mechanism.

Overall Budget Policy

The FY 1998 budget request for the National Human Genome Research Institue is $202,197,000. This amount represents an increase of $15,669,000 or 8.4 percent over the FY 1997 estimate. Funds for NHGRI AIDS research activities are included in the NIH Office of AIDS Research budget request. Funding for the NHGRI for the past 5 years has been as follows:





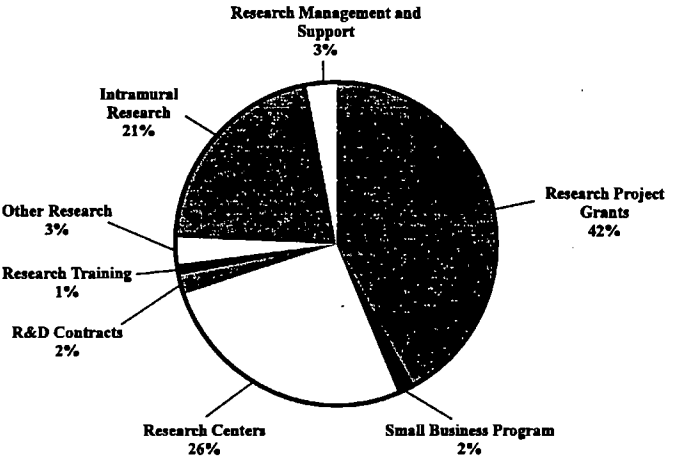
This FY 1998 budget request includes specific increases for NIH special initiative areas, these include genetic medicine, developmental instrumentation, and new preventive strategies against disease. The funds requested for the above initiatives will be used to support additional research project grants and increases to current genome science and technology centers. These activities fund research to develop genomic maps and the methods and technology needed to help scientists find the genes for the various diseases more rapidly. During FY 1998, the NHGRI expects to provide an increase to DNA sequencing techology and production, bringing the total level of support for human DNA sequencing to $60,000,000.

NIH policy links RPG average cost increases to total program budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for research project grants (RPGs). In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs will increase by up to two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP).

Funds provided to the Division of Intramural Research, will allow NHGRI investigators to continue their research on fundamental mechanisms of inherited and acquired genetic disorders. During FY 1998, the DIR expects to focus on mapping genes for common disorders in humans, including cancer, diabetes, and autoimmune diseases.

Funding for the scientific leadership and management of the NHGRI is $5,877,000, the same as FY 1997. Streamlining adminstrative activities, adopting NIH reinvention activities, and reducing all discretionary spending to below FY 1995 levels, allows NHGRI to fund mandatory pay related increases while keeping a level budget.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE
FY 1998 BUDGET REQUEST
$202,197,000*



	FY 1998 Request
Research Project Grants	$84,365,000
Small Business Program	4,002,000
Research Centers	53,280,000
Other Research	5,314,000
Research Training	2,883,000
R&D Contracts	4,060,000
Intramural Research	42,416,000
Research Management and Support	5,877,000
Total	202,197,000

*Funds for NHGRI AIDS research are requested through the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No	Amount	No.	Amount
Research Projects						
Noncompeting	82	$49,254,000	73	$45,335,900	102	$47,374,000
Administrative supplementals	(8)	466,000	(4)	1,100,000	(4)	515,000
Competing.						
Renewal	12	3,896,000	32	13,834,000	24	10,205,000
New	32	14,098,000	39	15,750,000	62	26,271,000
Supplemental	1	151,000	0	0	0	0
Subtotal, competing	45	18,145,000	71	29,584,000	86	36,476,000
SBIR/STTR	13	2,560,000	13	3,661,000	17	4,002,000
Subtotal, RPGs	140	70,425,000	157	79,680,000	205	88,367,000
Research Centers						
Specialized/comprehensive	15	42,600,000	14	47,814,000	14	53,280,000
Clinical reseach	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research centers in minority institution	0	0	0	0	0	0
Subtotal, Centers	15	42,600,000	14	47,814,000	14	53,280,000
Other Research						
Research careers	10	924,000	13	1,345,000	13	1,368,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	0	0	0	0	0
Other	27	1,960,000	21	3,414,000	23	3,946,000
Subtotal, Other Research	37	2,884,000	34	4,759,000	36	5,314,000
Total, Research Grants	192	115,909,000	205	132,253,000	255	146,961,000
Training	FTTPs		FTTPs		FTTPs	
Individual	36	940,000	31	904,000	31	923,000
Institutional	62	1,820,000	62	1,917,000	62	1,960,000
Total, Training	98	2,760,000	93	2,821,000	93	2,883,000
Research & development contracts	9	2,989 000	10	3,808,000	12	4,060,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	132	40,773,000	130	41,769,000	130	42,416,000
Research management and support	55	5,887,000	57	5,877,000	57	5,877,000
Cancer prevention & control	0	0	0	0	0	0
Construction	0	0	0	0	0	0
Total, NHGRI	187	168,318,000	187	186,528,000	187	202,197,000
(Clinical Trials)		(2,427,000)		(4,122,000)		(4,882,000)

Note Includes FTEs associated with HIV/AIDS research activities Funds to support these FTEs are included in the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Human Genome Research		$121,658		$138,882		$153,904		15,022
Subtotal, Extramural research		121,658		138,882		153,904		15,022
Intramural research	132	40,748	130	41,769	130	42,416	0	647
Research management and support	55	5,887	57	5,877	57	5,877	0	0
Total obligations	187	168,293	187	186,528	187	202,197	0	15,669
Unobligated balance lapsing		25		0		0		0
Total, Budget Authority	187	168,318	187	186,528	187	202,197	0	15,669

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Summary of Changes

1997 Estimated budget authority	$186,528,000
1998 Estimated budget authority	202,197,000
Net change	15,669,000

	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$11,656,000		148,000
b. Annualization of January 1997 pay increase		11,656,000		97,000
c. January 1998 pay increase		11,656,000		250,000
d. Legislative proposal, 1.51% increase in the CSRS rate		11,656,000		11,000
e. Service and supply fund		2,477,000		64,000
f. Increased cost of laboratory supplies, materials, and other expenses		22,290,000		580,000
Subtotal				1,150,000
2. Research Management and Support:				
a. Within grade increase		3,910,000		67,000
b. Annualization of January 1997 pay increase		3,910,000		33,000
c. January 1998 pay increase		3,910,000		84,000
d. Legislative proposal, 1.51% increase in the CSRS rate		3,910,000		19,000
e. Service and supply fund		232,000		6,000
f. Increased cost of laboratory supplies, materials, and other expenses		659,000		17,000
Subtotal				226,000
Subtotal, Built-in				1,376,000

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute
Summary of Changes--continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	73	46,435,000	29	1,454,000
b. Competing	71	29,584,000	15	6,892,000
c. SBIR/STTR	13	3,661,000	4	341,000
Total	157	79,680,000	48	8,687,000
2. Centers		47,814,000		5,466,000
3. Other research	34	4,759,000	2	555,000
4. Research training		2,821,000		62,000
5. Research and development contracts	10	3,808,000	2	252,000
6. Intramural research:				
a. Programmatic changes		41,769,000		(1,150,000)
b. Special emphasis areas		41,769,000		647,000
Subtotal, intramural		41,769,000		(503,000)
7. Research management and support		5,877,000		(226,000)
Subtotal, program		186,528,000		14,293,000
Total changes				15,669,000

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Budget Authority by Object

	FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	187	187	---
Full-time equivalent of overtime and holiday hours	2	2	---
Average ES salary	$119,852	$123,387	$3,535
Average GM/GS grade	10.7	10.7	---
Average GM/GS salary	$49,353	$50,809	$1,456
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$44,746	$45,999	$1,253
Average salary of ungraded positions	$63,734	$65,614	$1,880

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	7,204,000	7,491,000	$287,000
11.3	Other than Full-Time Permanent	2,446,000	2,542,000	96,000
11.5	Other Personnel Compensation	316,000	329,000	13,000
11.8	Special Personnel Services Payments	3,119,000	3,221,000	102,000
11.9	**Total Personnel Compensation**	**13,085,000**	**13,583,000**	**498,000**
12.0	Personnel Benefits	2,473,000	2,575,000	102,000
13.0	Benefits for Former Personnel	8,000	8,000	0
	Subtotal, Pay Costs	**15,566,000**	**16,166,000**	**600,000**
21.0	Travel & Transportation of Persons	596,000	607,000	11,000
22.0	Transportation of Things	147,000	149,000	2,000
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	13,000	13,000	0
23.3	Communications, Utilities & Miscellaneous Charges	764,000	782,000	18,000
24.0	Printing & Reproduction	65,000	64,000	(1,000)
25.1	Consulting Services	289,000	279,000	(10,000)
25.2	Other Services	6,113,000	5,779,000	(334,000)
25.3	Purchase of Goods & Services from Government Accounts	14,513,000	14,815,000	302,000
25.4	Operation & Maintenance of Facilities	924,000	948,000	24,000
25.5	Research & Development Contracts	500,000	512,000	12,000
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	466,000	463,000	(3,000)
25.8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**22,805,000**	**22,796,000**	**(9,000)**
26.0	Supplies & Materials	5,601,000	5,732,000	131,000
31.0	Equipment	5,846,000	5,992,000	146,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	135,074,000	149,844,000	14,770,000
42.0	Insurance Claims & Indemnities	51,000	52,000	1,000
43.0	Interest & Dividends	0	0	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**170,962,000**	**186,031,000**	**15,069,000**
				0
	Total, Budget Authority by Object	**186,528,000**	**202,197,000**	**15,669,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$7,204,000	$7,491,000	$287,000
Other Than Full-Time Permanent (11.3)	2,446,000	2,542,000	96,000
Other Personnel Compensation (11.5)	316,000	329,000	13,000
Special Personnel Services Payments (11.8)	3,119,000	3,221,000	102,000
Total Personnel Compensation (11.9)	**13,085,000**	**13,583,000**	**498,000**
Civilian Personnel Benefits (12.0)	2,473,000	2,575,000	102,000
Benefits to Former Personnel (13.0)	8,000	8,000	0
Subtotal, Pay Costs	**15,566,000**	**16,166,000**	**600,000**
Travel (21.0)	596,000	607,000	11,000
Transportation of Things (22.0)	147,000	149,000	2,000
Rental Payments to Others (23.2)	13,000	13,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	764,000	782,000	18,000
Printing and Reproduction (24.0)	65,000	64,000	(1,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	289,000	279,000	(10,000
Other Services (25.2)	6,113,000	5,779,000	(334,000
Purchases from Govt. Accounts (25.3)	11,205,000	11,267,000	62,000
Operation & Maintenance of Facililties (25.4)	924,000	948,000	24,000
Operation & Maintenance of Equipment (25.7)	466,000	463,000	(3,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**18,997,000**	**18,736,000**	**(261,000**
Supplies and Materials (26.0)	5,589,000	5,719,000	130,000
Subtotal, Non-Pay Costs	26,171,000	26,070,000	(101,000
Total, Administrative Costs	**41,737,000**	**42,236,000**	**499,000**

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 1997 House Appropriations Committee Report Language

Item

Primary immune deficiency diseases -- The Committee stated...More than seventy primary immune deficiency diseases have been identified by researchers to date. Research into the human genome has resulted in the discovery of the genetic defects that result in 17 of these 70 diseases, in which the body is incapable of fighting off infection. Discovering the defective genes that cause each disease is a critical step toward early and accurate diagnosis and treatment, which can relieve great suffering, and eventually toward prevention and cure. The Committee notes the advances that have occurred in research into primary immune deficiency diseases as a clear example of the prospects that result from the research of NCHGR and strongly encourages the Center to continue to focus on the identification and sequencing of genes that cause genetic-based illnesses.

Action Taken or to be Taken

The Clinical Gene Therapy Branch and the Laboratory of Gene Transfer, Division of Intramural Research, have as a major foci studies of the primary immunodeficiency diseases, including the Wiskott-Aldrich Syndrome and three forms of severe combined immunodeficiency (SCID) caused by unique genetic defects--adenosine deaminase deficiency, JAK3 deficiency, and X-SCID deficiency. These studies include clinical investigation into the basic defects causing the immune problems and therapeutic clinical trials including gene therapy. The NHGRI was directly involved in the determination of the gene defect in the Wiskott-Aldrich syndrome, X-SCID deficiency, and JAK3 deficiency. Clinical trials for both X-SCID and JAK3 deficiency SCID are planned. Genetic and clinical studies of X-SCID are continuing, and a Workshop for Families With X-SCID jointly sponsored by the Immune Deficiency Foundation, the Office of Rare Diseases, and the NHGRI is planned for April 18-19, 1997.

Item

Fanconi anemia -- The Committee stated...Fanconi anemia is a fatal, inherited, genetic disorder in which patients manifest various congenital abnormalities and are predisposed to cancer. Recent research has indicated that mutations in at least four different genes can cause Fanconi anemia. The DNA for one of the genes has been cloned and found to encode a novel protein. Even though the protein's function is unknown at present, research has now reached the point where rapid progress to a detailed understanding of this syndrome may be possible. The Committee encourages the Center to pursue additional research opportunities into this disorder.

Action Taken or to be Taken

Efforts to treat Fanconi anemia have recently met with gratifying success. A gene for one form of Fanconi anemia was cloned this year using the tools developed by the Human Genome Project. The NHGRI continues to monitor progress in research related to Fanconi anemina and has formed a number of collaborations with other NIH institutes to improve the understanding of human genetic disease, including Fanconi anemia.

FY 1997 Senate Appropriations Committee Report Language

Item

Genetic discrimination -- The Committee stated...The Committee commends the NCHGR for its leadership in research and policy development related to the important ethical, legal and social implications of the human genome project and human genetics research. The Committee is particularly pleased with the attention to genetic discrimination in health insurance and the development of concise, cogent policy recommendations. The Committee supports the NCHGR's ongoing efforts to examine many of the other important issues related to human genetics research and its consequences including: the appropriate use of genetic tests; the use of genetic information in the workplace; human subjects concerns, such as informed consent in the genetic research; the education of health professionals about genetics and its application in health care; and the protection of genetics and its application in health care; and the protection of genetic privacy. The Committee also supports efforts to include a diverse group of interested parties in all of its research and policy development activities.

Action Taken or to be Taken

The NHGRI has long been concerned about the fair use of genetic information. In response to this concern, the NHGRI-DOE ELSI Working Group formed a Task Force on Genetic Information and Health Insurance. The Task Force released its recommendations in 1993, which included prohibiting the use of genetic information in denying or limiting health care coverage or services and ensuring universal access to and participation in a program of basic health services, including genetic services.

Building on their shared concerns about genetic discrimination, the ELSI Working Group and the National Action Plan on Breast Cancer have co-sponsored two workshops on discrimination. The first, held in July 1995, addressed the issue of genetic information and health insurance discrimination. Based on the information presented at the workshop and subsequent discussions, recommendations designed to protect against genetic discrimination in health insurance were developed, published, and widely disseminated. The second workshop, held in October 1996, addressed genetic information and employment discrimination. The recommendations from this workshop will be published in the coming months and will be widely disseminated. It is anticipated that these recommendations will provide meaningful information to policy makers as

they discuss the need for additional legislative protections. The NHGRI will continue its efforts in the area of genetic discrimination and will expand them to include efforts in the broader area of genetic privacy.

In early 1995, the NHGRI-DOE ELSI Working Group formed a Task Force on Genetic Testing to examine the current state of genetic testing in the U.S. to make recommendations that will ensure the development and delivery of safe and effective genetic tests. Specific issues addressed were the scientific validation of new genetic tests; laboratory quality assurance; and education, counseling, and delivery of genetic tests. Several federal agencies including the Food and Drug Administration, Health Care Financing Administration, Centers for Disease Control and Prevention, and Agency for Health Care Policy Research, professional societies, as well as the biotechnology industry, insurers and consumers participated in the Task Force. In March 1996, the Task Force released a set of draft Interim Principles for public comment. The final Principles and Recommendations of the Task Force are expected to be released in the Spring of 1997.

To ensure that our nation's health care providers have the knowledge, skills, and resources to effectively integrate new genetic knowledge and technologies into the prevention, diagnosis, and treatment of disease, the NHGRI has been working with the American Medical Association and the American Nurses Association to establish a National Coalition for Health Professional Education in Genetics (the Coalition). The Coalition will bring together and establish collaboration between leaders in health care professional, consumer, government, genetics, and industry organizations for the purpose of developing and implementing a comprehensive, national genetics education effort for health care professionals. An organizational meeting of the Steering Committee, which included representatives from consumer organizations, medical professional organizations, nursing professional organizations, and genetics professional organizations, was held in July 1996. The first meeting of the full Coalition will be held in March 1997.

Item

Primary immune deficiency diseases -- The Senate in its report 104-368, page 112 stated...More than seventy primary immune deficiency diseases have been identified by researchers to date. Research into the human genome has resulted in the discovery of the genetic defects that result in 17 of these 70 diseases, in which the body is incapable of fighting off infection. Discovering the defective genes that cause each disease is a critical step toward early and accurate diagnosis and treatment, which can relieve great suffering, and eventually toward prevention and cure. With 500,000 diagnosed cases and another 500,000 estimated as undiagnosed, the Committee notes the advances that have occurred in research into primary immune deficiency diseases as a clear example of the prospects that result from the research of NCHGR and strongly encourages the Center to continue to focus on the identification and sequencing of genes that cause genetic-based illnesses.

Action Taken or to be Taken

The Clinical Gene Therapy Branch and the Laboratory of Gene Transfer, Division of Intramural Research, have as a major foci studies of the primary immunodeficiency diseases, including the Wiskott-Aldrich Syndrome and three forms of severe combined immunodeficiency (SCID) caused by unique genetic defects--adenosine deaminase deficiency, JAK3 deficiency, and X-SCID deficiency. These studies include clinical investigation into the basic defects causing the immune problems and therapeutic clinical trials including gene therapy. The NHGRI was directly involved in the determination of the gene defect in the Wiskott-Aldrich syndrome, X-SCID deficiency, and JAK3 deficiency. Clinical trials for both X-SCID and JAK3 deficiency SCID are planned. Genetic and clinical studies of X-SCID are continuing, and a Workshop for Families With X-SCID jointly sponsored by the Immune Deficiency Foundation, the Office of Rare Diseases, and the NHGRI is planned for April 18-19, 1997.

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$183,707,000	Indefinite	$199,314,000
National Human Genome Research Institute	Section 485B	42§285g	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288(d)	Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208)	2,821,000	Reauthorizing legislation will be submitted	2,883,000
Total, Budget Authority				186,528,000		202,197,000

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1989				
1990	$100,000,000	$62,000,000	---- 2/	$59,938,000
1990 Sequester				-400,000
1991	108,029,000	66,131,000	108,264,000	87,418,000 3/
1991 Sequester				-1,000
1992	110,487,000	93,115,000	109,309,000	104,762,000 4/
1993	110,429,000	107,217,000	107,217,000	106,239,000 5/
1994	134,549,000	119,030,000	131,925,000	127,112,000 6/
1995 7/	152,010,000	151,878,000	151,878,000	151,518,000 8/
1995 Rescission				-331,000
1996	166,678,000 7/	170,041,000	163,943,000 7/	169,041,000 7/
1996 Rescission				-266,000
1997	177,788,000 7/	189,267,000	180,807,000 7/	189,529,000 9/
1998	202,197,000 7/			

1/ Reflects enacted supplements, rescission, and reappropriations.

2/ The Senate did not provide funds for the National Human Genome Research Institute; however, the Senate allowance included $61,847,000 for the Human Genome Initiative within the National Institute of General Medical Sciences' account.

3/ Excludes enacted administrative reductions of $2,313,000 and the enacted rescission of $116,000.

4/ Excludes enacted administrative reductions of $383,000.

5/ Excludes enacted administrative reductions of $978,000.

6/ Excludes rescission of $1,589,000.

7/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS research.

8/ Excludes enacted administrative reductions of $161,000.

9/ Excludes enacted administrative reductions of $128,000.

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	6	5	5
Office of Admin. Mgmt.	21	21	21
Office of Policy Coordination	9	9	9
Office of Info. Systems Mgmt.	4	4	4
Office of Scientific Review	4	4	4
Division of Extramural	11	14	14
Division of Intramural	132	130	130
Total, ICD	187	187	187
	Average GS/GM Grade		
1993	10.2		
1994	10.3		
1995	10.5		
1996	10.7		
1997	10.7		
1998	10.7		

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Human Genome Research Institute

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	1	1	1
ES-5	0	2	2
ES-4	2	1	1
ES-3	1	0	0
ES-2	0	0	0
Subtotal	4	4	4
Total - ES Salary	$464,774	$479,407	$493,549
GS/GM-15	11	11	11
GS/GM-14	16	16	16
GS/GM-13	16	16	17
GS-12	24	26	26
GS-11	23	21	20
GS-10	2	2	2
GS-9	13	13	12
GS-8	11	11	12
GS-7	11	10	10
GS-6	2	3	2
GS-5	1	1	2
GS-4	2	2	3
GS-3	5	5	3
GS-2	1	1	2
GS-1	0	0	0
Subtotal	138	138	138
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	1	1	1
Senior Grade	2	2	2
Full Grade	3	3	3
Senior Assistant Grade	1	1	1
Subtotal	7	7	7
Ungraded	46	48	48
Total permanent positions	140	143	144
Total positions, end of year	195	197	197
Total full-time equivalent (FTE) employment,end of year	187	187	187
Average ES level	4	5	5
Average ES salary	$116,194	$119,852	$123,387
Average GS/GM grade	10.7	10.7	10.7
Average GS/GM salary	$47,847	$49,353	$50,809

THURSDAY, FEBRUARY 27, 1997.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

ANTHONY S. FAUCI, M.D., DIRECTOR

JOHN J. McGOWAN, M.D., ACTING DEPUTY DIRECTOR

GEORGE W. COUNTS, M.D., DIRECTOR, ORMWH

STEVEN J. BERKOWITZ, ACTING ASSOCIATE DIRECTOR FOR MANAGEMENT AND OPERATIONS

THOMAS D. WILLIAMS, BUDGET OFFICER

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

Dr. Fauci, we somehow scheduled both you and Dr. Collins in the same two-hour timeframe. I think it's insufficient for either one of you, and we will ask you also if you would consider coming back later in the year when we can spend a little more time. I just think this timeframe is simply too short.

Dr. FAUCI. I'd be delighted to do so.

Mr. PORTER. With that, I am going to ask you to introduce the people with you, and then proceed. We will see how expeditious we can be and perhaps we can save some time at this point in the proceedings.

INTRODUCTION OF WITNESSES

Dr. FAUCI. Thank you very much, Mr. Chairman.

Let me first introduce my colleagues at the table. This is Dr. George Counts on my far left, who is the Director of our Office on Research on Minority and Women's Health; Dr. John McGowan, who is the Deputy Director of the Institute; Mr. Steven Berkowitz, who is the Associate Director for Management and Operations; Mr. Thomas Williams, who is our Budget Officer; and you know Dr. Varmus and Mr. Dennis Williams.

You have my written statement, Mr. Porter. What I would like to do is just take a few minutes and summarize some of the salient features of that, with some visual aids.

OPENING STATEMENT

The question that I often get asked relates to the cover of *Newsweek* magazine and other popular lay magazines that we've seen over the years; are we really approaching or at the cusp of the end of HIV/AIDS? And the answer is, although there have been sub-

stantial and dramatic advances over the past year, the answer to this question is no.

[See figure 1.]

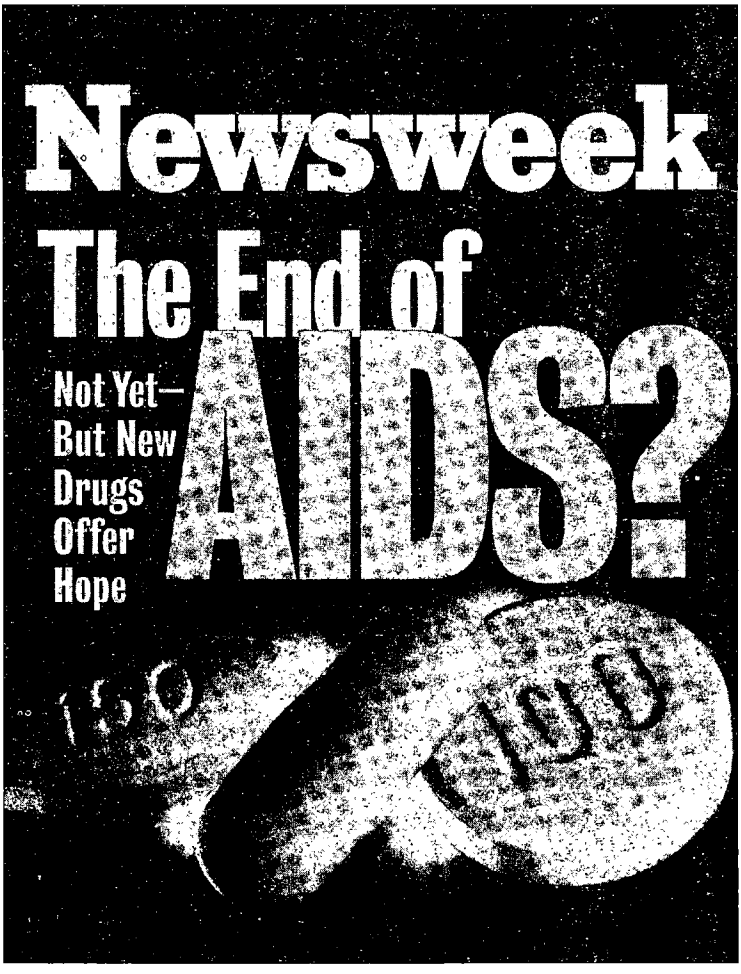


Figure 1

Dr. Varmus appropriately spoke about culminations and inspirations. Certain aspects of AIDS research are almost but not quite yet culminations, and there are probably more inspirations than there are culminations.

Since I have testified before this committee about the advances in AIDS several times over the past years, what I would like to do very briefly is summarize, in a temperate fashion, some of the things that I've actually told you in this committee regarding the evolution of treatment strategies for HIV/AIDS.

You might recall that in 1987 when I came before the committee and told you about the use of AZT as a single drug monotherapy, let me put into perspective what this drug and other drugs have done, one, to the virus, and two, to the patient in question.

[See figure 2.]

Evolution of Treatment Strategies for HIV Disease

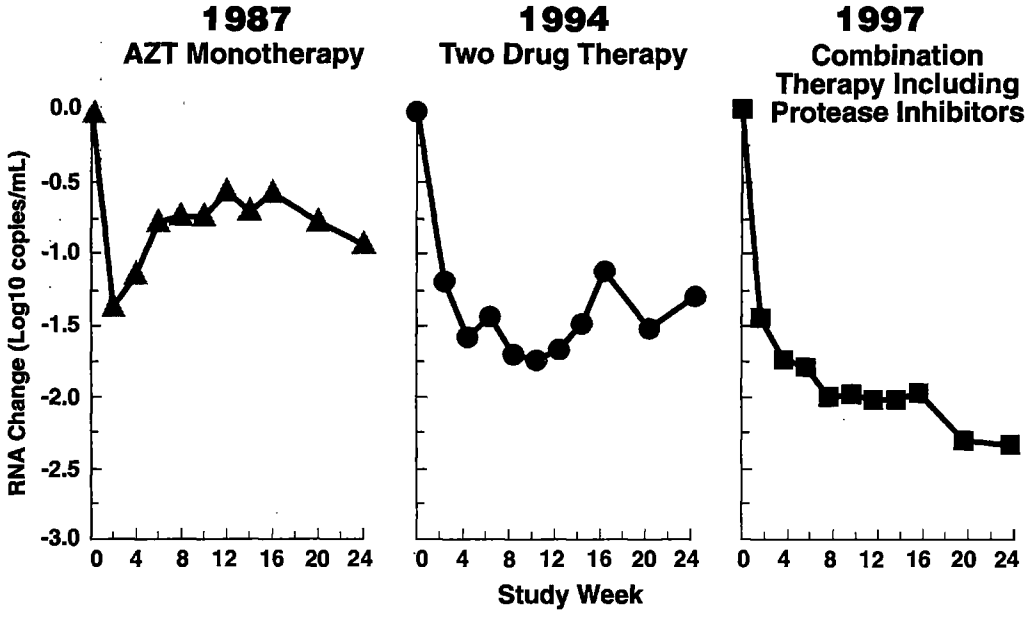


Figure 2

This is a measurement of level of virus, and this is week of study or time upon the antiviral. When we had AZT alone in 1987, this is what we call a logarithmic scale, so that when you go down from 1 to 2, you are actually going down by 10—10 times the amount, not twice the amount.

As you can see, there is a substantial drop in the level of virus, but that drop is transient, and comes back down with mutations that are resistant to the drug. So in the short run, AZT was good for people with advanced disease, but proved in people with early disease to not be sufficient to have a significant clinical impact.

Then in 1994, just a couple of years ago, I came before the committee and told you about the double-drug combination which not only brought the virus down further, but it was more sustained, and for the first time it was actually a clinical benefit in early disease.

What we are seeing now in 1997 with the combination of three drugs, including the protease inhibitor, is the virus going, in many cases—and sometimes the majority of cases, depending on the study—to below detectable level in the blood. But as we know from recent studies, the virus has not been eliminated from the body, because you can still isolate it. But in the blood it is below detectable level, and that is sustained.

Just a couple of days ago we had a study which compared three drugs in late disease, including protease, with two drugs, and for the first time a clinical benefit with regard to death and adverse events in late disease was shown. What we don't know is if there is going to be a clinical benefit if given over a long period of time, and whether the cumulative toxicities and the emergence of resistance might outweigh some of the beneficial effects that everyone seems to be so excited about.

I said this, actually, in an editorial last summer at the time of the Vancouver meeting, when I stated—which is really summarized right here—that there has been much accomplished in AIDS research, but still much to do. What I would like to spend the next couple of minutes on is talking to you about some of those things that Dr. Varmus referred to as "inspiration." Again, going back historically, several years ago, more than just a few, I came before the committee and told you about the different targets of our antiviral drugs. Looking at the life cycle of HIV, very quickly, the virus binds to the cell; enters it; uses an enzyme to convert its genetic material—this is the target of AZT and ddI and ddC. It integrates into the nucleus, and then it has production of additional virions. This is the target of the protease inhibitors. But what we just discovered this year is very exciting because it's the example of the convergence of two areas of research, one that was directly AIDS. You've heard several of the members talk about the overlap between AIDS and non-AIDS. Investigators were looking at the physiology of a cell and the receptors that it uses, and investigators were looking at how you block the virus in a particular cell, and a co-receptor or a co-factor was found by investigators who were looking at why cells, when they get infected, fuse with each other. This co-receptor turned out to actually be a normal receptor for a protein that the body uses to mount an inflammatory response.

[See figures 3, 4, and 5.]

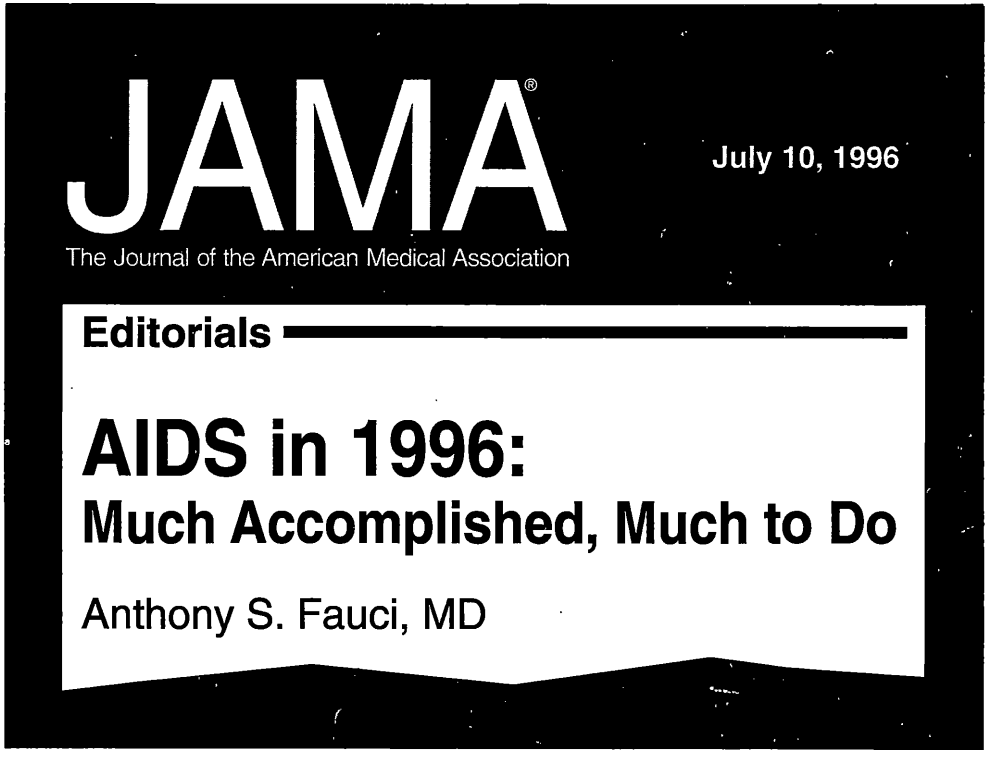
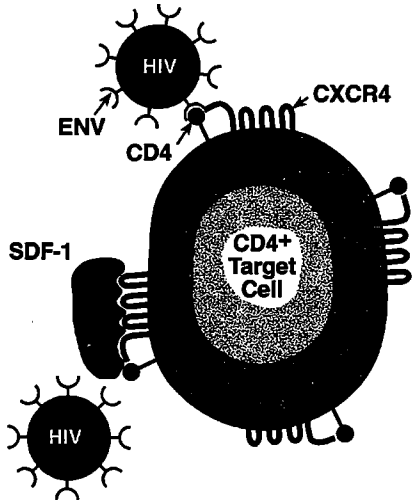

JAMA®
The Journal of the American Medical Association
July 10, 1996
Editorials
AIDS in 1996:
Much Accomplished, Much to Do
Anthony S. Fauci, MD

Figure 3

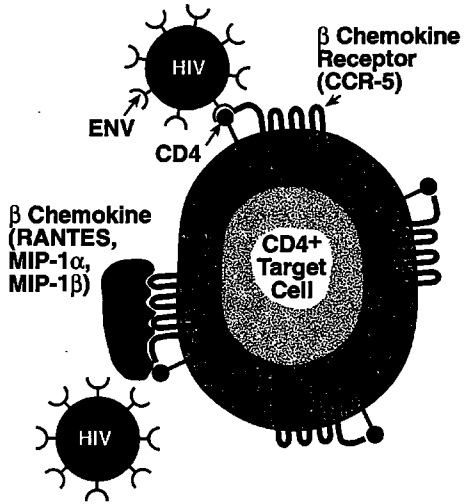
Life Cycle of the Human Immunodeficiency Virus (HIV)

Figure 4

Co-Receptors for Various Strains of HIV-1 and Their Respective Inhibitory Ligands



T Cell Line-Tropic
Strain of HIV-1



Macrophage-Tropic
Strain of HIV-1

Figure 5

So investigators have been working on this for years, having relatively little interest in AIDS. AIDS investigators were looking for the receptor for the virus. You put them together, and what you find out is that these natural proteins are very, very potent in blocking the ability of the virus to bind to the cell because they occupy the same receptor.

So just on a fundamental basic science observation, we now have a brand new target, not only for the development of therapeutics, but perhaps for the development of a vaccine. This is a classic example of how something came out of basic research, and hopefully in future hearings I will be telling you about some of these clinical trials.

We heard yesterday a bit about where we are in AIDS vaccine. You know that we have a renewed effort in AIDS vaccine. We have Dr. David Baltimore now who is heading our Advisory Committee.

Rather than go into any detail about this, I would say that we have a balance of the fundamental basic research approach with an empiric approach of looking at candidates that are in various stages of development, and you'll be hearing more about this over the next year or so.

[See figure 6.]

A Balanced Approach to the Development of an HIV Vaccine
Industry Partnerships
Community Participation
Empiric Approaches
Basic Research
Organizational Collaborations (e.g. DOD, WHO, etc)
The National Institutes of Health

Figure 6

Speaking of basic research, you might also remember one thing that hit the newspapers, which is that the Nobel Prize for 1996 in medicine was given to two immunologists, Dr. Peter Doherty and Rolf Zinkernagel, a current and a former grantee of NIAID. And more than 20 years ago, they made a fundamental observation that had nothing to do with any particular disease. They were able to very clearly demonstrate that when a T cell, which is the major guardian cell looking for disease in the body, encounters a virus-infected cell, that the molecules that form the fit of a lock-and-key account for both the specificity and the restriction of that response, opening up an entire new avenue of research to explain many immunological phenomena. They didn't even fully realize then, when they were dealing with an animal virus, that they would open up so many doors in immunology.

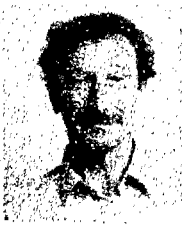
[See figure 7.]

NIAID Grantees Win Nobel Prize for Basic Immunology Research



Peter C. Doherty

Rolf M. Zinkernagel



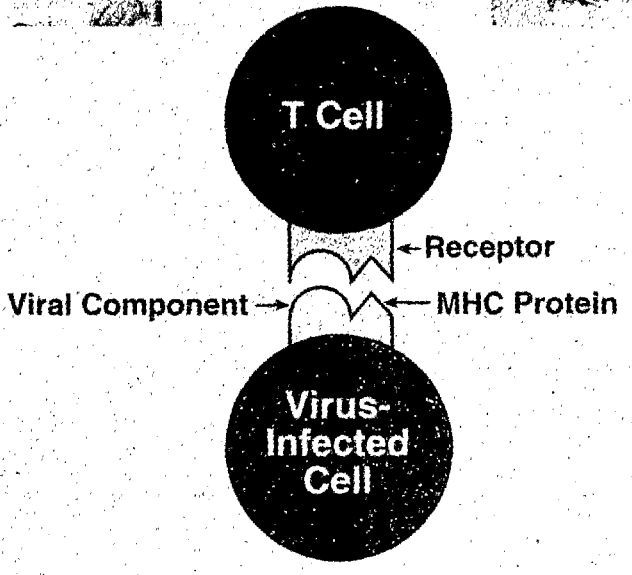


Figure 7

One of the doors that they opened for us has to do with vaccines, because the vaccines of the future—again, this has been in the newspapers a lot over the last year—is the DNA vaccine. You actually take the gene that codes from a protein of a microbe, so that it's perfectly safe; you don't take the whole microbe. You inject it into the muscle of an individual, and that protein presents itself to the body in association with the right molecules that Doherty and Zinkernagel spoke about over 20 years ago, giving you a very potent immunological response of both antibody and cell-mediated response.

[See figure 8.]

Vaccines of the Future:
Naked DNA Vaccines
Influenza
HIV
Measles
Tuberculosis
Malaria
Other Emerging Infections
DNA
Expression of Protein
Immune Recognition
Immune Response

Figure 8

We already have clinical trials looking at it in influenza. We've begun them in HIV, and it's going to open up new possibilities for diseases for which we don't have a vaccine: malaria. We can get an approved vaccine for measles, hopefully; but also, the other emerging microbes that I spoke to this committee about, that we haven't even identified yet. But once you identify them, once you use the genetic technology that we have available, you can go right into this type of vaccine work.

This is another example of basic research leading to very important and potentially practical results.

So let me close on this introduction by getting back to the thing that I started with, the fundamental area of basic research and how this is the source of the inspirations that Dr. Varmus spoke about yesterday. For our Institute, it's immunology and infectious disease. But this chart could just as well apply to virtually all of the Institutes that you're going to be hearing from over the next week or so. And in our case, the fundamental research leads to these types of advantage.

[See figure 9.]

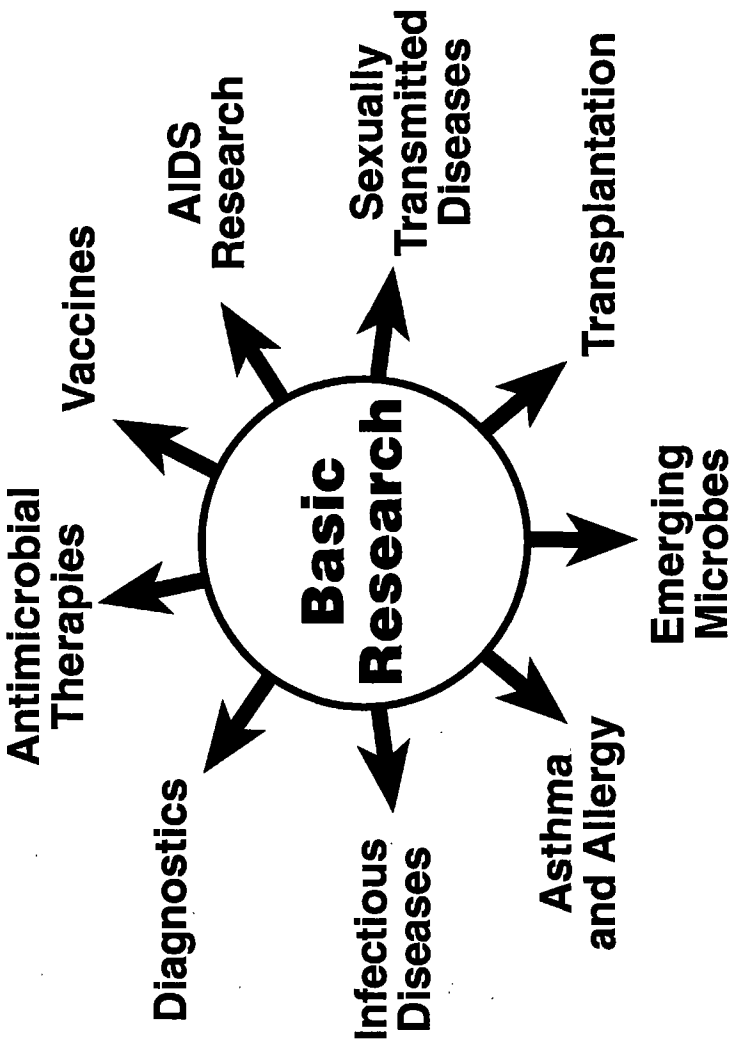

Basic Research
Vaccines
AIDS Research
Sexually Transmitted Diseases
Transplantation
Emerging Microbes
Asthma and Allergy
Infectious Diseases
Diagnostics
Antimicrobial Therapies

Figure 9

We would, again, thank you very much for the support that you have given us—not only for the practical things, like for an identifiable disease, but for the basic research that is the source for the inspirations that lead us to those practical applications.

I would be very happy to answer any questions.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Statement of the Director
National Institute of Allergy and Infectious Diseases

The past year has been a time of considerable accomplishment at the National Institute of Allergy and Infectious Diseases (NIAID), as NIAID-supported scientists made major strides in understanding, preventing and treating important infectious and immunologic diseases that threaten the health of people in the United States and abroad.

NIAID-supported investigators reported significant new advances in fighting several of the leading reportable infectious diseases in the United States, including the acquired immunodeficiency syndrome (AIDS), chlamydia and other sexually transmitted diseases, tuberculosis, and Lyme disease. Significant progress was made in the research effort against infectious killers of children, such as diarrheal diseases. Other findings suggested new approaches for treating autoimmune diseases such as multiple sclerosis.

Each of these recent accomplishments was facilitated by knowledge gleaned through basic research. For example, the fundamental discovery in the 1970s of how the immune system distinguishes "self" from "non-self," for which two long-time NIAID grantees were awarded the 1996 Nobel Prize for Physiology or Medicine, influenced many of the advances I will discuss.

The translation of basic research findings into practical applications has been particularly noteworthy in the fight against the human immunodeficiency virus (HIV), the virus that causes AIDS. Fundamental research into the structure and function of the HIV protease enzyme led to the development of a powerful new class of anti-HIV medications that block this enzyme, and hence the replication of the virus. Three of these drugs, called protease inhibitors, were recently approved for marketing in the United States; others are in late stages of clinical testing. Protease inhibitors are now widely prescribed as part of combination treatment regimens for HIV-infected people, and in some patients have controlled the replication of HIV to a degree not previously possible. NIAID currently is conducting clinical trials to determine how best to use protease inhibitors ard whether their significant short-term benefits are sustainable for prolonged periods without prohibitive toxicities or the widespread development of drug resistance.

In another major development in AIDS research, two separate fields of scientific inquiry converged to provide long-sought information on the HIV disease process and important new targets for therapies. One group of researchers demonstrated that certain immune signalling molecules called chemokines, normally secreted as part of the body's inflammatory response, can suppress certain strains of HIV. Other investigators identified molecules on the surfaces of immune system cells that play key roles in enabling different strains of HIV to infect the cells.

It soon became clear that these findings were related and complementary. In important instances, chemokines suppress HIV because they bind to the same cell surface molecules needed by the virus for entry. These discoveries suggest that it might be possible to treat HIV infection with drugs that block these cell surface molecules, or to prevent infection with vaccines that elicit antibodies that inhibit the binding of HIV to the molecules. Scientists around the world are now pursuing these and related approaches, building on the exceptional leads provided by NIAID-supported researchers.

The development of an HIV vaccine remains an important goal of the Institute, one we are pursuing with a two-pronged strategy of basic and applied research. Basic researchers are uncovering important clues about the specific immune responses that might protect an individual from HIV infection or disease progression. Parallel with

basic research efforts, the Institute continues to test candidate vaccine products in small-scale trials around the world. Since 1988 more than 2,300 non-HIV infected adult volunteers have enrolled in approximately 30 phase I and II vaccine trials conducted in the United States by NIAID's AIDS Vaccine Evaluation Group (AVEG). These trials have involved 16 experimental vaccines, 12 immune-stimulating substances called adjuvants and a variety of delivery vehicles and routes, dosages and immunization schedules.

Early clinical studies of experimental HIV vaccines focused on products based on a single protein from the envelope of HIV. These have given way to more complex strategies, including a two-step approach in which a person is injected with a harmless virus genetically engineered to make HIV proteins, and later given a booster shot of an HIV-derived protein. This so-called "prime-boost" strategy has shown promise in non-human primate models of AIDS, protecting a significant proportion of animals. Small-scale studies in human volunteers suggest that the approach is safe and can stimulate anti-HIV antibodies, as well as cytotoxic T cells, which kill HIV-infected cells.

The HIV epidemic is inextricably linked to other sexually transmitted diseases (STDs). HIV and other STDs share a common mode of transmission, and people with STDs are more likely to transmit HIV or become infected with HIV than people without STDs. It is often underappreciated, however, that STDs are an enormous problem in their own right; they comprise a "hidden epidemic" that the Institute of Medicine recently addressed in a lengthy report. Altogether, more than 12 million Americans acquire a sexually transmitted disease (STD) other than HIV each year, at a total cost to the Nation that exceeds $10 billion (Institute of Medicine, 1997). In addition to their huge economic burden, STDs can have devastating health consequences. For example, hepatitis B virus is a leading cause of liver cancer, and certain types of human papillomavirus account for nearly all cancers of the cervix, vagina, vulva, anus and penis. Untreated chlamydial and gonorrheal infections frequently lead to pelvic inflammatory disease (PID), which in turn can result in life-threatening tubal pregnancies and scarring of a woman's fallopian tubes leading to infertility.

The NIAID has addressed the challenges posed by STDs with a multidisciplinary research strategy encompassing basic, applied and behavioral research. For example, the Institute is developing topical microbicides, substances that a woman can use in her vagina before intercourse to prevent the transmission of sexually transmitted microbes, including HIV. Several promising microbicides are in various stages of pre-clinical and clinical development. NIAID-supported scientists also are developing better diagnostic tests to help clinicians detect and treat asymptomatic STDs before they cause serious health problems. Sensitive, non-invasive urine tests for chlamydia and gonorrhea hold particular promise for detecting both symptomatic and asymptomatic cases of these diseases, especially in the context of large-scale screening programs. Screening for asymptomatic STDs can have a notable effect: a recent NIAID-funded trial demonstrated that women screened and treated for asymptomatic chlamydial infection were 60 percent less likely than unscreened women to develop pelvic inflammatory disease.

Dehydration due to diarrheal diseases is a leading causes of death worldwide, particularly among children. Rotaviruses cause 35 to 50 percent of the world's severe diarrhea cases in infants and young children, resulting in more than 800,000 deaths annually. In the United States, more than 1 million cases of rotaviral diarrhea and 50,000 hospitalizations occur each year. Because of a lack of a specific drug to treat this condition, scientists at NIAID designed and tested a vaccine that combines human and animal rotavirus genes. In large-scale clinical trials, this vaccine has been found safe, with only mild side effects, and effective 80 to 90 percent of the time. The vaccine is

now nearing licensure and promises to have a major impact on the health of the world's children. The successful development of this vaccine exemplifies the synergy between basic and applied research, as well as the fruitful collaborations that are possible between the private and public sectors.

NIAID-funded investigators are now working on the vaccines of the future: "naked DNA" vaccines, which contain the gene or genes for the antigenic portion of a pathogen, injected directly into the muscle of a patient. These vaccines have many potential advantages over conventional vaccines, including greater purity and stability, economy and ease of purification, and relative safety in immunocompromised individuals. The use of naked DNA vaccines may offer a way to develop a better childhood vaccine that is easily delivered and provides durable immunity against multiple pathogens without requiring refrigeration.

Recent studies in mice show the feasibility of designing naked DNA vaccines to prevent tuberculosis. Naked DNA vaccines also have shown promise for many other conditions. For instance, a naked DNA influenza vaccine has protected laboratory animals from multiple strains of influenza virus. Further development of this approach may one day reduce the need to prepare new vaccines each year to prevent epidemics caused by different strains of influenza virus.

Lyme disease, first recognized in the 1970s, is the most common vector-borne infection in the United States. Much of the progress in understanding this condition has been facilitated by NIAID-supported discoveries. An NIAID investigator identified the causative bacterium, and NIAID-supported research subsequently revealed how the bacterium is transmitted and causes disease. NIAID-supported researchers also identified the bacterial surface antigens on which improved diagnostic tests and experimental vaccines are based.

Although most patients diagnosed with Lyme disease are successfully treated soon after infection, a small proportion develop a chronic condition called Post-Lyme Disease Syndrome, characterized by persistent musculoskeletal and peripheral nerve pain, fatigue and memory impairment. Scientists have speculated that the syndrome may be caused by ongoing infection with the Lyme bacterium or another tick-borne pathogen, or perhaps by persistent inflammatory or immune responses; however, the precise pathogenesis is unclear. Recently, the Institute launched a five-year initiative to study the pathogenesis and treatment of this elusive syndrome.

The Institute also continues its concerted efforts to unravel the mysteries of the chronic fatigue syndrome (CFS), a debilitating illness for which a definitive cause or treatment remains elusive. In a recent NIAID-supported study, investigators found that therapy for abnormally low blood pressure alleviated the symptoms of chronic fatigue syndrome (CFS) in 9 out of 23 patients. This finding has led to an NIAID-supported clinical trial involving treatment of CFS with a specific drug typically used to treat hypotension.

Autoimmune diseases such as multiple sclerosis (MS) occur in 5 percent of adults in the United States, two-thirds of them female. MS is the most common progressive neurologic disease of young Americans, affecting an estimated 250,000 to 350,000 people in the United States. Using a mouse model of multiple sclerosis (MS) called experimental allergic encephalomyelitis (EAE), NIAID-supported scientists have discovered that a specific interaction between two types of critical immune cells is associated with the symptoms of EAE and MS. Moreover, they found that blocking this interaction prevented EAE in mice and dramatically improved symptoms in mice that already had EAE. These findings suggest a potential new approach for alleviating symptoms of MS in people.

As the above examples illustrate, new insights in fields such as immunology and

microbiology, the cornerstones of the NIAID research effort for nearly fifty years, continue to drive the development of new treatments, vaccines, diagnostic tests and other technologies crucial to the health of the Nation. With a continued commitment to basic and applied research, even greater accomplishments can be expected as we approach the 21st century.

PROTEASE INHIBITORS

Mr. PORTER. Thank you, Dr. Fauci.

You may have answered this in part, but let me ask it anyway. Viral load testing of the patient's blood is thought to be the most accurate measure of the severity of a patient's HIV infection. Some reports, however, indicate that even though viral load testing may indicate no evidence, which you indicated on the chart, of the virus, it may still be present in the lymph nodes.

Dr. FAUCI. Right.

Mr. PORTER. How can we be confident that we are correctly measuring the impact of the protease inhibitors?

Dr. FAUCI. It is very clear from a number of studies, Mr. Chairman, that the level of replication of the virus is reflected in the level of the virus in the blood that we measure by our sensitive techniques.

Also of importance is that there have been good retrospective and prospective studies that indicate that the level of virus in a particular individual accurately predicts where that person is going with their disease. So that if you have a very high level, you know that the curve of disease is like that, and they will deteriorate more rapidly than someone who has a low level.

That doesn't tell you that the virus is completely absent if this goes below detectable level. In fact, we know from experiments that it isn't. But what it does accurately tell you is that there is a correlation between the level of virus and the clinical course, so that it is better to bring down the virus to below detectable level, even if you haven't gotten rid of it.

I tend to explain this to people by saying that this means there's good news; we've gotten the virus to below detectable level. How good that news is going to turn out to be over the long run, vis-a-vis how long we can keep it suppressed, remains to be determined by clinical trials. But just because you can't get rid of the virus doesn't mean that bringing the virus down is not a very good thing with regard to the clinical course of a patient.

HIV MULTIPLE DRUG THERAPY

Mr. PORTER. How long have we been testing the multiple drug therapy? How long do we know that it keeps the level down?

Dr. FAUCI. Well, again, it depends—and this is a very interesting, complicated situation vis-a-vis the sometimes lack of appreciation of the scope of this throughout the country. If you look at a very well controlled population of individuals who are highly motivated in a clinical trial, with triple combinations of drugs, you could bring down the virus to below detectable level in about 80 to 85 percent of individuals and keep it there for anywhere from 40 to 52 weeks. After a while, a certain percentage of them will start to break through with resistant viruses.

If you go into the trenches, as we call it, in people who have had a number of different types of antiviral drugs, the percentage of getting those people down is somewhere around 40 or 50 percent. So what we can say, in direct answer to your question, is that for at least a year we know that in the majority of people we can keep that virus down. But since we know that the virus can stay latent

for a long period of time, it won't be until several years from now that we can say confidently that we've been able to keep it down.

Mr. PORTER. You talked about motivated patients. Who would be not a motivated patient? An IV drug user maybe? Who would fall in the class that aren't highly motivated?

Mr. FAUCI. I don't want to use the word "motivated" in a pejorative or a laudatory sense. What I'm talking about is that when someone is within the confines of a clinical trial and they have a clinic and a doctor that's very interested in them, encouraging them to stay on the trial despite the fact that there are toxic side effects to the drug, encouraging them to continue to take their medicine, that's an excellent environment. That is much different than a situation where someone may not have a doctor that readily follows them or a clinic that has an intensive interest in them, gives them some drugs, the person feels better, then after three weeks to a month they stop taking the drug.

That's what I mean by motivated, not necessarily in a pejorative sense of someone is not motivated. It's accessibility of the kind of care and environment that allows someone to feel good about staying on this type of regimen.

AIDS CLINICAL TRIALS

Mr. PORTER. It's been reported that three or four trials being supported by your AIDS Clinical Trial Group include potentially suboptimal treatments because they were designed before the new potent drug combinations were available.

Dr. FAUCI. Right.

Mr. PORTER. Do you plan to modify the design of these trials?

Dr. FAUCI. Definitely. And that's already underway right now. There are a few trials—when you say suboptimal, you have to look at both the laboratory and the clinical data. For example, literally just a couple of days ago, and I alluded to it briefly in my opening statement, a trial called ACTG–320, by the number of the trial, was looking at triple combination of drugs compared to two nucleoside analogues, either AZT and D4T or AZT and 3TC, compared to that same regime together with Indinovir or Crixivan, which is one of the several protease inhibitors. And before the study was over, as the data and safety monitoring board analyzed the data, it became clear that there was a distinct advantage to three drugs compared to two drugs in late disease, not early disease.

So we go back now, when we look at all the protocols in which there are two drugs in late disease, and since we know that that's suboptimum, you must reconsider then adding the option of a third drug and a protease inhibitor. However, what is still an open question is two drugs versus three drugs in very early disease. That's something where, as I alluded to before, you have to balance the potential clinically beneficial effect with the possibility of cumulative toxicities and the emergence of resistance.

The answer to your question is that they are being carefully looked at on a protocol-by-protocol basis.

Mr. PORTER. We've heard that as many as five new types of protease inhibitor drugs are in the pipeline. Do you expect them to

overcome some of the difficulties with the current protease inhibitors?

Dr. FAUCI. The answer is yes, some, but not all. Each of these drugs are potent drugs and each of them will either have similar or different types of toxicity. One of the things we would like to see overcome, and we already have some indication that this is the case, is that the mutation that is induced by one might not lead to a virus that is cross-resistant to the other. In other words, you can measure little changes in the genetics that lead to amino acid changes in the proteins of the virus. Sometimes protease inhibitor No. 1 would lead to a mutation at this particular point. If protease inhibitor No. 2, even if it leads to mutations, if it's a different mutation, you could wind up putting them together and still having the virus be susceptible. So that's our hope for developing new protease inhibitors in the pipeline.

Mr. PORTER. Do you think it is realistic to ever expect the drug companies to invest resources in the development of an AIDS vaccine, since its market would be undeveloped countries in large part?

Dr. FAUCI. The answer is, I don't think it's going to be easy because it will follow the same pattern as we see with any vaccine. This is not a field where there are many, many pharmaceutical companies which are breaking the doors down to try and get into the field. However, as we have consulted closely with our colleagues in industry, the limiting factor is really the scientific opportunity.

If we can get a concept that proves to be having at least a reasonable chance of working, I think you'll see a larger number of drug companies than you see currently involved in the field. As part of our renewed effort in vaccine at the NIH vis-a-vis HIV/AIDS, we are engaging our industrial colleagues in discussions and collaborative efforts. So it's not going to be a simple problem to overcome, but I don't think it is going to be prohibitive if we get a good scientific concept to prove.

Mr. PORTER. Does the need to halt clinical trials due to ethical considerations limit your ability to measure the emergence of resistance?

Dr. FAUCI. The answer is, from a purely technical standpoint, if you stop a trial before you show that there's a relationship between a resistant mutant and a clinically deleterious course, one can say yes. But that's just part of the turf of research. The most important thing that we understand and guide ourselves by is to "do no harm" to the patient. So if a situation arises where there is an ethical consideration, that's what we call a non-starter. That's the first thing that takes preference. It may take a little longer to get to the truth, but we have done it successfully.

You might recall, in fact, I think we had somewhat of a similar conversation several years ago when we had AZT proved to be effective and we couldn't have a placebo. There were those who threw up their hands and said we'll never show again that another drug works if we can't do a placebo trial. And now I just showed you three examples of how we did it within the realm of having people on drugs that ultimately turned out to be not as good as the one we were testing, but we didn't know it at the time. So, in the

real world, I don't think it is a serious negative impact on our ability to answer questions.

Mr. PORTER. Thank you, Dr. Fauci.

Ms. Pelosi.

HIV DRUGS AND VACCINES

Ms. PELOSI. Thank you very much, Mr. Chairman. Welcome, Dr. Fauci. It's always an honor when you are here. We are indeed blessed to have Dr. Varmus, at the head of NIH, and you in your capacity. I just wanted to call to my colleagues' attention the fact that Dr. Fauci has over 850 scientific publications, and that of the one million scientists in the world who publish each year, Dr. Fauci is the second most quoted among those. I think that, again, the NIH and our country are indeed blessed with your contribution.

In that spirit, I wanted to follow up on a question asked by our Chairman about the involvement of the private sector. My question had been what actions can NIH and Congress do to help harness pharmaceutical expertise to the challenge of HIV vaccine research. You have said scientific opportunity is the key. But is there anything else that we could be doing to smooth the way?

Dr. FAUCI. I think you made the point. You are in some respects inadvertently doing it by supporting us. But a specific question that comes up, and I don't think it's a major problem, but it does come up and should be considered, and that is the question of the concern that drug companies have about liability and concern that they have about interference with pricing.

We've come to a good agreement in our CRADAs in discussions about fair pricing in the sense that we don't have strict regimented controls on that. That has opened up the doors to more easy negotiations with them. With regard to the liability, that's a very difficult issue. But if it can be discussed with them at least that there is an intention of working with them to make sure that we can draw people in without that sometimes unrealistic concern, but sometimes realistic concern, regarding liability, that might be helpful.

HIV THERAPY

Ms. PELOSI. I think that is a tremendous challenge, including that non-interference in the pricing. Although we want to be the free market, we also do not want an exploitation of the need of these people.

That brings me to standards of care. It is my understanding that the NIH panel to define principles of therapy for HIV infection has a draft report under review.

Dr. FAUCI. Right.

Ms. PELOSI. As a committee co-chair, you expect to issue a report on standards of care for HIV disease shortly. Could you outline your timeline for these two reports?

Dr. FAUCI. Yes. There are actually two committees that are working in synergy; one is the committee that is a fundamentally NIH-based committee that is looking at principles of care. The other is a departmental committee, of which I'm co-chair with Dr. John Bartlett from the Johns Hopkins University, and what we're doing in that group is that we're actually going to be making rec-

ommendations based on the principles that were established by the NIH committee.

We actually have a meeting next week, March 6th, I believe. We will be looking at the hopefully next to final, if not final, draft of the two committee recommendations. We will then, after we fine tune it and get it in a presentable form, send it out for public comment. After that, we will publish it in the MMWR and hopefully in a standard medical journal. So the timeline we're talking about is, if you include a month or so period for public comment, would probably be sometime in the early spring.

Ms. PELOSI. Early spring. Mr. Chairman, you have been so receptive to our having a full discussion of this issue, and even in your own questioning about what the penetration is among people with HIV having access to these new therapies, and I would hope that in your willingness to pursue more information we might have a hearing specifically geared toward the new therapies; how they are available, how they meet the standards of care. I know you've always been open on these subjects.

Mr. PORTER. If I could respond to the gentlelady. I am not sure you were here when I said that I felt that we were short-changing the subcommittee in the sense that we have too much scheduled in too narrow a timeframe, and I've already asked Dr. Collins and Dr. Fauci as well as Dr. Varmus if they will make themselves available later in the year when we might follow up with them.

HIV VACCINES

Ms. PELOSI. Thank you, Mr. Chairman. I'm sorry, in my capacity as ranking member on another committee, I couldn't be in the room to hear that, but I am very encouraged by it. I would hope at that time we could have people with HIV as well as their health care providers and hear directly from HIV-infected people and their care providers at such a hearing. Some of the stories are absolutely, to use Dr. Varmus' word of yesterday, "miraculous" in that people who were looking for help to make out a will now need help getting a job; people who were going on disability are now being made partner in their law firms. The stories are quite remarkable. But everyone doesn't have access to these drugs and everyone doesn't respond to them. So I would think that hearing directly from people with HIV and their care providers, in addition to our very distinguished witnesses, would be useful.

In terms of the vaccine, I had a very specific question, because Dr. Varmus addressed it yesterday, and certainly the President did in his State of the Union address. Concerns have been raised about at least two structural issues concerning the way NIH awards funding to researchers. First, the peer review process often rewards proposals that demonstrate innovative science at the cost of more practical and less ground-breaking research which may be needed in order to develop an HIV vaccine. Second, the absence of a study section for vaccines has sometimes meant that the vaccine research is underfunded. How can these concerns be addressed, and how can Congress be of assistance in making NIH the engine of discovery?

Dr. FAUCI. A very important point, Ms. Pelosi, and we're aware of that. One of the ways you can do that, and it is short of creating a study section, because we've done it in other areas, is to create

a special emphasis panel of review where you make known, as we have already done with the reconstituted advisory committee, about certain areas that absolutely need to be addressed. In fact, we've even gone so far as to establish a new kind of grant mechanism that is very rapid in its implementation, called an IDEA Grant, that has to do with the basic questions that need to be asked and answered in HIV vaccine research. You bring up a very good point. It is a problem and we are addressing it. I don't think there's anything that Congress could do. I think it is a question of being aware that we must look at these applications and the questions that they're asking in somewhat of a different light than just throwing them in the hopper with everything else.

Ms. PELOSI. Is that it?

Mr. PORTER. I don't know. No, you've got a couple more minutes.

Ms. PELOSI. Would Mr. Hoyer be able to finish?

Mr. HOYER. Mr. Chairman, you're going to have Dr. Fauci come back, is that it?

Mr. PORTER. Later in the year, yes, if the subcommittee wishes to do so, and I think they will.

Mr. HOYER. We have no members here, but I want Dr. Fauci at some point in time either to come before the committee or for the record to supplement Dr. Varmus' response on what clearly is going to be part of the debate when we mark this bill up in terms of how we allocate the resources to various diseases or Institutes within NIH. I think it is very important for us to understand on this committee, first of all, the fungibility of the research, if that's an appropriate way to refer to it, and secondly, the rationale behind the allocation that has been proposed. That was the question I was going to ask. I know we have a vote now, and I want Ms. Pelosi, who, in my opinion, is probably the expert, along with yourself, on this issue, to pursue her questions. But at some point in time, I want that question addressed by Dr. Fauci.

Mr. PORTER. Fine. If the gentleman would yield, I think it is a question that seems to be on the minds of a number of members and I think it might be an appropriate subject for us to have a panel from NIH to address together for us.

Mr. HOYER. Fine. That's an excellent idea, Mr. Chairman.

Mr. PORTER. Perhaps that's the way we ought to pursue it.

Mr. HOYER. I yield back to Ms. Pelosi.

NEW THERAPIES

Ms. PELOSI. If I could just make one comment in closing, and that is when we have Dr. Fauci back, I hope he would be prepared to tell us when we would have new therapies that are easier to tolerate for many people for whom there's hope of new drugs.

Dr. FAUCI. Yes. I would be happy to, Ms. Pelosi.

Mr. PORTER. I've asked Dr. Fauci to stay until 12:30. We do have a vote on. Are you going to be able to come back here, Ms. DeLauro?

Ms. DELAURO. I cannot come back.

Mr. PORTER. That's what I was afraid of.

Ms. DELAURO. I've got several questions but I can submit them for the record. There will be opportunity to ask them again at a later time. I think Mr. Hoyer has said it, and Ms. Pelosi has asked

appropriate questions, and we have the kind of work that you have been doing that Ms. Pelosi has talked about. So I can submit my questions for the record.

Mr. PORTER. Well, we did not expect, at least I did not expect to have a vote that we're going to have to address. Mr. Dickey, have you voted?

Mr. DICKEY. That's a personal question. [Laughter.]

Mr. PORTER. Yes, I know. I'm going to ask you to take the Chair.

Mr. DICKEY. Oh, boy! [Laughter.]

Mr. HOYER. Mr. Chairman, I'm going to have to go vote with everybody else and will not be back. Obviously, these hearings are a little bit difficult for me. But I want to say to Dr. Fauci and his colleagues that I know how difficult it is when we confront disease. But Dr. Fauci, Dr. Varmus has been with us for a long time and I consider myself a good friend of his and totally subjective, as is Ms. Pelosi, when dealing with him. We have extraordinary people at the Institutes, at NIH. I particularly on the record want to say that I was not here for the Cancer Institute yesterday purposefully. I didn't think I could make that. But Dr. Rosenberg was incredibly supportive at a very difficult time for me, and I want to thank you.

OFFICE OF AIDS RESEARCH

Mr. DICKEY [assuming chair]. Thanks for sharing that, Steny. We've all been thinking about you.

Dr. Fauci, I don't know if you've answered this question, but I would like to ask it of you. It seems redundant to have an Office of AIDS Research, OAR, in addition to your Institute which spends half its resources on AIDS. Couldn't the functions of OAR be handled by NIAID?

Dr. FAUCI. The NIH has a number of components besides NIAID. True, the NIAID is the major component of the AIDS research effort at the NIH, but it really spans multiple Institutes. The OAR, as it is constituted now, has functioned very well in the coordination of the research among the Institutes. We've had a very good working relationship with the OAR. So, I'm sure at any given time you could change the configuration, but the OAR actually is performing their function of coordinating research among the NIH Institutes.

Mr. DICKEY. Is it wasting money in any fashion by having a duplication?

Dr. FAUCI. No, I don't think that it's a money situation at all.

Mr. DICKEY. Why is it not a duplication?

Dr. FAUCI. Because the NIAID is an individual Institute. Since there are substantial efforts in other Institutes, such as the Cancer Institute, the Child Health Institute, and on and on, virtually every Institute, an office that is apart from the Institute is functioning in a coordinating fashion. There was concern about having an individual Institute be coordinating efforts of a variety of other Institutes as opposed to having a body outside of any Institute to coordinate the work of the individual Institutes.

Mr. DICKEY. Did you want to add to that?

Dr. VARMUS. Just that there have been very appreciable gains in just the past couple of years that could be attributable to the planning and evaluation processes of the OAR. The OAR, as you know,

does not support research directly—all of the research is done through the Institutes—but the OAR carried out a review of the entire AIDS portfolio that does involve, as Dr. Fauci mentioned, every Institute of the NIH and came up with a number of important recommendations that I think are going to make our expenditures in the AIDS field get more productive. It did not ask for more money for AIDS; it asked for better use of the money. I believe that attitude is one that actually contributes to a savings.

AIDS FROM OTHER COUNTRIES

Mr. DICKEY. Dr. Fauci, what are we doing as far as preventing AIDS from coming to us through other countries?

Dr. FAUCI. Well, that's not a question that I have any responsibility for. But I would not be concerned, as I mentioned before, about AIDS coming from other countries when you have about 800,000 people in this country already infected with HIV. So, if you were dealing with a disease that's transmitted by a respiratory route, then you would have a different kind of a situation.

Mr. DICKEY. I see.

Dr. FAUCI. Whereas, if you have a disease that's spread by a behavioral pattern, be that sexual behavior or intravenous drug use, since the pool of infected people in this country is substantial, I don't see any public health benefit in trying to keep out other people who are infected rather than educating the public on how they can avoid infection within this country.

AIDS CURE VERSUS TREATMENT

Mr. DICKEY. Are your expenditures divided so that you can answer the question, what percent of your expenditures is being spent in the AIDS area on research to find a cure, and what percent is being spent on trying to cure people who already have AIDS?

Dr. FAUCI. If you look at the way we have the breakdown of the budget, according to what we call the NIH AIDS Plan, within that plan are two major categories that you're referring to. One is therapeutics, the other is vaccine, and then there is another called behavior that in some respects has to do with prevention. With regard to the percent of the total, 35 percent of what we do is for the treatment, either the development of drugs or the clinical trials of individuals. In our Institute, 15.7 percent is on vaccines. For the NIH as a whole, it's going up each year but it is somewhat less than 10 percent, about 8.9 or 9 percent. But in the NIAID it is 15.7 percent. And in our Institute we have a relatively small amount on behavior research. But Institutes such as the Mental Health Institute and the Drug Abuse Institute have a substantial amount more on behavior.

Mr. DICKEY. I'm not getting enough numbers here. I wanted, and I don't mind it being divided three ways, behavioral, preventive——

Dr. FAUCI. Behavioral, vaccine, and therapeutics.

Mr. DICKEY. Okay. And therapeutics is after you get it.

Dr. FAUCI. Therapeutics is drug development and clinical trials, and that's after you get it; correct.

Mr. DICKEY. Bring me to 100 percent on those.

Dr. FAUCI. Okay. The rest is 14.8 percent in what we call the epidemiology or natural history, where we follow cohorts of individ-

uals who are infected and follow them and look at the transmissibility from mother to infant or among sexual partners.

Mr. DICKEY. Isn't that aimed toward curing it or finding a cure?

Dr. FAUCI. That overlaps with virtually every aspect, because they are cohorts of patients that we study that you can examine pathogenesis in them, you can initiate them into clinical trials, and even some cohorts of individuals who are not yet infected might be put in a vaccine trial.

Mr. DICKEY. Are we spending more money on taking care of the patients who have AIDS, or are we spending more money on trying to find a cure?

Dr. FAUCI. Right now, percentage-wise, there is more money in trying to find a therapy, as I discussed earlier, for the treatment of infected people as opposed to preventing it. But if you look at the trend of where we're going over the last couple of years, the vaccine trend is steadily increasing at a time that the therapy has stayed either flat or is coming down somewhat. The trends are going now much more towards prevention either with a vaccine or with behavior modifications. But if you look at the numbers, there's more money going to treatment.

Dr. VARMUS. One comment, Mr. Chairman. It is inherent in nature of clinical trials that they are expensive. Therefore, it is probably not fair to look at the effort solely in monetary terms. The number of answers you can get may be equally great with a smaller amount of money in the prevention area. You heard that there is hesitancy on the part of pharmaceutical industries to enter into the vaccine area because of a lack of fundamental ideas about how to approach vaccine development. So there may be a large number of small projects, any one of which might give the inspiring result that would then result in development of a vaccine; whereas, probably, simple ideas for testing the various combinations of drugs, which Dr. Fauci alluded to, is a very expensive process involving hundreds or thousands of patients and many different combinations of drugs.

Mr. DICKEY. Do you share talent in those two areas, therapeutic and vaccine?

Dr. FAUCI. Definitely.

Mr. DICKEY. You do?

Dr. FAUCI. Yes. Not only do we share it in those two distinct categories, but, as Dr. Varmus just alluded to, those categories are very heavily fed into by the basic researchers that are looking at the pathogenesis, either the viral or the immunological pathogenesis, and both of those areas feed directly into both therapeutics. In fact, we have trials of therapies that are called pathogenesis-based and all of pathogenesis, or understanding how the virus works, will ultimately feed into vaccine development. That's the reason why, as appropriately referred to by Dr. Varmus, it is sometimes misleading when you look at strict coding of how you spend money because of the overlap and spill-over from one to the other.

Mr. DICKEY. I understand that.

Dr. VARMUS. To give you one very straightforward example. You've heard a lot about viral mutants. That is a particular problem with viruses, especially viruses like HIV, that become resistant to therapies and are potentially resistant to protection by vaccines.

Attempts to understand the source of genetic change in these viruses, to categorize the viruses by genetic makeup, is fundamental to all the areas you've heard about. People who are studying the genetic properties of HIV have to be in touch with all the areas you've mentioned.

BEHAVIORAL RESEARCH

Mr. DICKEY. What are you doing in behavioral?

Dr. FAUCI. In my Institute, the behavioral research that we do at NIAID is linked very closely to two components. One is the vaccine effort where we are building up cohorts that might ultimately serve as the group that we would try a vaccine on. Inherently built into that is behavioral modification.

Mr. DICKEY. Does that include abstinence?

Dr. FAUCI. Oh, absolutely.

Mr. DICKEY. How are our Federal dollars encouraging abstinence in the AIDS area?

Dr. FAUCI. If you look at the instructions of when you put someone in a vaccine trial, there are discussions of doing whatever you possibly can to avoid infection, and that's both for the people who are going to receive the vaccine as well as for the people who are not going to receive the vaccine. It is very clear and right up front that the most surefire way of avoiding HIV infection is abstinence, number one, and number two, if you're going to have sex with a person whose HIV status you are not sure of, then you use a condom. That's very clear. That's now essentially in every public health discussion that you have about prevention.

Dr. VARMUS. In fairness to Dr. Fauci, a number of the studies that address the issue of abstinence, that you've raised with me before privately and are now raising with him, are under study in other Institutes—the Child Health Institute, and the Mental Health Institute. There are a number of——

Mr. DICKEY. On AIDS?

Dr. VARMUS. Yes, absolutely. Many programs have incorporated a consideration of sexual avoidance or abstinence in relation to HIV transmission. Obviously, we understand that abstinence is very good protection. But how do you get there? One of the interesting things that we've learned is that in instructing children and young adults about the risks, it is very important to be explicit about sexual practices. There is early evidence from some of these attempts to understand the role of sex education and education about sexual habits that it is important to understand that if individuals don't learn about the means for protection, when they actually engage in sexual activity later that they put themselves at higher risk. There is some evidence already that individuals who have simply learned that abstinence is important without being similarly educated about the need for protection engage in much higher levels of risky behavior when they do become sexually active.

Mr. DICKEY. Mr. Miller, do you want to ask some questions?

PROTEASE INHIBITORS

Mr. MILLER. Thank you, Mr. Chairman. It is always a pleasure to see you. It's always exciting to be going through this series of sessions because I learn so much.

Let me start off with the issue of protease. I remember last year talking about the issue of whether there was a breakthrough. First of all, when were protease inhibitors made available commercially?

Dr. FAUCI. It became available within the last year. The initial trials were a year ago last fall. The first licensure for it came about six months after that, last spring. So they've been out now about a year commercially available.

Mr. MILLER. Just before we had our hearing last year.

Dr. FAUCI. Right. Exactly.

Mr. MILLER. The question was raised then, in our discussion, "is this a breakthrough?" I forget how you qualified it. How do you evaluate that now? And has anything else come up more significant than protease since that last time?

Dr. FAUCI. In answer to the question, as Dr. Varmus joked about yesterday, I rarely, if ever, call anything a breakthrough, but I would say that this has now turned out to be an extremely important therapeutic advance. No question about that. [Laughter.]

Mr. MILLER. "Therapeutic advance."

Dr. FAUCI. Yes. The point that I made, I don't believe that you were there when I was presenting it in my formal presentation, is that there is some confusion about how good this will ultimately turn out to be. If it does nothing other than what we've already observed it can do—namely, profoundly bring down the level of virus in many cases to below detectable level, associated with a clear-cut clinical benefit in people with advanced disease, and, in my opinion, will likely also be shown, as the clinical trials come to fruition, to have a clinical benefit in people who get the combinations with protease even earlier in the course of the disease—that, we know, is a very important advance in and of itself. If you want to call that a breakthrough, you can call that a breakthrough.

The questions that remain open, since we know this is an extraordinary illusive virus and these drugs are very potent and can have terrible toxic side effects and can be difficult to take over a long period of time, are two among several very important questions: one, will the cumulative toxicity over a period of two, three, four years lead to an imbalance or somewhat negating the beneficial effects; and number two, will the emergence of resistant mutants in those individuals who haven't had complete suppression of the virus' ability to replicate, will those mutants now come back with a vengeance, as it were, and be refractory to other drugs.

That gets us to the thing that you alluded to in your second question, which is: has anything else come along. What has come along have been other protease inhibitors that are more than just complementary to the existing ones in that they induce a resistant mutant that's a little bit different than some of the originals. Which means that if you give them, and there are various trials that they are now undergoing, two protease inhibitors either alone or together with the AZT class of drug, we want to determine if that can actually give you even more benefit than having the triple combination with one protease inhibitor.

The other answer to your second question is that we are constantly looking for new targets in the life cycle of the virus. I gave an example of one, which was serendipitous, as it were, with regard to AIDS research, the discovery of a particular receptor that

the virus absolutely needs to get into the cell but which may not necessarily be absolutely essential for the survival of the person. So that if you block that receptor, you might be able to profoundly interfere with the ability of the virus to replicate.

There's an intensive amount of activity going on in biotech firms, et cetera, to try to develop molecules that can be used to interfere with that binding side. So there are other things going on. We're constantly looking for new targets and/or new drugs for the same targets.

MEDIA

Mr. MILLER. Yesterday, we had Doctor Klausner from the Cancer Institute. I saw him on ABC News earlier in the week and it was about a new idea, which you brought up here a few minutes ago. The question I asked him is regarding the treatment of the media to scientific breakthroughs. Kind of like the *Newsweek* phenomena. The implication is maybe that headline is not what you would have written.

Dr. FAUCI. No, definitely not.

Mr. MILLER. How much of a problem is that? I read it, and this was *Newsweek,* and I watch ABC News whenever I get a chance, or MacNeil-Lehrer, and Business Week is always interesting because they have that material a lot of times because of the financial interest. But it is always interesting how the media overplays certain areas.

Dr. FAUCI. Right. So how much of that is a problem for me?

Mr. MILLER. Yes. How much of a problem is that with you, and then maybe Dr. Varmus would make a comment, too.

Dr. FAUCI. Actually, to be honest with you, none as a scientist. The problem, if there is a problem, is trying to clarify, and we have to put in more time on that. I have spent a considerable amount of time trying to be the moderating force in this hype aspect of the drugs. Even though the drugs are quite good, I have found that the media has perhaps pushed it over in the eyes of the general public to be a little bit more than we know it actually is right now. But from a scientific standpoint, it doesn't really have any impact on what we do. And it involves several of us here in the room; it involves Dr. Varmus, who doesn't get impressed with that at all, and, in fact, has his areas of emphasis based on scientific opportunity, not what's in the newspaper. Quite frankly, I also applaud not only the administration for not responding to that, but also the appropriations subcommittee—Mr. Porter, yourself, and all the other members of the subcommittee—for allowing us to make scientific decisions based on the scientific opportunity and not what's in *Newsweek.* So I'll end my answer by saying thank you for not making it a problem for me.

Mr. MILLER. I remember reading about Dr. Ho, I believe, that won the Nobel Prize. He was very reluctant, at least in what I was reading, because why should one person be singled out? That is a very legitimate question when there is a wide range of people contributing to that.

Do you have any comment, Dr. Varmus?

Dr. VARMUS. I think Tony has covered many of the important aspects. We appreciate the attention that's being paid to medical

science in these articles. Sometimes they have an emphasis that we may not share, but the fact is that *Time* magazine devoted nearly an entire issue to research on AIDS. They did endow many of the properties in the field on a single individual, but it made the story better reading. *Time* magazine also recently ran a wonderful piece about early development of the nervous system, featured on the cover. And there's been a tremendous interest in genetics. All of this has had a very strong educational influence on the public and has had a role in attracting young people to the ferment that exists in biomedical research.

HEMOPHILIA

Mr. MILLER. I guess the point is that it makes the American people feel good that there are some good things that government is doing, and this is obviously one of the good things.

Let me switch my line of questioning to an area that I'm very interested in, which is hemophilia. The statistics have levelled off with respect to hemophiliacs. Their exposure was way back in the early 1980s or whenever and I assume blood is not now a major factor any more.

Dr. FAUCI. No.

Mr. MILLER. And most of it is either drug related or sexual transmission. I think the gay community has levelled off too, as I understand.

Dr. FAUCI. Yes.

Mr. MILLER. But specifically hemophilia, how does it relate to the effectiveness of treatment today versus others? Do drug users have a different reaction versus the gay community and all for the different protocols available?

Dr. FAUCI. No. We have as a component of our AIDS Clinical Trial Group, our ACTG that you hear me refer to frequently, the Hemophilia Foundation as a designated AIDS clinical trial unit with several subunits. So we have incorporated the treatment of hemophiliacs into our AIDS treatment agenda in a totally integrated manner. As we can tell thus far, they respond to the drugs in the same manner as individuals who have been infected from other routes.

Mr. MILLER. There's no difference then?

Dr. FAUCI. No. No.

DRUG ISSUES

Mr. MILLER. Okay, onto the drug issue. The drug companies—is there any problem about the sharing of information with the drug companies between themselves, and the fact of the potential amount of money here is enough incentive for a lot of them getting into it. In cancer there is a much larger market dollar-wise from an investment standpoint.

Dr. FAUCI. Right.

Mr. MILLER. How does that play in this whole issue?

Dr. FAUCI. There are a couple of parts to your question. With regard to HIV therapeutics, there certainly is an extraordinary market for that. So there's not any constraints of companies getting involved because what they don't see as a profitable market margin for them. So that's not a question.

With regard to sharing information, whenever you have proprietary rights to something there is always the question of companies sharing information. But I must say I was very gratified a year-and-a-half, two years ago when some of the major drug companies brought themselves together in a consortium whereby they shared their Phase I or earliest data with each other so that other companies wouldn't go down a track that is a non-fruitful track that one of the other companies already did. It is the first time to my knowledge that I've ever seen that. The reason they did it I think was twofold. One, I think there was a bit of altruism in it. But also it was good for the companies because it was a give-and-take, they could learn something from another company about what direction they went. As it turned out, that has turned out to be very, very fruitful.

What we're also seeing now is more collaborations among companies in donating their drugs for a clinical trial to compare them head-to-head. A typical example was the Glaxowelcome/Merck collaboration on the study that I referred to just a little while ago where AZT and 3TC came from Glaxo and Merck gave us the Crixivan and Indinovir. So although you have competition, which is good, I think what we're seeing right now is a considerable amount of collaboration that you would not have predicted if you had thought that the market was very secretive. It isn't.

Mr. MILLER. Thank you. Thank you, Mr. Chairman.

MALARIA

Mr. PORTER [resuming Chair]. Thank you, Mr. Miller.

Dr. Fauci, there seems to be a resurgence of interest in the research community in malaria. The disease kills more than one million people a year. Efforts to develop a vaccine have been unsuccessful, and many anti-malarial drugs are becoming ineffective because of resistance. But early reports of a new vaccine candidate developed at Walter Reed are encouraging. A large malaria genome sequencing project is underway, and a major conference in Africa in January brought together scientists, including Harold Varmus, to kick off a new coordinated plan to attack malaria. With this encouraging news on several fronts, do you think it is likely that effective therapeutics and perhaps even a vaccine will be developed before we lose the battle against drug resistance?

Dr. FAUCI. The answer is that the battle against drug resistance is an ongoing battle. It is not a single battle that you win or lose. If you go to certain parts of developing countries, a substantial fraction of the malaria there will be drug resistant. What we're seeing now, and I feel very good about it, and there has really been a considerable amount of help from Dr. Varmus who has been very interested personally in this and has actually, as you mentioned, gone to Africa, is a resurgence of interest of combining the new technologies, for example, of being able to sequence the genome of microorganisms including the malaria microorganism, but also of getting the countries involved. We call them "Host Countries," countries in which you do clinical trials, to get their scientists involved and utilize the resources of their country as well as our own country, and, in addition, to train them to really be partners with us. That's something that we've seen little bits of but never really

in a full-blown effort, and we're starting to see that now. So, again, it is a convergence of the age of molecular technology, the ability to approach the question of resistance from that standpoint, as well as the idea of a vaccine. So I think things are going to be going in much more accelerated fashion with regard to malaria than they have been in the past.

Mr. PORTER. Dr. Varmus, do you want to comment on that?

Dr. VARMUS. Just briefly because Tony has covered many of the important points. One of the things that you learn when you go to Africa to see malaria in its native setting is that—while there is tremendous need for new research opportunities that will come from the malarial genome project and from more emphasis on vaccines and drug development and better understanding of the life cycle of the organism—there is also the need for research at the local level that addresses epidemiology, treatment patterns, health services research. One of the things that you learn very quickly is that in certain parts of Africa drug resistance is not really the problem at all. Drug resistance is very sparse in these places, but the real problem is getting the right drugs to the right people at the right time, and having people be able to recognize disease in young children where it is frequently lethal in the cerebral malaria form.

One of the things that I found very heartening was that in areas such as Mali—where NIH has established a research foothold, building a very excellent research team headed by African scientists—that the field stations that are used by those laboratories as sites for research on epidemiology and pathogenesis become treatment areas. In these places, the disease is controlled even though the infection rate is still extremely high from the tremendous number of Anopheles mosquitoes carrying the organism. But treatment is prompt, people don't die of the disease, and people learn about the disease. In many parts of Africa it is not understood that the mosquito is the transmitting agent, but it becomes very apparent when people are being recruited into the studies to capture mosquitoes that this is the way it is transmitted. That knowledge spreads to other communities, and other kinds of health benefits, like digging wells to prevent infantile diarrhea, follow from these initiatives on malaria.

TUBERCULOSIS AND CHOLERA

Mr. PORTER. Do you think a similar concentration of effort is necessary in the worldwide fight against tuberculosis and cholera? What makes these conditions different from malaria?

Dr. FAUCI. The answer to the question is yes. Both of those could benefit. You may be aware that we have accelerated greatly our tuberculosis effort both on the national and international front. Just a few short years ago, the tuberculosis effort in the NIH was just a few million dollars. We now have it up in my Institute alone to $37 million and there is activity in other Institutes as well. Cholera. We're testing a new cholera vaccine which we feel has some hope in giving us some good results with regard to cholera.

They're different because of the complexity. Cholera and tuberculosis are really spread from person-to-person. Both of them are bacteria. Malaria is a parasite, a larger organism that has an inter-

mediate vector, the mosquito. The complexity of malaria compared to tuberculosis, which is a difficult enough problem, as is cholera, is related to the fact that you have the vector itself to deal with. So it is a mosquito problem, a vector borne disease. The other is essentially a person-to-person disease. With cholera, it is because of the contamination of water supply. With tuberculosis, it is generally respiratory borne.

Dr. VARMUS. But you shouldn't go away with the idea that we're spending tremendous amounts of money on malaria. We spend only about $20 million at NIH. The NIH is the largest funder worldwide of malaria research. So our spending in the area of malaria research, despite the new initiatives for collaboration, is still, in my view, very small in relation to the magnitude of the problem.

Dr. FAUCI. Yes, this falls under the category of something that I've said several times before the committee. That is the discordance between the scientific opportunity and the resources available. You could look at a disease like tuberculosis, cholera, malaria, or even several others, notwithstanding the extraordinary world burden of it, there are scientific opportunities that don't match the resources that are in them. I can say that very clearly without any holding back. There's no question the opportunities we have in all three diseases that you just referred to are far greater than the resources that are in them.

HANSEN'S DISEASE

Mr. PORTER. Dr. Fauci, you've agreed to support in 1998 the Hansen's Disease research formerly funded by the Health Resources and Services Administration's Carville appropriation. What are your plans for continuing this effort in 1999? And will you open up Hansen's Disease research through competition to a potentially different set of researchers?

Dr. FAUCI. The answer to the question is yes. The way we have it now, we have had $3 million that has been put into our appropriation for the Hansen's Disease research that is going on now in Carville, in Louisiana, with the instructions that it should ultimately be turned over into a competitive grant line. In 1998, since it is difficult to so quickly do that, we're passing through the money back to them, and then in 1999 we're going to recompete and open up the granting process to anyone who wants to put in for a grant. So by the year 1999, it will be competed at the level that anyone either down in Louisiana or elsewhere could compete for that money.

Mr. PORTER. Dr. Fauci, thank you very much for your willingness to stay late. I have to say to both you and Dr. Varmus, you've seen from the questions today that there's a certain amount of concern on the subcommittee about the allocation of resources to different areas of health concern. I believe that what we probably ought to do, Dr. Varmus, is to bring back yourself and Dr. Fauci and the Institutes most concerned with cancer, heart, diabetes, and maybe some others and have a panel here where we can allow the subcommittee to raise these questions and get answers from everyone.

Dr. VARMUS. I think that would be extremely instructive.

Mr. PORTER. Wouldn't that be helpful?

Dr. VARMUS. Yes.

Mr. PORTER. And then we could perhaps raise other issues that we have not been able to cover in the abbreviated time we've had today. I would ask you to work with us on finding an appropriate time when everyone might be free. Perhaps setting it early, now, in other words, for sometime in April or May might serve everyone's interest best. We will be in touch with you about this and see if we can set aside maybe half a day or maybe even longer.

Dr. FAUCI. I would be happy to do that.

Mr. PORTER. Dr. Fauci, thank you for the absolutely wonderful job you do for humankind; not only for NIAID, and for health in general. You're one of our real treasures. Thank you so much.

Dr. FAUCI. Thank you very much.

Mr. PORTER. The subcommittee will stand in recess until 2:00 p.m.

[The following questions were submitted to be answered for the record.]

VARIOUS SPENDING LEVELS

Mr. Porter: Please identify FY96-98 spending (direct and related identified separately) on the following: Lyme disease, chronic fatigue syndrome, vaccine development, tuberculosis, sexually transmitted diseases, asthma, topical microbicides, and AIDS clinical trials (with adult and pediatric shown separately).

Dr. Fauci: The information in the table below reflects the combined direct and related spending estimates on the specific diseases requested. NIH does not generally collect information on spending by diseases that breaks out direct vs. related costs.

Disease Area	FY 1996 Actual*	FY 1997 Estimate*	FY 1998 Estimate*
Lyme Disease	$12,530	$13,031	$13,531
Chronic Fatigue Syndrome	4,984	5,484	5,593
Vaccine Development	189,873	208,992	225,443
Tuberculosis	36,435	37,892	38,649
Sexually Transmitted Diseases	66,065	68,708	70,908
Asthma	13,200	13,728	14,002
Topical Microbicides	12,053	12,535	15,535
Adult AIDS Clinical Trials Group	68,783	69,680	71,074
Pediatric AIDS Clinical Trials Group	34,500	32,000	32,640

*Dollars shown in thousands

PRIMARY IMMUNE DEFICIENCY

Mr. Porter: Last year we heard testimony about primary immunodeficiency diseases. Can you give us a sense of the scope of these diseases and the state of knowledge about them?

Dr. Fauci: Primary immunodeficiency diseases are a group of serious but little known disorders in which immune system malfunction causes increased susceptibility to infection, autoimmune diseases and malignancy. This is a group of more than 70 different diseases, many of which are inherited. It is estimated that together they affect approximately 500,000 individuals in the United States; of these between 5,000 and 10,000 people, many of whom are children, are severely affected by serious, recurrent, and often life-threatening infections. Morbidity, mortality, medical and social costs for severely affected individuals and their families are extremely high. The causative genes and pathogenic mechanisms for many of these diseases have not been identified. However, in a series of remarkable discoveries, researchers have identified the gene defects that cause many primary immunodeficiency diseases including: several forms of Severe Combined Immunodeficiency, X-linked Agammaglobulinemia, X-linked Hyper IgM Syndrome, Wiskott-Aldrich Syndrome, Ataxia-telangiectasia, Chronic

Granulomatous Disease, Leukocyte Adhesion Deficiency and many of the Complement Deficiencies. Identification of a defective gene has two important consequences. First, the role the gene product plays in the immune system can be evaluated. This information can be used to develop new therapies for immune system mediated diseases, including asthma and allergies, transplantation rejection, and autoimmune diseases. Second, identification of the defective gene allows for the development of gene therapy to correct the defect in the affected individual's own cells.

PROTEASE INHIBITORS

Mr. Porter: Are you concerned that the encouraging news about protease inhibitors may lead to a decrease in safe-sex practices and a subsequent increase in AIDS diagnosis?

Dr. Fauci: Although the news is extremely encouraging, protease inhibitors do not provide a "cure" for HIV infection or AIDS. While some people may think that the ability of protease inhibitors to decrease viral burden to undetectable levels is synonymous with a cure, the long-term effects of protease inhibitors are not yet known. Research is still underway to determine what happens when patients stop taking protease inhibitors and when, during the course of their treatment, this would be advised.

While there may be some risk that positive research findings such as these would lead some people to discontinue safe sex and safe needle injection practices, we continually emphasize the need for prevention. Patients are advised to always protect themselves from HIV infection and are counseled as to what constitutes high-risk behavior. Our informed consent emphasizes that regardless of whether or not someone is participating in a treatment or prevention trial, they should always protect themselves from HIV infection.

CHRONIC FATIGUE SYNDROME

Mr. Porter: Provide a complete list of intramural CFIDS research projects currently funded by NIH and funding totals for each project. If appropriate, identify promising findings from these projects.

Dr. Fauci: The NIMH Intramural Research Program (IRP) is funding three projects with relevance to chronic fatigue syndrome for a total of $950,000.

Project #	PI	Title	FY 1996 Actuals
Z01MH02585-05	Sternberg, E	Role of the CNS in the Susceptibility to Inflammatory Illness	$494,000
Z01MH02654-03	Brier, A	Risperidone Treatment Schizophrenia	$380,000
Z01MH02616-05	Rosenthal	Clinical Aspects of Winter Seasonal Affective Disorder	$76,000

The NIAID funds one intramural project:

Project #	PI	Title	FY 1996 Actuals
Z01AI00470-1	Straus, S	Chronic EBV Infection & Chronic Fatigue Syndrome	$729,000

NIAID's intramural scientists have been conducting a broad range of studies of CFS since 1979. These studies have covered multiple investigations for potential viral causes and cofactors in the syndrome. We have also conducted neurologic studies of brain function, neuropsychologic studies of mood and memory, studies of allergies in CFS, neuroendocrine studies, and therapeutic trials.

Mr. Porter: Provide a complete list of extramural CFIDS research projects currently funded by NIH. Indicate which projects seek to identify the etiological agents and markers for the pathophysiology of CFIDS.

Dr. Fauci: The NIMH Extramural Research Program funds two grants with relevance to chronic fatigue syndrome for a total of $1,151,000. Neither project seeks to identify the etiological agents and markers for the pathophysiology of CFIDS.

Title	FY 1996 Actuals
Research Center on the Psychobiology of Ethnicity	$1,061,000
Cognitive Dysfunction in Chronic Fatigue Syndrome	$90,000

The NIAID Extramural Research Program funds the following projects with relevance to chronic fatigue syndrome for a total of $4,255,000.

Pathogenesis of Epstein Bar Virus Infections	$120,000
Chronic Fatigue Syndrome Cooperative Research Center	$719,000
JHK Virus	$ 75,000
Exercise, Fatigue and Training in CFS	$335,000
Antigens of Human Herpesvirus-6	$100,000
Mechanisms of Immunologically Mediated Fatigue	$212,000
Social Processes and Somatization—The Course of CFS	$146,000
Estimating Rates of CFS in a Community Sample	$698,000
Virology and Immunology of CFS	$174,000
Chronic Fatigue Syndrome Cooperative Research Center	$646,000
Dysregulated 2-5A Syntehetase/Rnase L/PKR Pathways in CFS	$270,000
Scientific & Clinical Meeting on Chronic Fatigue Syndrome	$ 2,000
Coordinating Center for Clinical & Epidemiology Studies	$ 5,000
Clinical Monitoring of Chronic Fatigue Syndrome	$445,000
Trial of Fludrocortisone for CFS	$308,000

Each of the NIAID projects listed are relevant to the identification of etiological agents and/or markers for the pathophysiology of CFIDS.

HEPATITIS A

Mr. Bonilla: As you know, hepatitis A caused significant morbidity in U.S. Hispanic communities. With the availability of two hepatitis A vaccines in the U.S., some communicable disease directors in Texas and in the southwest border states are beginning to feel optimistic about the prospect of finally controlling hepatitis A in the Hispanic population. In my hometown of San Antonio, Texas the incidence of hepatitis A is about two to three times the national rate. In 1995, of all cases occurring in San Antonio 81 percent occurred in persons of Hispanic ethnicity. The disease is concentrated in central San Antonio in an area of poor, crowded neighborhoods. The incidence further South of San Antonio in my district is even higher. What initiatives is the NIAID taking to address/to control Hepatitis A along the Texas/Mexico border?

Dr. Fauci: Intramural scientists from NIAID were instrumental in developing a licensed vaccine against hepatitis A infection. Although two vaccines are now licensed and both are effective, the cost of the vaccine remains high due to inherent difficulties in growing the virus *in vitro* to make the vaccine. NIAID is sponsoring investigator-initiated research to improve the efficiency of growing the virus in tissue culture. This would lead to a cheaper, more accessible vaccine for target populations--the ones least likely to be able to afford the cost and most vulnerable to the disease.

While NIAID has the responsibility for research leading to improved vaccines and effective therapies, NIAID does not have the capacity to target problems in specific geographic areas such as the one you have cited in this question. State and local public health officials have the responsibility of managing the public health and disease control programs, which include fundamental hygiene initiatives, as well as effective immunization programs.

TUBERCULOSIS

Mr. Bonilla: What is NIAID doing in terms of tuberculosis research and control? My rural Texas district borders Mexico where the tuberculosis rate is high. Can you tell us what you are doing to control tuberculosis across the borders?

Dr. Fauci: NIAID supports research on many aspects of tuberculosis and its causative agent, *Mycobacterium tuberculosis* (*M.tb*) - including basic biology and pathogenesis, immunology, discovery and development of new and improved diagnostics, therapeutics and intervention strategies, and the development of new tools for molecular epidemiology. Recent accomplishments of our TB research Program include the identification of potential new anti-TB vaccine candidates and a potential new class of anti-TB drugs, and the development of promising diagnostic methods for the rapid identification and characterization of drug resistant strains of *M.tb* and for assessing effectiveness of therapeutic strategies, as well as development of innovative molecular epidemiological tools that are enabling us to acquire important new

knowledge on TB transmission patterns. We are supporting studies with particular relevance to the control of TB along the U.S./Mexico border. These investigators combine new and conventional epidemiologic tools to examine recent clinical isolates of TB in both San Francisco and Mexico, in order to analyze TB transmission patterns. The results of these studies suggest possible improvements in TB control strategies.

The mission of NIAID is to encourage and support biomedical research necessary to develop the tools and strategies to help solve infectious disease problems of public health importance. These efforts directly support disease control programs that are more appropriately managed by the U.S. Centers for Disease Control and Prevention and the State and Local Health Departments.

PRIORITIES

Ms. Northup: I have heard from immunologists who are concerned that the focus on AIDS is reducing funding in other areas which have been largely successful over the years. Would you please comment on this and how you would assure immunologists that NIAID will provide appropriate attention in other areas?

Dr. Fauci: AIDS research has been extremely important in furthering our progress in understanding other diseases and in research methodology in general. For example, scientists have a better understanding of cell biology, of how enzymes regulate virus replication, and the processes of cell division and apotosis. These findings have extremely broad, basic research implications.

In the area of molecular biology, PCR (polymerase chain reaction) was developed primarily as a diagnostic tool for HIV/AIDS. However, this methodology has been widely used for the diagnosis and evaluation of other infectious and malignant diseases, and has lead to the identification of new agents, such as cat scratch disease and herpesvirus.

HIV/AIDS research has also:

- Led to a better understanding of the role of cytokines in regulating the immune system. These findings are relevant for all other autoimmune disorders.

- Led to a better understanding of how cell-mediated immunity works to kill infected cells. These findings are relevant to infectious diseases and tumor disease.

- Improved our knowledge of how toxic agents affect neurons and neuroimmunology. These findings have direct relevance for Alzheimer's and Parkinson's diseases, as well as stroke research.

Immunology Research is a very high priority for the NIAID. We have increased our immunology spending by 16.6 percent from FY 1992 to FY 1996. Over the same period of time our Non-AIDS budget has increased by only 11.8%.

SEXUALLY TRANSMITTED DISEASES

Ms. Northup: How are you working with CDC to coordinate with its education program on sexual transmitted diseases?

Dr. Fauci: NIAID's STD Program and the CDC's Division of STD Prevention have a long standing history of collaboration and cooperation in the area of behavioral research. Some recent examples that illustrate the nature of the collaboration include:

- Collaboration on the monograph Research Issues in Human Behavior and Sexually Transmitted Diseases in the AIDS Era.

- Reciprocal representation in the strategic planning efforts and evaluations of the two programs.

- Sponsorship of young physician scientists supported by NIAID's STD Cooperative Research Centers in a CDC training program.

- Co-sponsorship of workshops on Adolescents and STDs.

- Collaboration on the monograph Adolescents and STDs.

Ms. Northup: There is a concern, again, about the focus on HIV rather than other sexually transmitted diseases. While related, how much funding will be designated to STD research?

Dr. Fauci: The NIAID will provide $70,908,000 in FY 1998 for research studying sexually transmitted diseases.

Ms. Northup: You mentioned that screening tests for STDs may be in the near future. Could you go into a little more detail on the expected time line of this screening possibility?

Dr. Fauci: The development of rapid, simple, inexpensive diagnostic tests, similar to the home-based pregnancy test, is a major priority of the NIAID's STD Program. We established the STD Diagnostics Initiative – an international task force that has enabled us to effectively coordinate and facilitate this effort on a global scale.

NIAID has also assumed a leadership role in a functional partnership with the commercial sector. Using the Small Business Innovative Research (SBIR) Program and cooperative agreements we are supporting research and development to test for the following STDs:

- Vaginitis including bacterial vaginosis (BV), trichomoniasis and vaginal yeast infections

- Genital Herpes

- Human Papillomavirus Infection

- Chlamydial infection

- Gonorrhea

NIAID has also established a cooperative agreement with a laboratory at the University of California at San Francisco to evaluate currently available STD diagnostic tests as well as those under development. In addition we have facilitated the evaluation of new tests in the context of NIAID's ongoing clinical trials. The potential to continue this effort is part of the STD Clinical Trials Unit which will be established this year.

DIARRHEAL DISEASES

Ms. Northup: While it is understandable to see dehydration resulting from diarrheal diseases causing death in third world countries due to living conditions, but why is the incidence so high in the United States? What is the time line of a possible vaccine that you mentioned?

Dr. Fauci: One million cases of severe rotaviral diarrhea occur in the U.S. in children under 5 including 65,000 hospitalizations. In developing nations diarrhea affects 18 million children, killing more than 870,000.

In developed areas of the world, drinking water is not a significant source of the infectious agent as it is in other areas. However, the lack of hand washing, improper handling and preparation of food, irrigation procedures, as well as person-to-person contact are significant factors leading to the diarrhea seen here in the United States.

Two rotavirus vaccines have been tested for safety and efficacy and should be licensed shortly. The vaccine RRV-TV was developed in 1986 and patented in 1988 by Dr. R. Chanock, Dr. A. Kapikian, and others at NIAID; it was tested in collaboration with Wyeth-Ayerst of Philadelphia. The second vaccine was developed by NIAID funded researchers at the University of Pennsylvania and is licensed to Merck, Sharp, and Dohme.

TUBERCULOSIS

Ms. Northup: There is a high incidence of TB in my home state of Kentucky due to coal mining and poor conditions in certain areas of the state. You briefly mentioned work on TB in your testimony. Could you provide more information on what your agency is doing in regard to this disease?

Dr. Fauci: NIAID supports research into many aspects of tuberculosis and *Mycobacterium tuberculosis*, the bacterium that causes TB. These areas include basic biology and pathogenesis, immunology, molecular epidemiology, and the discovery and development of new, improved diagnostics, therapeutic, and intervention strategies, such as vaccines. In addition, we are currently funding the sequencing of the complete genome of *Mycobacterium tuberculosis*, which we expect to help galvanize TB research on many of these fronts.

Recent accomplishments of our Tuberculosis Program include the identification of potential new anti-TB vaccine candidates and a potential new class of anti-TB drugs. An important area of our research includes the development of promising diagnostic methods for the rapid identification and characterization of drug resistant strains and for assessing effectiveness of therapeutic strategies, as well as development of innovative molecular epidemiologic tools that are enabling us to acquire important new knowledge on TB transmission patterns.

CHRONIC FATIGUE SYNDROME

Ms. Northup: I know many people, mainly women, believe they are afflicted with Chronic Fatigue Syndrome. This occurs in more areas of the country of the others. Besides the study regarding low blood pressure, has your Institute funded other CFS research projects? If not, why not? How much funding goes to CFS research?

Dr. Fauci: In FY 1998, the NIAID will provide $5.6 million to support CFS research. We fund projects concerned with natural history, epidemiology, diagnostic and/or prognostic laboratory markers, involvement of viruses, and comparisons of neurocognitive, neuropsychogical and neurophysiological parameters of chronic fatigue patients. NIAID's research program is designed to fill the gaps in knowledge of CFS with the recognition that interdisciplinary research offers the most promise of achieving an understanding of the mechanisms of chronic fatigue syndrome etiology and pathogenesis.

AIDS

Mr. Stokes: AIDS/HIV continues to take an enormous toll on families and the Nation. What is the extent of the problem? According to the Harvard AIDS Institute, the dramatic toll that the disease takes on the African Americans is staggering. Could you elaborate on that toll – as it relates to the changing faces of AIDS? Would you bring the subcommittee up-to-date on the status of enrollment of African Americans and other minorities in the Institute's AIDS clinical trials network?

Dr. Fauci: Recently, the Centers for Disease Control and Prevention (CDC) reported that AIDS deaths declined 13 percent in the first half of 1996 as compared to the first half of 1995, the first time since the epidemic began in 1981. Nonetheless, AIDS continues to take an enormous toll, especially in the African American community. While AIDS deaths declined among all racial/ethnic groups, declines were lowest among African Americans (2%) as compared to whites (21%) or Hispanics (10%). As of December 1996, the CDC reported a cumulative total of 581,429 cases of AIDS. For the first time, African Americans accounted for more cases of AIDS than whites – 41 percent as compared to 38 percent. Hispanics accounted for 19 percent and other races 2 percent.

One of the greatest challenges facing AIDS researchers today is the recruitment and retention of minority patients for clinical trials. People of minority background face unique social, economic, and medical problems in coping with the challenges attendant to HIV infection. As the epidemic expands in minority communities, inclusion of these patients in clinical trials is particularly urgent to ensure that the results of research are applicable to all populations impacted by the disease.

In treatment research, NIAID strives to (1) ensure that the number of underserved populations participating in clinical trials is representative of the national epidemic, (2) identify the need for and/or assist to develop culturally sensitive education materials, and (3) identify real or potential barriers to recruitment and retention in clinical research for these groups and develop mechanisms for overcoming these barriers. Current enrollment in our clinical trials networks is as follows:

- AIDS Clinical Trials Group -- 36% black, 39% white and 22% Hispanic.
- Terry Beirn Community Program for Clinical Research on AIDS – 39% black, 39% white and 19% Hispanic.
- Division of AIDS Treatment Research Initiative – 36% black, 14% white and 3% Hispanic.

In epidemiologic research, NIAID supports studies that explore the nature of HIV infection in a variety of populations. In these studies, demographic enrollment is as follows:

- Women's Interagency HIV Study – 56% black, 18% white, and 24% Hispanic.
- Women and Infant Transmission Study – 49% black, 14% white, and 35% Hispanic.

- Multicenter AIDS Cohort Study – 10% black, 83% white, and 5% Hispanic

In vaccine research, the AIDS Vaccine Evaluation Group has made an increased effort to enroll minorities in clinical trials of candidate HIV vaccines. In addition, in preparation for conducting HIV vaccine and other prevention efficacy trials through the HIV Network for Prevention Trials, NIAID is working with inner city communities to address their concerns and ensure that patients are fully informed of their rights.

AIDS VACCINE PROGRESS

Mr. Stokes: In view of the considerable progress that the Institute has made with regard to the therapies for HIV infection, where are we with regard to the development of a vaccine for AIDS/HIV?

Dr. Fauci: Several vaccines are currently being tested, the most promising approach thus far is a combination vaccine of gp120 and canarypox. The ability of this approach to induce a cellular and antibody response distinguishes it from the other approaches that have been tested. A phase II clinical trial using this approach is expected to begin in 1997. The study is being conducted jointly by NIAID's AIDS Vaccine Evaluation Group and the HIV Network for Prevention Trials and will include 400 volunteers at high risk for HIV infection at 14 domestic sites.

MALARIA

Mr. Stokes: Over the years, the Institute has conducted and supported research in malaria. Malaria remains a significant global public health problem. Do we know the scope of this problem, explain? What have been some of the most significant challenges facing the Institute in this particular field of research, and what is being done to capitalize on opportunities in malaria research?

Dr. Fauci: Malaria remains the most important of the tropical parasitic diseases in terms of annual mortality. Infection with these protozoan parasites, which are transmitted by mosquitoes, is a major public health problem in tropical and subtropical regions, where the disease exacts a heavy toll of illness and death. Although much effort has gone into controlling malaria in different parts of the world, initial successes have been reversed as a result of: (1) increased resistance of mosquitoes to standard insecticides, thus making control of transmission difficult to achieve; (2) increased resistance of the malaria parasite to inexpensive and effective drugs, thus presenting problems for the treatment of active infections; and, (3) changing epidemiological and ecological patterns, resulting from economic development within malarious areas, thus altering the distribution of the disease and requirements for control.

Malaria has been undergoing a dramatic resurgence in recent years, as reflected in the following figures from the World Health Organization (Weekly Epid. Rec. 69: 309-316, 1994; and WHO Statistical Information Service):

	1990 (millions)	1993 (millions)
People at risk	2,100	2,300
People infected	267	Not Available
Clinical cases	100	300-500
Estimated annual deaths (mostly children in Africa)	1-2	1.5 - 3.0

Not only because of the magnitude and rate of resurgence, but also because of the increasing lack of efficacy of conventional drug therapy, the limited number of promising new drugs under development, and the spread of insecticide resistant mosquitoes that transmit the disease, malaria was designated as an important emerging disease by the Institute of Medicine (IOM). The IOM report also warns of the potential for malaria to reestablish itself in the United States. In 1995 approximately 1,200 cases of malaria in the U.S. were reported to the CDC. The great majority of these were imported cases. Over the past ten years, however, malaria transmission in California and Florida has been documented and traced to migrant farm workers from endemic areas. Recently, additional cases of locally acquired malaria have also been reported in residents of New Jersey, New York City, Houston TX, and Michigan.

The following briefly summarizes some of the challenges facing malaria research:

- Difficulties in maintaining facilities for the entire life cycle of malaria which requires establishment of insectaries for the mosquito vector.
- Inherent difficulties in molecular cloning and sequencing of the malaria genome.
- Lack of small animal models for studies of pathogenesis and for preclinical evaluation of vaccines and drugs; primates are expensive and not readily available.
- An *in vitro* culture system exists only for *Plasmodium falciparum*. Other species of malaria which infect humans can not be cultivated *in vitro*.
- Lack of access to standardized immunological and molecular reagents and repositories of well-characterized parasites and vectors thereby limiting generalizability of results from different laboratories, field sites and clinics.
- Lack of adequate communication systems with international field sites and limited infrastructure at these sites, especially those in Africa.
- Limited interest by the private sector for further preclinical and clinical development of promising interventions including drugs and vaccines.

In concert with a number of other international agencies which support malaria research, the NIH sponsored an International Conference on Malaria in January 1997.

This meeting brought together scientists from the United States, Europe and Africa to consider the priorities for malaria research and to determine the steps needed to further this research. Participants in the meeting focused on research needs in the following areas: immunology, pathogenesis, drug and vaccine development, entomolgy and vector control, epidemiology, and health systems and operations research. As a result of that meeting, the NIH and the other funding agencies issued a Request for Letters of Interest for a Multilateral Initiative on Malaria in Africa which is intended to enhance the capacity of scientists to conduct collaborative/multicenter research relevant to malaria in Africa. The letters and requests for support will be considered at a follow-up meeting scheduled for July 1997 in the Hague. The NIH is also exploring mechanisms to increase the capacity to communicate electronically with sites in Africa and to provide African scientists with access to the Internet.

NIAID will continue to build upon its base of malaria research which has provided a number of new opportunities for future control efforts. The majority of NIAID support for malaria research will be used to support the traditional investigator-initiated mechanisms, thus enabling scientists to follow-up on innovative areas of study. In addition, support has been provided to jump start an effort to sequence the entire genome of *Plasmodium falciparum*. We envision that this effort will provide investigators with new targets for drugs and vaccines. This effort is being coordinated with other donors, including the DoD, the Burroughs Wellcome Fund, and the Wellcome Trust.

The Institute will continue to take an active role in interactions with other federal agencies involved in malaria research and development. In particular, NIAID will continue to work with USAID and USAMRDC to design, produce, and clinically evaluate candidate vaccines for malaria. Through the Federal Malaria Vaccine Coordinating Committee, NIAID will work with other federal agencies, including the DoD, CDC and USAID, that support ongoing malaria vaccine research efforts and collaborate to accelerate malaria vaccine research, development, and evaluation.

NIAID continues to promote collaborative studies between U.S. and foreign scientists working in endemic areas for studies of malaria pathogenesis, vector control, epidemiology as well as for clinical trials of drug therapies. Moreover, the Institute is soliciting proposals for research on the pathogenesis of malaria and for field studies in endemic areas which seek to identify immune correlates of protection. The information derived from these studies will contribute to the determination of appropriate case definitions, development of new disease intervention strategies, and selection of appropriate endpoints to be used in clinical trials of candidate vaccines and new therapies.

Finally, the NIAID will continue to expand its interactions on development of novel therapeutics for malaria with the World Health Organization and with the Walter Reed Division of Experimental Therapeutics. The participating agencies will share information and access to services and facilities for preclinical and clinical development of these compounds.

ASTHMA

Mr. Stokes: The budget submission indicates that an estimated 7 percent of all children aged 18 and younger have asthma, one of the most common chronic diseases of childhood. Despite improved treatments, asthma-related illnesses and deaths have increased, particularly in minority populations. Dr. Fauci, as you know, asthma takes a dramatic toll on African Americans and other minorities. What is the extent of asthma in African Americans and other minorities? Are there specific age groups that is more at-risk than others and if so, why?

Dr. Fauci: Asthma prevalence and mortality increased steadily in the U.S. during the decade of the 1980's and this trend has continued through 1994. The burden of asthma is greatest among disadvantaged people living in the poorest areas of our inner cities. Nationwide, prevalence estimates are higher for people living in "central city" regions, as compared to those living outside metropolitan areas (6.2% vs. 5.4%; all age groups). In 1994, asthma rates were considerably higher for those with family incomes under $10,000 as compared to those with family incomes greater than $35,000 (8.4% vs. 5.1%; children and adults under age 45). These findings are in close accord with recent observations that asthma deaths in New York City, Boston, and Philadelphia are localized primarily to those census tracts with the greatest poverty.

The prevalence of asthma in the African American population, as a whole, is not dramatically different than that for Whites, but among children and young adults the differences in severity of asthma are particularly striking. For example, in 1993, among 0-24 year olds, African Americans were 3-4 times more likely than Whites to be hospitalized for asthma and were 4-6 times more likely to die from asthma. Two recent studies found a two-fold excess asthma risk among Puerto Rican Hispanics, whereas asthma rates for Cuban Americans and Mexican Americans do not differ substantially from those for non-Hispanic Whites.

Poverty, family problems, psychological and behavioral problems, lack of education, lack of easy access to medical care, and a poor understanding of the need for preventive medications, all increase an asthma patient's risk of having a severe asthma attack or, more tragically, of dying from asthma. In addition, the poor quality of housing in many urban areas results in a heightened exposure to indoor allergens and to respiratory irritants such as nitrogen dioxide, a product of poorly ventilated gas stoves. To address these problems and to overcome obstacles to optimal care, NIAID initiated the National Cooperative Inner-City Asthma Study in 1991. This clinical trial identified risk factors associated with childhood asthma and studied the effectiveness of a comprehensive treatment and intervention program. Very striking results are now surfacing from this study and are highlighted in the responses below.

Mr. Stokes: To what extent are we continuing to make progress in unraveling the relationship between the environment and asthma?

Dr. Fauci: Exposure to high levels of indoor allergens (including cockroach, dust mite, cat, dog, mouse, rat, and mold allergens) contributes importantly to asthma severity. Over 70% of the children enrolled in the National Cooperative Inner-City Asthma Study had cockroaches in their homes and the 50% who were exposed to higher levels of cockroach antigen had nearly 3-fold more hospitalizations than did children who were not exposed. Other environmental factors that were strongly associated with asthma severity included tobacco smoking among caretakers and family members (a risk factor for ~60% of children enrolled in the study) and exposure to nitrogen dioxide (a respiratory irritant present at high levels in ~25% of inner city homes).

An international workshop on "Asthma and the Environment" was held in May 1996 and was sponsored by the Environmental Protection Agency, the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, the National Institute of Environmental Health Sciences, the Center for Disease Control and Prevention, and the National Institute of Occupational Safety and Health. While few carefully controlled, longitudinal studies have been published, there was general agreement among the workshop participants that exposure to outdoor pollutants (including ozone, diesel exhaust, and airborne particulate matter) may not cause asthma, *per se*, but may contribute to the exacerbation of existing asthma. Investigators supported by NIAID are now beginning to unravel the molecular and cellular events whereby these outdoor pollutants cause chronic inflammation of the airways.

Within the past year several carefully performed epidemiologic studies have shown that common cold viruses (rhinoviruses) are responsible for a large proportion (~85%) of asthma exacerbations that require hospitalization or emergency room care. Since rhinoviruses cause little cytopathology, it is likely that the immune response to the virus, and not the virus *per se*, is responsible for the severe and prolonged respiratory inflammation and airways hyperreactivity in virus-induced asthma. Studies of the immune response to common respiratory viruses may yield new approaches to control the most costly asthma exacerbations.

Interactions between respiratory viruses, indoor allergens, and outdoor air pollutants may also be important in the induction of airway inflammation in asthmatics. An emerging area of research focuses on the mechanisms by which environmental agents, such as these, synergistically exacerbate disease.

Mr. Stokes: The National Cooperative Inner-City Asthma Study was designed to help address this problem. I understand that the first phase of the study has been completed. Would you please provide the Subcommittee an update on the findings thus far? The justification indicates that over half of the participants in the National Cooperative Inner-City Asthma Study would find it difficult to get follow-up care for their asthma. Would you elaborate on this?

Dr. Fauci: The National Cooperative Inner City Asthma Study (1991-1996) was a randomized, multi-site clinical trial of an asthma intervention for inner-city children ages 4-11 years with moderate to severe asthma. The study was conducted at eight Asthma Study Units located in seven major metropolitan areas (Baltimore, Chicago, Cleveland, Detroit, New York, St. Louis, and Washington). Participants lived in inner-city census tracts where an average of 30% of the population was below the federal poverty line. Spanish speaking families were recruited at three of the sites and, overall, ~75% of participants were African Americans and ~20% were Hispanic. Phase I of the study was designed to identify factors associated with asthma severity. Phase II evaluated the effectiveness of a comprehensive intervention to develop improved knowledge about asthma, to promote better asthma self-management skills, and to decrease or eliminate exposure to environmental factors associated with increased morbidity from asthma. The intervention was conducted by an asthma counselor, a social worker who received training in management of asthma. The asthma counselors maintained close follow up with patients and their families, but did not interact with the patient's physician or dictate medical care.

Phase I enrolled 1,528 children and Phase II enrolled 1,033 children. Greater than 92% participation was maintained throughout the study. This represents exceptionally high recruitment and retention of subjects in a longitudinal study of this type. Involvement of the community and implementation of strategies to enhance patient self-management were key to the success of the study.

The study found that multiple factors were associated with asthma severity. These included: psychological and behavioral problems; exposure to high levels of indoor allergens, especially cockroach allergen; high levels of tobacco smoking among family members and caretakers; and exposure to nitrogen dioxide, a respiratory irritant found at high levels in ~25% of homes. The importance of cockroach allergen was unanticipated and, based on this finding, cockroach avoidance measures have now been incorporated into the Asthma Care Guidelines of the National

Asthma Education and Prevention Program of the National Heart, Lung, and Blood Institute.

While essentially all children had access to medical care for their asthma, over half of the families reported difficulties in obtaining follow-up care. Over the course of the study, these patients had asthma that was considerably more severe than did the study population as a whole. Many of these patients identified a local emergency room as their primary source of follow-up care. This caused problems in establishing telephone contacts between patients and their physicians. Other problems included difficulties in scheduling or paying for transportation to the physician's office or clinic, lack of child care during a sibling's illness, and problems related to absenteeism from work during a child's illness.

Because no single factor stood out as a primary determinant of asthma severity, the interventions were tailored to the specific needs of individual patients based on the findings of an asthma risk profile. Overall, the intervention resulted in a striking 30 percent reduction in asthma-related hospitalizations and doctor visits. The improvement was greatest at the close of the intervention, which coincided with the annual autumn peak in asthma exacerbations. Telephone follow-up with patients and their families is being continued for an additional year to determine the magnitude and duration of these promising results.

Mr. Stokes: What are your future plans for the project, and to what extent will the FY 1998 budget request allow you to exploit this opportunity?

Dr. Fauci: Based on the promising results of this study, NIAID and the National Institute of Environmental Health Sciences co-sponsored a four year follow-up study begun in FY 1996. This is a multi-site cooperative clinical trial that will be conducted at sites throughout the U.S. (Boston, Chicago, Dallas, New York, Seattle, and Tucson) and is planned for in the FY 1998 budget request. A common intervention protocol is under development and patient enrollment is planned to begin this summer. The protocol will focus more attention on environmental and behavioral interventions and will include a rigorous economic evaluation of cost-effectiveness.

PATIENT REGISTRIES

Mr. Stokes: Infectious diseases remain the most common cause of death for children worldwide, and disorders of the immune system afflict more than one in 10 Americans. Would you bring the committee up-to-date on the Institute's patient registries program for primary immunodeficiency diseases? To what extent are there plans to develop additional patient registries?

Dr. Fauci: In 1992, the NIAID provided support to the Immune Deficiency Foundation to establish a registry for U.S. residents affected by chronic granulomatous disease (CGD). This was considered a pilot project to determine the feasibility and usefulness of a registry for one of the 70 primary immunodeficiency disease. In February, 1996 the Scientific Advisory Committee of the registry reviewed progress and the information obtained and concluded that considerable information about CGD was obtained that was not previously available. Moreover, the nearly 350 individuals in the registry are available and being utilized in research studies. The NIAID is currently in the process of requesting proposals to support a five-year program to establish and maintain a registry of clinical information on U.S. residents affected by additional primary immunodeficiency diseases. Based on the recommendations of a group of experts, the diseases to be included are: Severe Combined Immunodeficiency Disease (SCID), X-linked Agammaglobulinemia (XLA), Wiskott-Aldrich Syndrome (WAS), Common Variable Immunodeficiency (CVID), and CGD. The expected outcomes include: 1) improved access of investigators to patients for both basic studies and clinical

trials; 2) provision of accurate and up to date information useful to clinicians and genetic counselors; 3) improved access of affected individuals to the latest therapy; and 4) establishment of a database which can be used to determine the socioeconomic costs of these diseases. Other diseases which will benefit from the research advanced by this resource include immunodeficiency, host defense against infection, inflammation, and autoimmune diseases.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists' cloning of adult sheep. These articles expressed excitement with regard to opportunities for advances in medical treatments, and concern with regard to misuse of the technology and the possibility of human cloning. This is another area where we must now be certain to assess and address the ethical, legal, and social issues of research on the front end. As a leading researcher and as an institute Director, what is your professional opinion of this technology and what are your most serious concerns ?

Dr. Fauci: The technological advance is significant and provides a tool to explore basic research questions. However, with any new technology comes the risk that it may not be used appropriately. I believe any concerns that I might have will be addressed by the National Bioethics Advisory Commission. They have already been asked to review what ramifications cloning would have for humans and issue a report on their findings within 90 days to the President.

Mr. Stokes: With regard to the diseases and disorders studied by your institute, what are the most significant benefits that the cloning technology would yield for your major areas of research ?

Dr. Fauci: Cloning could be a tool utilized in animal models to study a range of issues, for example:

- the genetic interactions needed in normal gene regulation of the immune system
- what defects in regulation lead to immunologic disorders: autoimmune and immunodifficiency diseases, asthma and allergies
- examining the genetic susceptibility to disease that varies among individuals and using that information to guide us in the development of new treatment and prevention strategies

TUBERCULOSIS RESURGENCE

Mr. Stokes: According to your budget justification, tuberculosis is the leading cause of death worldwide. More people died from TB in 1995 than in any previous year

in history, and 8 million new cases of TB developed. The budget submission goes on to state that during the next decade an estimated 300 million more people will become infected with TB. Would you explain why this disease is on the rise?

Dr. Fauci: Several factors appear to be working together to cause the current rise in tuberculosis. These include inadequate public health infrastructures, increasing poverty and homelessness in many areas, and the global AIDS epidemic. Tuberculosis and AIDS are synergistic infections - each appears to accelerate the course of the other disease in co-infected individuals. The rising number of drug-resistant strains of *Mycobacterium tuberculosis* is attributable largely to poor compliance with the standard course of therapy, which involves taking a combination of several drugs for many months.

Mr. Stokes: As researchers continue to learn more about the multi-drug resistant strains of tuberculosis, are we getting better at being able to quickly determine effective therapies?

Dr. Fauci: Several promising approaches are currently being developed to identify and characterize drug-resistant strains in a matter of 1-2 days rather than the several weeks now necessary. In addition, new molecular epidemiology tools enable us to track and monitor the spread of multi-drug resistant strains much more effectively than was previously possible.

CHRONIC FATIGUE SYNDROME

Mr. Stokes: Chronic Fatigue Syndrome appears to be a poorly understood illness. What progress do you have to report this year with respect to Chronic Fatigue Syndrome?

Dr. Fauci: In response to Congressional FY96 report language recommending studies of chronic fatigue syndrome pathogenesis the NIAID co-sponsored with 6 other Institutes (NIAMS, NIMH, NHLBI, NIEHS, NIDDK, and NINR) and the ORWH a Program Announcement to accelerate multi-disciplinary research on the Pathophysiology of Chronic Fatigue Syndrome. We have received the first responses to this Program Announcement, and it appears many new investigators are being drawn to this field of research.

We have also initiated a placebo-controlled double-blinded randomized trial of fludrocortisone for CFS based on the finding that there is an association between CFS and a treatable blood pressure disorder, neurally mediated hypotension. The trial uses objective measures to establish neurally mediated hypotension at baseline and to confirm outcome and compliance. The trial also includes a battery of subjective measures to assess outcomes as well as health status at baseline and will involve the collaborative effort of intramural and extramural scientists.

Mr. Stokes: According to the budget justification, recent reports from Johns Hopkins University suggest that a form of abnormally low blood pressure, known as neurally mediated hypotension, is common among CFS patients. What is the significance of this finding? What other categories of diseases are yielding significant insight to further understand Chronic Fatigue Syndrome?

Dr. Fauci: The investigators at Johns Hopkins University have found that some patients which meet the CDC case definition for CFS suffer from neurally mediated hypotension - a well defined clinical entity that is usually treatable. The NIAID has recently funded a clinical trial at Johns Hopkins University to test whether therapies used for treating neurally mediated hypotension will benefit some people with CFS. This discovery of an overlap of symptomatology of CFS and neurally mediated hypotension is the type of breakthrough that may lead to better refining the case definition of CFS. A recent Program Announcement seeking applications to study the pathophysiology of CFS is attracting research applications with new approaches to studying CFS. We envision that this newly stimulated research will provide insights as to other disease categories which may be involved in this syndrome.

NEW AND IMPROVED VACCINE DEVELOPMENT

Mr. Stokes: What are the most significant opportunities that are ready to be exploited with regard to the development of new vaccines and the improvement of existing vaccines? How much is included in the FY 1998 budget request for this effort and how does it compare with the FY 1997 funding level?

Dr. Fauci: There are a number of exciting opportunities to be pursued in vaccine research. Advances in recombinant DNA technologies, the elucidation of the genome of important microbes that still cause infectious diseases, and ongoing work in human mucosal immunology are making possible new approaches. While existing vaccines, such as the available pneumococcal and influenza vaccines, do offer protection, their success is limited by moderate efficacy, and thus NIAID is testing new candidates targeted for children and adults. Intranasal and oral vaccines are being developed to simplify immunization and protect against respiratory and gastrointestinal diseases transmitted through mucosal surfaces. Other new approaches to vaccine development include:

- DNA vaccines to protect against influenza, HIV, and tuberculosis
- Oral vaccines from transgenic plants that contain genes from infectious agents
- New adjuvants to improve the response to weak vaccines
- Vaccine vectors that incorporate the important genes from a pathogen into a safer nonpathogenic microbe
- Combination vaccines to simplify the immunization of babies against multiple diseases

The amount requested for non-AIDS vaccine development for FY 1998 is $108,801,000, a 2.0 percent increase over the FY 1997 level of $106,668,000.

RESEARCH ACCOMPLISHMENTS

Mr. Stokes: As the Institute looks ahead to celebrating its 50th anniversary, in 1998, and looks back to assess its accomplishments, what would you say have been the Institute's major landmark achievements? What improvements in health were realized.

Dr. Fauci: The NIAID has made significant contributions to the fight against many diseases through its portfolio of research grants and contracts. We have supported the research of a number of Nobel Prize laureates during the past 50 years. These include Peter Dougherty and Rolf Zinkernagel (1996 laureates), Baruj Benacerraf (1980), D. Carleton Gadjusek (1976).

Accomplishments in the area of Acquired Immundeficiency:

In the seventeen years since AIDS cases first began appearing in the U.S. we have made significant advances in understanding how HIV causes disease and in treating infection. In this short period of time the virus that causes AIDS was found, scientists have learned how HIV causes disease, is transmitted, and damages the immune system; tools for diagnosing HIV and predicting disease progression have been developed; and new treatments have been discovered and developed.

Specific accomplishments in the area of Natural History and Pathogenesis in HIV include:

- Recognition that the CD4+ T cell is the primary target for HIV and that both quantitative and qualitative defects in CD4+ T cell function occur during HIV Infection.
- Definition of the patterns of change, predictors of decline, and alteration in function of CD4 and CD8 T cells during the course of infection.
- Characterization of risk factors for HIV transmission.
- Demonstration of a marked increase in the risk of developing *pneumocystis carinii* pneumnoia and other opportunistic infections associated with CD4 cell counts below 200.

Specific accomplishments in the area of Vaccines for HIV include:

- Definition of the extent and spread of HIV during the acute stage of infection and the dynamics and breadth of immune responses. Definition of the key role of cytotoxic T-lymphocyte in helping to control the acute phase of the disease.
- Compilation and analysis of the genetic sequence for HIV. This information has helped in understanding the variability of HIV and in determining its clades.

- Demonstration that protection from HIV is possible; animals have been protected from infection after vaccination and individuals have been identified who have not become infected despite repeated exposure.

Specific accomplishments in the area of Therapeutics for HIV include:

- Demonstration that zidovudine can reduce the risk of perinatal transmission of HIV from 25% to 8%.
- Demonstration and definition of the efficacy of ZDV, ddC, and ddI as monotherapies and in combination for a wide variety of clinical conditions.
- Demonstration that a protease inhibitor in combination with two reverse transcriptase inhibitors can delay disease progression or death.

Accomplishments and improvements in Microbiology and Infectious Diseases include:

- Safer pertussis vaccine. The NIAID led a 15 year research effort on safer pertussis vaccines for babies, leading to the successful conclusion of two large efficacy trials and the subsequent licensure of three acellular pertussis vaccines- over the past year. The success was based on scientific advances leading to the identification and purification of antigens, and was marked by interagency as well as critical public-private collaboration.

- *Haemophilus influenzae* type b vaccine (Hib). The NIAID led the research effort that culminated in the 1989 introduction of conjugate Hib vaccines and the 1990 recommendation that they be used universally in infants to protect against invasive *Haemophilus influenzae* type b. Prior to this time Hib was the leading cause of meningitis in children in the United States. From 1989 to 1995, the incidence of invasive Hib disease decreased 99 percent among children under 5 years of age, virtually eliminating the significant morbidity and mortality previously attributable to this disease in the United States.

- Identification and characterization of new infectious agents, e.g., hepatitis viruses, cholera 0139, rotavirus B strain, Helicobacter pylori.

- Identification of the role of infectious agents in chronic and persistent diseases: hepatitis viruses and liver disease, *Helicobacter pylori* and gastric ulcer, human papilloma virus and cervical cancer, *Campylobacter jejuni* and Guillian Barre syndrome, *Borrelia burgdorferi* and arthritis.

- Development of the first human rotavirus vaccine shown to be highly effective in both developed and developing countries. FDA approval of the vaccine is imminent. The NIAID live attenuated virus vaccine is currently being considered by the World Health Organization for routine use in pediatric immunization, worldwide.

- Hepatitis A Vaccine Licensed: NIAID scientists were the first to identify hepatitis A virus (HAV) and define its epidemiology. Later, they adapted a strain of HAV to

grow efficiently in cell culture and identified the genetic changes in the virus responsible for its adaptation to a cell culture system suitable for use in vaccine production. Finally, they collaborated with SmithKline-Beecham to develop the vaccine commercially. It was licensed by FDA in 1995 and is now in widespread use.

- First demonstration that pneumonia caused by *Mycoplasma pneumoniae* could be cured by an antibiotic, namely tetracycline.

- Discovery of several major infectious pathogens of man, such as: the Lyme Disease agent, Hepatitis A virus, and Human Herpes virus 6.

- NIAID scientists were the first to identify a new important form of epidemic human hepatitis, now known as hepatitis E. A recently developed experimental hepatitis E virus vaccine was shown to be highly effective in protecting monkeys against hepatitis E virus (HEV) challenge. These encouraging observations have provided the basis for current efforts to apply a similar strategy to the development of an inactivated HEV vaccine for human use.

Accomplishments in the area of Allergy, Immunology and Transplantation include:

Fifty years ago, it was known that "factors" in the blood were responsible for defense against pathogens; however, virtually nothing was known about what those factors were and how they functioned. At this time the field of monologue consisted of a few scientists who were involved in the purification of immune response proteins, now known to be antibodies. Since that time, immunology has grown into one of the largest biological fields and many aspects of the immune system are now understood at the cellular and molecular levels. NIAID has been responsible for supporting many scientists who helped to define the immune system "players" and who aided in gaining understanding of how these "players" work, how they malfunction, and more recently, how they can be manipulated clinically. While all of the science funded by NIAID greatly contributed to the evolution of immunology, a few major discoveries stand out as landmark achievements in the field of basic immunology research.

- The identification of cells which respond to a specific bacterial or viral antigen, their division of labor, and how they cooperate in generating an immune response: These cells include phagocytes which engulf and destroy pathogenic organisms, as well as antibody-producing B cells, cytotoxic (killer) T cells, and helper T cells. Each of these cells has special functions in the recognition and eventual clearance/killing of foreign antigens. Understanding the roles of these cells has furthered our knowledge of infectious disease pathogenesis, autoimmune disorders, allergy and transplantation, and has facilitated the development of vaccines.

- The link between immune responses and the genetic background of individuals: This knowledge led to the concept and subsequent discovery of the major histocompatability locus (MHC), a region of genes which encode proteins found on

all cells of the body. These proteins vary considerably among individuals and must bind foreign antigens before the antigens can trigger T lymphocytes to activate the immune system. MHC proteins also tell the immune system how to distinguish self from non-self; therefore, they are central in suppressing autoimmunity while allowing immunity to pathogens. The question of why some individuals/populations are immune to certain pathogens, while others are not, were answered by these findings. The identification of the MHC also explained why transplanted tissue is rejected in non-MHC matched individuals.

- Solving of the three dimensional molecular structures of MHC proteins complexed with foreign antigens: This finding revolutionized our understanding of how T cells recognize foreign antigen and confirmed the fact that there is a genetic component to immune responses. Besides allowing for remarkable advancement in basic immunology research, elucidation of the MHC:antigen structures which trigger T cell responses has provided a basis for new vaccine approaches and an ability to design molecules for modulating immune responses in an antigen-specific.

- One of the NIAID's long-standing missions has been to support basic research to enhance our understanding of the molecular mechanisms underlying the control of the immune response. This support led directly to the identification of an important molecule responsible for controlling the immune response. This knowledge led to the theory that interruption of the cells having this molecule could prevent and/or treat diseases mediated by an immune response.

- One highly successful example of the application of this knowledge is the use of antibodies to this molecule to prevent and treat rejection of a transplanted organ. The theory was that since the rejection process is an immune response to a "foreign" organ, if the immune response could be interrupted at the time of the rejection, the rejection process would be interrupted and the organ would not be lost. This theory led to the testing of many antibodies against the T-cell receptor in treating graft rejection. The most successful was OKT3, an antibody that is now routinely used to prevent and treat graft rejection. OKT3 has a 95% success rate in reversing ongoing rejection of a transplanted organ. This success, attributable directly to NIAID support of basic research on the immune system, has led to a significant decrease in the loss of transplanted organs, with major savings of money and an improvement in the patient's quality of life.

And let us not forget our earlier accomplishments from the 1940's and 1950's during the first years after the inception of the Institute:

- Discovery and characterization of St. Louis encephalitis virus and lymphocytic choriomeningitis virus (two important neurotropic pathogens).
- Isolation and characterization of the etiologic agent of rickettsial pox, a previously unrecognized disease.

- Identification of the role of Coxsackie B viruses in pleurodynia ("Devil's grippe") and Coxsackie A viruses in herpangina (a common form of febrile sore throat during the summer).
- Discovery of the human adenoviruses and definition of their importance in acute febrile respiratory tract disease and eye disease.
- First prediction of the presence of oncogenes in the host genome.
- First identification and characterization of non-structural tumor (T) antigens encoded by DNA tumor viruses.

EMERGING INFECTIOUS DISEASES

Mr. Stokes: The budget justification states that history has proved time and again that new infectious agents will continue to emerge, and previously recognized pathogens will reemerge. According to the budget submission, the Institute has launched a new initiative for expanded research on emerging diseases. Can you explain how this effort is designed to allow the Institute to rapidly respond to emerging infectious diseases? Can you briefly summarize the extent of the problem in the United States?

Dr. Fauci: Between 1980 and 1992, the death rate due to infectious diseases rose 58% in the United States, making them the third leading cause of death in this country. The potential for increasing risk has to do with several factors: the capacity of microbes to change and adapt in ways that make them more virulent or resistant to currently available drugs and vaccines; demographic and environmental changes that place people in situations where disease transmission is more likely to occur; and increased international travel and trade that allow infections to spread rapidly and widely. We can all think of recent examples, such as the increase in multiple drug-resistant tuberculosis, the outbreaks of waterborne cryptosporidiosis and foodborne *E. coli* and cyclospora infections, and the outbreak of hantavirus associated with exposure to infected rodents. In addition, ever improving scientific technology is allowing us to identify microbial pathogens that are associated with diseases whose cause was previously unknown or poorly understood, such as the relationship between *Helicobacter pylori* and gastric carcinoma.

NIAID believes that research is an integral component of the national capacity to respond to the threat of emerging and re-emerging infections. Research provides the tools, such as diagnostics, vaccines and drugs, required to prevent and control infectious diseases. NIAID has developed a Research Agenda for Emerging Infectious Diseases that focuses on three overall goals. The first goal is improved prediction and prevention of future threats, which is being addressed by support of fundamental research on the influences underlying disease emergence, as well as support of applied research on improved technology for diagnosis and prediction of outbreaks. The second major goal, development and validation of new or improved control strategies, is being addressed by applied research on the discovery, design, and evaluation, through preclinical and clinical testing, of drugs and vaccines. The third focus of the NIAID research agenda is

strengthening of the national and international capacity to detect and respond to infectious disease threats, which the Institute is addressing through support of multidisciplinary research projects, focused training programs, and international research.

The implementation of these activities has taken the form of both disease-specific and approach-specific initiatives. Recent examples of the former include NIAID initiatives to expand research on Lyme and other tick-borne diseases, tuberculosis, Hanta, and other emerging viral infections. Examples of approach-specific initiatives include drug discovery and development programs for medically important mycoses, and emerging viral diseases. In 1996, NIAID initiated a three year solicitation to expand research on the environmental and microbial factors influencing disease emergence, and on improved detection and prediction of emerging diseases. Additionally, in fiscal year 1997, NIAID is providing supplemental funding for two new initiatives: 1) expansion of international research on emerging diseases, including transmission patterns, host and pathogen-related risk factors, and environmental influences; and, 2) establishment of networks to encourage investigators working on complementary aspects of emerging diseases to improve communications and establish collaborations that will contribute to current control activities and facilitate a rapid response to future infectious disease threats. The overall intent of the NIAID research agenda is to provide an integrated, proactive, research program that will contribute to national and international preparedness to meet new infectious disease challenges.

GRANT SUCCESS RATE

Mr. Stokes: According to the budget justification, the NIH considers investigator-initiated research project grants its highest priority. How many "new" research project grants will your institute support in FY 1997, and how does this compare to the number supported in FY 1996 and proposed for FY 1998? Please include in the record a chart displaying your Institute's grant success rate for each of the last five fiscal years, and the FY 1998 budget request projected rate.

Dr. Fauci: NIAID plans to support 262 new non-AIDS research project grants for FY 1998. This compares to 240 new non-AIDS research project grants in FY 1996 and 308 in FY 1997. The following displays the NIAID yearly success rates for non-AIDS research:

Fiscal Year	Success Rate
1994	20.6%
1995	20.1%
1996	27.1%
1997	27.7%
1998 request	27.4%

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are currently underway and what are the expected benefits to be achieved from this investment?

Dr. Fauci: Described below are some of NIAID's most significant clinical research areas and their expected benefits:

Influenza

The NIAID is currently conducting a multicenter efficacy trial of a nasally administered influenza vaccine in toddlers. This vaccine was developed by NIAID intramural scientists, and is part of a CRADA with Aviron. It is expected that this vaccine will be an important control strategy for influenza in children, due to its ease of delivery as well as its efficacy.

Congenital Cytomegalovirus CNS Infections

The Cooperative Antiviral Study Group, a multicenter group of investigators who are supported by a NIAID contract, is evaluating antiviral therapies for congenital infections of the CNS, the most common cause of progressive deafness in infants, as well as a prominent cause of mental retardation.

Improved Therapy for Shingles

The NIAID Collaborative Antiviral Study Group completed a study combining acyclovir and prednisone for the treatment of herpes zoster (shingles). Including prednisone with standard treatment accelerated healing, and enhanced resolution of acute neuritis. Treatment also dramatically improved measurements of the quality of life such as time to return to normal activities, amount of uninterrupted sleep, and cessation of analgesic use.

Trachoma

The NIAID is sponsoring a community-based treatment trial to prevent and control blinding trachoma in children living in three African countries. The trial compares single-dose azythromycin therapy with weeks of ocular tetracycline ointment, the current standard of care for chlamydial eye infection. Results of the trial indicate the oral therapy is equivalent if not significantly better than ocular antibiotics.

Cholera

Live attenuated oral cholera vaccines are currently being evaluated both for international travelers to prevent cholera during visits to endemic areas as well as populations who are at risk of epidemic cholera. This includes studies of safety and immunogenicity in immunocompromized and refugee populations.

Kidney Transplantation

The goal of these clinical research programs is three-fold: to evaluate the efficacy of new treatments to improve short- and long-term kidney graft survival; to enhance our understanding of the immunological basis for graft rejection; and to improve our limited knowledge about the pediatric immune system. Poor long-term graft survival rates and the deleterious side effects of life-long immunosuppressive therapy remain the major obstacles in renal transplantation. One of the specific long-term goals of these clinical trials is to achieve acceptance of the transplanted organ without the use of immunosuppressive drugs by inducing "tolerance," i.e., a state in which the recipient does not reject the transplanted organ because his/her body does not recognize the new organ (or cells or tissues) as foreign. If this tolerant state can be achieved, transplant recipients would no longer have to rely on toxic, expensive, and life-long immunosuppressive drugs to avoid rejecting the transplanted organ.

Asthma

The first National Cooperative Inner-City Asthma Study is the largest study of its kind conducted in an inner-city environment. The intervention resulted in substantial reductions in asthma symptoms among inner-city children ages 4-11, despite many socioeconomic, medical, and psychosocial obstacles to improving the health of this population. We anticipate that interventions based on this study will be widely implemented and will lead to significant reductions in asthma severity, nationwide. The second National Cooperative Inner-City Asthma Study will enroll patients beginning this summer. We expect this study to provide further information on the importance of environmental and behavioral interventions to improve asthma and new information on the cost-effectiveness of these approaches.

Protease Inhibitors-AIDS

This class of drugs can reduce the amount of HIV virus in the blood to undetectable levels. New findings from a recent NIAID study (ACTG 320) showed that protease inhibitors, when used in combination with reverse transcriptase inhibitors, can also delay disease progression or death. We have studies in development to build upon this knowledge.

For example, the Pediatric AIDS Clinical Trials Group has studies in development to understand the use of combination regimens using protease inhibitors in children and adolescents. In addition, they are pursuing more effective regimens (some of which include protease inhibitors) for preventing mother-to-infant transmission.

Other studies that are currently ongoing are designed to examine the effect of protease inhibitors on the immune system. Preliminary results from one study (ACTG 315) showed that combination therapy that included protease inhibitors partially restored immune function.

Studies are also planned to determine if the reduction in viral load is permanent and if there is clinically safe time when protease inhibitor treatment can be stopped. ACTG 343 will start all patients on six months of AZT/3TC/Indinavir therapy. After six months patients with undetectable viral loads will be randomized to receive the triple combination, ZDV/3TC or indinavir alone. After 12 months, if the reduction in viral load is sustained, treatment will be withdrawn gradually in six month intervals. If this strategy proves successful, patients will potentially not need lifetime treatment.

Opportunistic Infections in HIV

It is not clear what protease inhibitors and the drop in viral load mean for preventing opportunistic infections. ACTG 362 is a study that will examine the implications of combination therapy with protease inhibitors on MAC prophylasis. The study will randomize patients, after their viral load has decreased, to either placebo or azithromycin. This is the first study to examine if prophylaxis against OIs is still necessary after virus levels have been reduced and immune function has rebounded.

These studies will provide valuable information about the effectiveness of combination strategies in other stages of disease and populations and the impact of this approach on our understanding of HIV treatment and disease.

Mr. Stokes: What major clinical trials that are ready to be implemented will the FY 1998 budget request allow the Institute to pursue?

Dr. Fauci: We plan to implement the following clinical trials in FY 1998 :

- Evaluation of Vaccines in the Elderly
- Phase III trials on interleukin-2 treatment of HIV infection
- The role of IL-2 as a treatment for HIV-infected Individuals with Disseminated Histoplasmosis.
- Development and Clinical Evaluations of Malaria Vaccines
- Clinical Use of Anti-IL-12 in the Treatment of Crohn's Disease
- A trial to evaluate the effectiveness of treatment of the lactic acidosis in children, a feature of cerebral malaria in Africa, will commence shortly in Ghana. This

condition accounts for a large proportion of malaria deaths in children for which there is no effective therapy at this time.

- Group B Streptococcus (GBS) polysaccharide-tetanus toxoid conjugate vaccines will be tested for safety and immunogenicity in adult women. It is hoped that immunization of women with GBS capsular polysaccharide-based vaccines will protect their infants from GBS sepsis through transplacental passage of protective antibodies.

- The NIAID, through the Vaccine and Treatment Evaluation Units across the U.S. will launch an efficacy trial of acellular pertussis vaccine in 2,000 adults. The information from this trial will be important to the control of this infectious diseases in both infants, who contract this disease from adults, as well as adults. This is the continuation of the PHS effort to develop safe and effective acellular pertussis vaccines to control this disease in the U.S.

SEXUALLY TRANSMITTED DISEASES

Mr. Stokes: According to the budget justification, the United States has the highest rate of sexually transmitted diseases in the industrialized world. And, each year, more than 14 million Americans acquire an STD. The treatment of pelvic inflammatory disease in 1996 alone cost an estimated $7.0 billion. What are the most significant opportunities that the FY 1997 appropriations and the FY 1998 budget request would allow the Institute to exploit in order to reduce the burden of STDs?

Dr. Fauci: During the next two years NIAID's STD Program will focus on a number of key research areas: Topical Mircobicides; STD Diagnostics; STD Vaccines; STDs as emerging causes of infertility in men; STDs as emerging causes of adverse outcomes of pregnancy; and STD prevention and control as a key strategy to prevent HIV infection.

Specific opportunities that NIAID plans for FY 1997 and FY 1998 include:

- Expansion of our Topical Microbicide Program Projects: This will increase our capacity in the areas of product development research and allow us to conduct additional clinical studies on topical microbicides.

- A Sexually Transmitted Diseases Clinical Study Group: This will provide dedicated clinical facilities and laboratories staffed by multidisciplinary teams of STD experts in clinical, behavioral, and basic biomedical research to conduct clinical studies in STDs, with special emphasis on PID. This Trial will test safety and efficacy of biomedical and behavioral interventions aimed at prevention and control of STDs.

- An Adolescent and Sexually Transmitted Disease Cooperative Research Center: The objective of this research is to develop a systematic approach to assessing

biological and behavioral factors that determine susceptibility to STDs during adolescence. We will develop effective tools and subsequently develop behavioral and biomedical interventions to control STDs in adolescents.

AIDS RESEARCH

Ms. Lowey: Is AIDS research important in our progress towards cures for other diseases? Why? Please provide examples of the role AIDS research has played in our progress towards cures for other diseases, generally, and for those affecting women specifically.

Dr. Fauci: AIDS research has been extremely important in furthering our progress in understanding other diseases and in research methodology in general. For example, scientists have a better understanding of cell biology, of how enzymes regulate virus replication, and the processes of cell division and apotosis. These findings have extremely broad, basic research implications.

In the area of molecular biology, PCR (polymerase chain reaction) was developed primarily as a diagnostic tool for HIV/AIDS. However, this methodology has been widely used for the diagnosis and evaluation of other infectious and malignant diseases, and has lead to the identification of new agents, such as cat scratch disease and herpesvirus.

HIV/AIDS research has led to:

- A better understanding of the role of cytokines in regulating the immune system. These findings are relevant for all other autoimmune disorders.

- A better understanding of how cell-mediated immunity works to kill infected cells. These findings are relevant to infectious diseases and tumor disease.

- Improved our knowledge of how toxic agents affect neurons and neuroimmunology. These findings have direct relevance for Alzheimer's and Parkinson's diseases, as well as stroke research.

- The development of therapies against, and the diagnosis of opportunistic infections in HIV infected patients has relevance for other immune-suppressing diseases. For example, opportunistic infections develop in cancer patients undergoing chemotherapy and in transplant patients.

- Changes in approaches to clinical trials and access to experimental therapies. Drug development for life-threatening diseases is now compressed by both changes in FDA requirements and the frequent use of surrogate markers in the development and approval of new therapies. These developments have broad implications.

With regard to diseases that affect women, a great deal of research has been conducted in the area of Human Papilomavirus Virus (HPV). Researchers have gained a better understanding of the pathogenesis of HPV, and how it manifests differently in HIV-infected women who require aggressive therapy. Such research has implications for other women with HPV and cervical cancer.

TOPICAL MICROBICIDES

Ms. Lowey: Please give us an update on the status of clinical trials for over-the-counter spermicides as microbicides and for new topical microbicide products.

Dr. Fauci: In the United States, two types of vaginal spermicides are currently approved for contraceptive use: nonoxynol 9 (N-9) and octoxynol (O-9) products. NIAID is currently sponsoring several clinical trials of products containing N-9 and or O-9. Additional trials are in the planning process. These trials include:

- An efficacy study of Vaginal Contraceptive Film (VCF): A study of 1200 women in the Cameroon who used VCF. We anticipate that data on HIV and STD infection rates will be available in April 1997.

- Safety and efficacy study of 0-9 product: We plan to conduct both domestic and international studies of the efficacy of O-9 products as topical microbicides and protocols are in development.

- A safety study of Buffer Gel: This product maintains the acidic environment found in a normal healthy vagina. A study assessing cervical/vaginal inflammation is in progress in the United States. Safety and efficacy studies at an international site are planned, dependent upon the results of the U.S. study.

- A safety study of Lactin Vaginal: We are conducting a study of this vaginal suppository which is designed to restore normal vaginal flora. Lactobacilli are associated with maintaining an acidic pH and secreting microbicidal hydrogen peroxide. Loss of these bacteria correlates with increase risk of gonorrhea, bacterial vaginosis and HIV infection.

- An efficacy study of Advantage 24 (contains N-9): A study of 800 women in Kenya who will use this gel product. Currently, participants are being enrolled for this study.

Ms. Lowey: Please explain NIH's relationship with industry in terms of topical microbicide product development efforts. Are there obstacles to engaging in effective collaborations with the commercial sector in this effort?

Dr. Fauci: NIH is collaborating closely with industry in the conduct of clinical trials as well as in development of formulations and on pre-clinical evaluation. We have utilized our topical microbicide program projects and our contracts for animal models and formulations to help develop and evaluate new products. Resource availability, both human and financial, will determine the depth and breadth of these collaborations. Through the International Working Group on Microbcides we have evaluated the perspective of industry on the development and evaluation of these products. Three

generic issues are often raised in our meetings with sponsors: 1) assessment of market size; 2) product liability; and 3) regulatory hurdles. The European Union has contracted for a formal market assessment, which is in progress.

Ms. Lowey: What are the plans for the growth of the topical microbicide research program, given the limitations of resources?

Dr. Fauci: In 1997 the NIAID will award a contract for an STD clinical trials unit. This unit will have the capacity to conduct clinical trials of topical microbicides. In 1998 the NIAID hopes to expand current STD research efforts, including our topical microbicides program projects, current contracts for formulation development and for animal models, and clinical trials. NIAID spending in topical microbicides is estimated to be $12.535 million in FY1997 and $15.535 million in FY 1998, an increase of $3 million or 24 percent.

Ms. Lowey: In order to deliver safe, effective topical microbicides in a timely fashion, clinical trials evaluating safety and efficacy of topical microbicides must be given a higher priority. Please explain existing capacity for these trials; in your opinion, is it adequate to accommodate the needs and opportunities for fast track development of these products?

Dr. Fauci: The NIAID is currently using an investigator initiated award (R01), two contract mechanisms and a cooperative agreement for clinical evaluation of topical microbicides. In 1997 we will award an additional contract with the capacity to conduct microbicide clinical trials. The three contracts represent an effective flexible infrastructure for the conduct of these clinical trials for products that are brought to our attention by the commercial sector as well as by others. The flexibility inherent in the contract mechanism would facilitate evaluation of promising new products, should additional resources become available.

PEDIATRIC AIDS

Ms. DeLauro: I am happy to see that NIAID has identified several important pediatric research areas, and I am particularly pleased with your participation in the Children's Vaccine Initiative. However, there has been some concern about the limited role children have played in clinical trials for anti-HIV medications. What has NIAID done to address treatments and preventions for pediatric AIDS? What kind of role do you see pediatric AIDS playing in the development of a vaccine for HIV?

Dr. Fauci: NIAID has conducted a great deal of research on therapies for HIV-infected children through its pediatric AIDS Clinical Trials Group (PACTG). The PACTG has initiated 60 trials; 27 studies are now recruiting patients. Among its most significant contributions, the PACTG has: 1) demonstrated that antiretroviral therapy given to HIV-infected pregnant women and their newborns can reduce the risk of perinatal transmission by two-thirds; 2) shown that IVIG can effectively prevent serious bacterial infections in children with HIV; 3) demonstrated that ddI or ddI plus AZT are superior to AZT monotherapy for children with symptomatic HIV infection or AIDS; and 4) developed guidelines for preventing *Pneumocystis carinii* pneumonia in HIV-infected children.

It is important to recognize that children present unique challenges to researchers trying to expedite the delivery of new treatments. Children often absorb, use, and eliminate medications differently than adults. Formulating a drug in a liquid that is stable and palatable to children is one of the greatest obstacles to developing drugs for children. When this is done, appropriate safety and dosage studies are still required.

Nonetheless, the PACTG will continue to pursue research on the appropriate dosage and efficacy of combination therapies in children. One such trial evaluating ritonavir (ACTG 338) in combination with other antiretroviral therapies is currently underway. Several other combination trials are being planned and should be open to enrollment over the next few months.

NIAID is also very interested in developing a vaccine that would prevent maternal-infant transmission. The prevention strategy that is being pursued is based on the successful work that has been done in Hepatitis B, which uses both passive and active immunization (vaccine). In passive immunization the product would act directly against HIV; in active immunization the agent would generate an immune response.

In the area of passive immunization several phase I trials have been completed or are in development. These studies involve HIVIG and CD4-IgG. There is also a phase III study of HIVIG (ACTG 185) currently underway. The HIVIG is given to the mother and one dose is given to the infant in an effort to prevent maternal-infant transmission. Another phase I study of HIVIG is underway in Uganda through NIAID's HIV Network for Prevention Trials; a phase III study is being planned in follow-up once the safety is determined. NIAID is examining the us of later generation CD4-IgG HIV monoclonal antibodies for immunizing HIV-infected women and their children.

With regard to active immunization, one phase I study has been completed (AVEG 104/ACTG 235) in which HIV-infected pregnant women were immunized with gp120. We are currently analyzing the data from this study.

Another study (ACT 230) in which infants born to HIV-infected women were immunized with gp120 within 72 of birth has just completed accrual.

There is also a great deal of enthusiasm for a phase I trial (ACTG 326) using the combination of two vaccines ALVAC (canarypox) and gp120, which is about to enter a phase II trial in adults. This pediatric trial is still in development.

SEXUALLY TRANSMITTED DISEASES

Ms. DeLauro: Last year's report language encouraged NCI and NIAID to collaborate in sponsoring basic and clinical research on HPV diagnosis and prevention. I asked Dr. Klausner about NCI's efforts in this area, and I was hoping you could provide your insight into HPV and the work NIAID is doing in this area.

Dr. Fauci: The NIH has established an Human Papilloma Virus (HPV) working group to facilitate communication and coordination of HPV research efforts. This group shares information about currently funded research, and future initiatives. The NCI and the NIAID collaborate on the HPV DNA Sequence Data Base. NIAID and NCI are collaborating on plans for two HPV vaccine trials. In order to facilitate research collaborations NCI intramural scientists attended the STD Cooperative Research Centers meetings and will participate in the NIAID STD program review.

NIAID also supports a large multidisciplinary research effort on Sexually Transmitted Diseases. Specific to HPV, the NIAID supports the HPV Sequence database. This database serves as an international research resource for the compilation, analysis and dissemination of genetic sequence and associated data for HPV and related papillomaviruses. We recently expanded this effort to include a complementary to look at protein and RNA structure/function relationships.

We are also supporting a pilot study on the feasibility of using automated cell cytology to type HPV infection and determine if oncogenic types are present. We are currently working with investigators on a proposed study to evaluate self-administered vaginal swabbing as an approach for getting samples for PAP smears and HPV testing.

Ms. DeLauro: The impact of sexually transmitted diseases is particularly severe for women. Chlamydia affects an estimated 2.4 million women each year. Gonorrhea affects an estimated 400,000 women. And the number of women infected by syphilis has been ever increasing. Given these disturbing figures, could you please profile for us

the research NIAID is doing in these areas, and specifically how your Institute is addressing how women are affected by these diseases?

Dr. Fauci: The STD Program of the NIAID fosters, develops, and administers a research program the mission of which is to contribute to the reproductive health of people and specifically lead to prevention and control of STDs. The strategic plan for this research program reflects long-term public health goals: 1) prevention of infertility; 2) prevention of adverse outcomes of pregnancy; 3) prevention of reproductive tract neoplasia; 4) prevention of other chronic STD sequelae; and 5) prevention of human immunodeficiency virus (HIV) infection.

The central theme of the STD program is the synergism of combined biomedical, behavioral, clinical and epidemiological research efforts. Women and their infants are disproportionately impacted by these infections. Our STD Research Program is a systematic attack that emphasizes the health effects of STDs in women and the inter-relationships between STDs and AIDS. STDs and associated chronic sequelae are the central focus of the STD Research Program.

The NIAID supports a number of multidisciplinary research efforts, either in the form of program projects, cooperative agreements or contracts that cover a broad range of STDs such as Chlamydia, Herpes, Gonorrhea, HPV, etc. These include:

- Sexually Transmitted Diseases Cooperative Research Centers
- Research on Molecular Immunology of STDs Program Projects
- Tropical Microbicides Program Projects
- Genital Herpes Program Project
- STD Diagnostic Development Groups
- STD Diagnostic Evaluation Group
- STD Clinical Trials Unit
- Adolescent Sexually Transmitted Diseases Cooperative Research Center

Some specific accomplishments in the area of STD research include:

- A NIAID-supported study demonstrated that women who were screened and treated for asymptomatic chlamydia infection were 60% less likely than unscreened women to develop PID.

- NIAID-supported researchers have shown that a highly sensitive and non-invasive urine test that detects the genetic material of Chlamydia trachomatis holds promise for large scale screening programs to detect both symptomatic and asymptomatic cases of chlamydia.

- Establishment of a cooperative agreement with a manufacturer to develop and antigen detection system for gonorrhea using urine as a sample.

- Support of genomes sequencing of N. gonorrhoeae, C. trachomatis and T. pallidum. Sequencing the genomes of these important STD pathogens is anticipated to provide new insights into pathogenesis and will identify new antigens for evaluation as vaccine candidates.

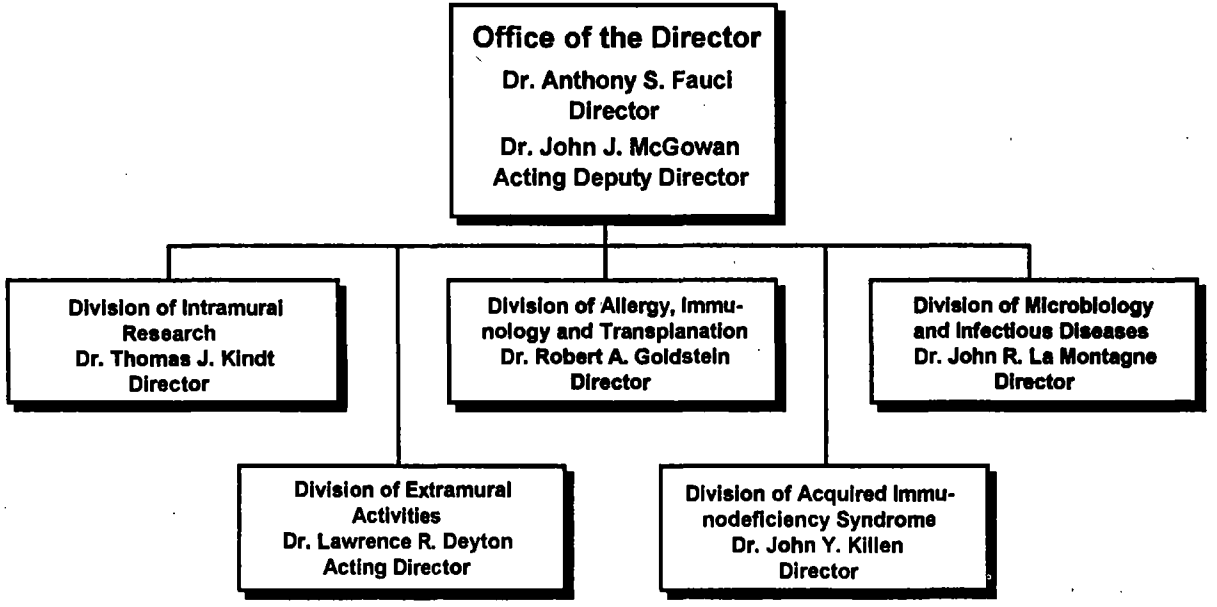
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

FY 1998 Budget	Page No.
Organization chart	1
Appropriation language	2
Amounts available for obligation	3
Justification narrative	4
Budget mechanism table	34
Budget activity table	35
Summary of changes	36
Budget authority by object	38
Administrative costs	39
Significant items in House and Senate Appropriation Committee Report	40
Authorizing legislation	46
Appropriation history	47
Detail of full-time equivalent employment (FTE)	48
Detail of positions	49

National Institutes of Health
National Institute of Allergy and Infectious Diseases
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to allergy and infectious diseases, [$1,257,234,000] *$634,272,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriation Act, 1997, P.L. 104 - 208).

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$1,169,628,000	$1,257,234,000	$634,272,000
Rescission in accordance with P.L. 104-134	(1,145,000)	---	---
Reduction in accordance with P.L. 104-208		(575,000)	---
Subtotal, Adjusted Appropriation	1,168,483,000	1,256,659,000	634,272,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority	(1,315,000)	---	---
Comparative transfer to Office of AIDS Research, NIH for HIV activities	(595,549,000)	(647,709,000)	---
Subtotal, adjusted budget authority	571,619,000	608,950,000	634,272,000
Unobligated balance, lapsing	(8,000)		
Total obligations	571,611,000	608,950,000	634,272,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1996 - $14,685,000; FY 1997 - $20,000,000; FY 1998 - $25,000,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research:
FY 1998 - $678,230,000

Note Excludes $6,400,000 in FY 1996 and $7,000,000 in FY 1997 for royalties.

Justification

National Institute of Allergy and Infectious Diseases

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 1996 Actual		FY 1997 Appropriation		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
1,006	$571,619,000	1,006	$608,950,000	1,006	$634,272,000	-0-	$25,322,000

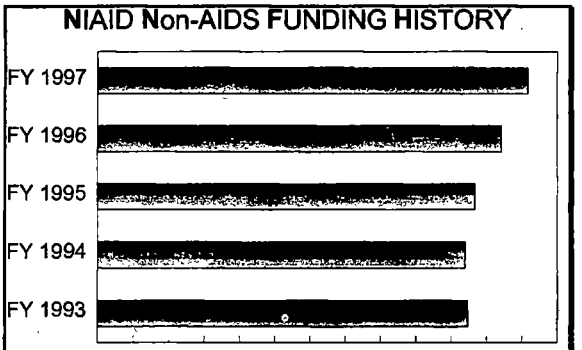
NIAID Director's Statement

The National Institute of Allergy and Infectious Diseases (NIAID) celebrates its 50th anniversary in 1998. With the establishment of the NIAID in 1948, scientists began the quest for better diagnostic tools, drugs, and vaccines to decrease or eliminate the burden of allergic and infectious diseases. Over the past 50 years, the investment in NIAID medical research has significantly benefited the health of Americans. Our Nation's investment in NIAID research is still paying enormous dividends today. The past year, in particular, has been a time of considerable optimism and excitement at the NIAID. NIAID intramural and extramural researchers provided new insights into the pathogenesis of many important infectious and immunologic conditions, and the Institute's initiatives in the development of new and improved vaccines, drugs, and diagnostics yielded extraordinary results.

Challenges abound, however, as we encounter new and re-emerging problems, such as acquired immunodeficiency syndrome (AIDS), chronic fatigue syndrome (CFS), Lyme disease, ebola hemorrhagic fever, hantavirus pulmonary syndrome and other emerging microbes. Other diseases, such as tuberculosis (TB), enterococcal infections and pneumococcal pneumonia are increasingly problematic because of the development of resistance to currently available drugs. The NIAID has bolstered research efforts that address the continued threat posed by these and other emerging pathogens and has developed a comprehensive research agenda in this arena. In addition, allergic diseases, including asthma, are currently among the major causes of illness and disability in the United States, affecting as many as 40 million Americans. These diseases result in considerable morbidity, mortality, pain and suffering; they result in absenteeism from work or school; consequently, they contribute to high medical care and economic costs. The NIAID is diligently striving to develop better ways to diagnose, treat, and prevent these illnesses.

The NIAID Budget: Program Purpose and Method of Operation

The President's budget request for NIAID non-AIDS research is $634,272,000, a 4.2 percent increase over the fiscal year 1997 level. Funding for the NIAID non-AIDS research program during the last five years has been as follows:



	FY 1993	FY 1994	FY 1995	FY 1996	FY 1997
Amount	$524,529,000	$522,857,000	$536,940,000	$571,619,000	$608,950,000
FTEs	1,104	1,053	1,022	1,006	1,006

Infectious diseases remain the most common cause of death for children worldwide, and disorders of the immune system afflict more than one in ten Americans. NIAID-supported medical research has advanced the prevention and treatment of diseases to individuals and society. These advances reduce suffering, save lives, and they translate into significant economic cost savings by reducing the use of health care services and improving human productivity. The NIAID's mission is to conduct and support research and research training aimed at alleviating the suffering caused by illnesses.

To accomplish this mission, NIAID supports research and training grants, and contracts at many universities and medical centers in the United States. The Institute also conducts basic and clinical investigations in its intramural laboratories at Bethesda, Rockville, and Frederick, Maryland; and at Hamilton, Montana. The NIAID has four major research divisions: Allergy, Immunology, and Transplantation; Acquired Immunodeficiency Syndrome; Microbiology and Infectious Diseases; and Intramural Research.

Overall Budget Policy

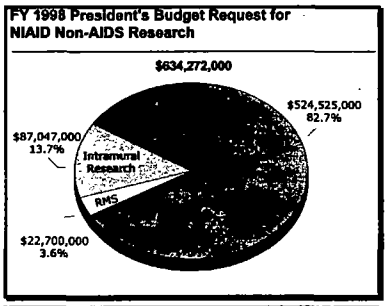
The NIAID FY 1998 budget request for non-AIDS research is $634,272,000, an increase of $25,322,000 or 4.2 percent over the comparable FY 1997 level of $608,950,000. This request includes an increase of $3,800,000 for research targeted to new approaches to pathogenesis; $8,500,000 targeted to research on new preventive strategies against disease; $3,000,000 targeted

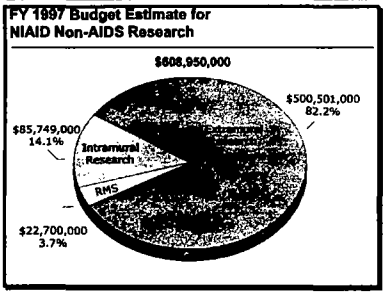
to therapeutics and drug development research; $1,650,000 targeted to research on the genetics of medicine; and $3,000,000 for the support of Hansen's disease research at the Hansen's Disease Center to be funded through a reimbursable agreement with the Health Resources and Services Administration. The FY 1998 request will support 1,746 research project grants (RPGs) in the amount of $430,474,000, an increase of 49 awards and $21,339,000 over the FY 1997 comparable amount.

This budget was developed according to the principles of the NIH Cost Management Plan. NIH policy links RPG average cost increases to total program budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of 2.0 percent will be provided for RPGs. In general, individual noncompeting RPGs will receive increases of 2.0 percent over FY 1997 levels. The average cost of competing RPGs will increase by up to two percent over FY 1997 levels. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP).

Major NIAID Budget Categories

The NIAID's research activities are divided into three broad budget categories, Extramural Research, Intramural Research, and Research Management and Support (RMS). The FY 1998 President's Budget Request funding level for each of these budget categories is compared to the FY 1997 Budget Estimate in the charts below:

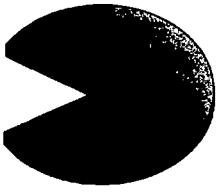




The FY 1998 budget request for NIAID non-AIDS extramural research is 524,525,000. This represents an increase of $24,024,000, or a 4.8 percent increase over the FY 1997 level. Extramural research will comprise 82.7 percent of the NIAID budget in FY 1998.

The FY 1998 budget request for NIAID non-AIDS intramural research is $87,047,000. This represents an increase of $1,298,000, or a 1.5 percent increase over the FY 1997 level. Intramural research will comprise 13.7 percent of the NIAID budget in FY 1998.

The FY 1998 budget request for NIAID non-AIDS research management and support activities is $22,700,000. This represents the same amount as the FY 1997 estimate. In FY 1998, 3.6 percent of the NIAID budget will be devoted to RMS activities.



In FY 1998 the NIAID will invest 82.7 percent of its budget in extramural research compared to 82.2 percent in FY 1997.

Extramural Research: The NIAID Extramural Research Program is committed to supporting basic research studies on infectious and immunologic diseases. This basic research translates into prevention and treatment strategies for sexually transmitted diseases, asthma, allergies, parasitic, and fungal diseases; it results in improved diagnostics for infectious diseases and better evaluations of antiviral drugs; and it fosters an improved understanding of transplantation immunology.



In FY 1998 the NIAID will invest 13.7 percent of its budget in intramural research compared to 14.1 percent in FY 1997.

Intramural Research: The NIAID conducts in-house research through the Division of Intramural Research (DIR). DIR scientists study immunologic, allergic, and infectious diseases in NIAID laboratories located in Bethesda, Maryland, at the main NIH campus, with satellite laboratories in adjacent Rockville and Frederick; and the Rocky Mountain Laboratories in Hamilton, Montana. The Bethesda facility also provides space for DIR's clinical activities at the NIH Clinical Center. Patients are frequently admitted to this clinical unit to participate in new and promising treatment or diagnostic procedures derived from the basic research conducted in DIR's laboratories. In addition, DIR offers many laboratory and clinical research training opportunities for physicians and scientists who go on to positions of scientific leadership in universities across the country.



In FY 1998 the NIAID will dedicate only 3.6 percent of its budget to Research Management and Support compared to 3.7 percent in FY 1997.

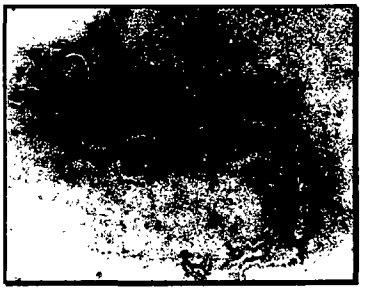
Research Management and Support: The Research Management and Support activity is an extension of our extramural research program, providing the resources that contribute to charting the future direction of the Institute's extramural research enterprise. The managerial and scientific functions encompassed by this activity ensure the quality of research and research personnel; provide accountability for research performance and results; measure program performance against program goals; and provide accountability and stewardship over the funds invested in the Institute's research enterprise.

Rationale for the Budget Request

This document provides justification for the FY 1998 non-AIDS activities of the NIAID. Justification for the NIAID's AIDS research activities are included in the NIH Office of AIDS Research request. The following also presents an overview of the scientific advances brought forth from our Nation's investment in NIAID medical research, the public health and economic benefits gained from this investment, and future opportunities for investment in NIAID research.

Emerging Infectious Diseases

The remarkable advances made in this century in the fields of science, medicine, and public health resulted in a public sense that infectious diseases have virtually been conquered. This perception has more recently been challenged, due to epidemics such as AIDS and outbreaks such as those of hanta and ebola viruses. Infectious diseases have always posed, and will almost certainly continue to pose, a threat to human health both in the United States and worldwide. Between 1980 and 1992, the death rate due to infectious diseases rose 58 percent in the United States, making infectious diseases the third leading cause of death in this country[1].



The ebola virus: an extremely deadly emerging pathogen

The NIAID Research Agenda for Emerging Infectious Diseases

The NIAID is the lead U.S. Government agency responsible for the support of research and research training on infectious diseases. The NIAID recently developed a Research Agenda for Emerging Infectious Diseases to provide an integrated and proactive research strategy that will ensure preparedness to address the health problems presented by emerging and reemerging infectious diseases. Underlying this Agenda is the certainty that continued support for both basic research in infectious diseases and a strong national research infrastructure is absolutely essential for facing future microbial threats.

Advances Against Emerging Infectious Diseases

In 1997, the NIAID launched a new initiative on Expanded Research on Emerging Diseases to further address the threat of emerging diseases. This initiative is supporting basic and applied research on emerging and reemerging diseases of parasitic, viral, bacterial, and fungal etiology in order to facilitate detection and control of these diseases.

We also launched a new initiative on Modern Vaccines for Targeted Emerging and Reemerging Diseases in 1997. This endeavor is designed to stimulate research on two areas that have a need for new or improved vaccines, mycoses and measles. Prior to the AIDS epidemic, 25,000 to 100,000 new mycosis infections occurred each year. As the AIDS epidemic expands so will the incidence of mycoses. This disease is not limited to immunocompromised persons. The recent epidemic in California resulted in more than 3,000 cases in 1992 and 1993, with medical costs estimated at more than $45 million[2]. The major cause of the recent reemergence of measles in the United States was due to a failure to vaccinate children at the appropriate age

[1] JAMA, vol. 275, p. 189, 1996.
[2] MMWR 43(23)421-423, 1994; MMWR 43(10)194-5, 1994.

rather than failure of the vaccine. However, currently licensed vaccines do have deficiencies as public health tools. In developing countries, measles continues to be a deadly disease causing over 1.5 to 2.0 million deaths each year[3].

Exciting basic research advances have also come from NIAID sponsored intramural research. Transmissible spongiform encephalopathies (TSE), such as "mad cow disease," are another form of emerging disease. Investigators from the NIAID Intramural Research Program have developed the first test tube system for making a specific toxic disease-associated protein and identified molecules that inhibit its formation. These findings will facilitate further research into the molecular nature of TSE and may simultaneously provide clues about similar abnormal proteins in Alzheimer's disease.

Cholera is another major problem in developing nations where it contributes significantly to infant mortality. Epidemic cholera continues near the United States in South and Central America. NIAID researchers have discovered that the genes for cholera toxin are located on a bacteriophage, a virus that infects bacteria. Elucidation of the structure containing the cholera toxin genes will lead to a better understanding of cholera pathogenesis and facilitate the development of new vaccines and therapies.

Future Opportunities for Investment in Emerging Diseases Research

In 1998, the NIAID will launch a second research initiative on Expanded Research on Emerging Diseases that will further expand our research programs to facilitate the detection and control of a variety of microbes. The NIAID will also invest in another new initiative, Research Needs in Bacteriology and Mycology. This initiative will support investigations on human ehrlichioses, a tick-borne disease, and the impact of co-infection on the diagnosis, host susceptibility, pathogenesis, and treatment of Lyme disease.

In 1998, the NIAID will launch an initiative, Research Opportunities and Needs for Respiratory Pathogens, to address emerging and reemerging diseases such as pneumonia, tuberculosis, influenza, otitis media, and meningitis. Respiratory infections caused by viruses and bacteria are the major cause of acute illness in the United States and a major cause of morbidity and mortality worldwide.

NIAID: Poised to Rapidly Respond to Emerging Infectious Diseases

History has proved time and again that new infectious agents will continue to emerge and previously recognized pathogens will reemerge. Because we do not know exactly where or when they will appear, what they will look like, or how they will behave, our task is to be prepared not only with an adequate surveillance system but also with the appropriate scientific expertise to develop whatever new tools are necessary to rapidly respond to and control the threats posed by emerging infectious diseases.

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[3] Expanded Programme of Immunization, WHO; WHO Weekly Epidemiological Record; MMWR 1993, 42(50): 975, MMWR 1994, 43(27):496.

Vaccine Development

The development of new or improved vaccines provides an excellent example of the multidimensional nature of the benefits of NIAID research. Because vaccine-preventable diseases account for millions of dollars in health care costs each year, the development of vaccines represents opportunities to dramatically reduce these costs. At the same time, additional economic benefits are derived from the commercialization and sale of vaccine products. Since their introduction a little more than 200 years ago, vaccines have become one of our most important public health tools.



Vaccination: an extremely cost-effective means of dealing with infectious diseases

Millions of lives have been saved and unimaginable human suffering has been prevented through the widespread use of vaccines. However, effective vaccines are not available for many infectious diseases such as malaria, tuberculosis, AIDS, certain forms of viral hepatitis, sexually transmitted diseases, tropical diseases, and many emerging and reemerging diseases.

Newborns and the elderly are unusually susceptible to many infectious diseases due to immaturity and aging of the immune system, respectively. Similarly, the emergence of AIDS and other emerging microbial threats and the use of chemotherapeutic and immunosuppressive agents has created populations that are difficult to immunize and that are unusually susceptible to infection.

In addition to these concerns, there is now the challenging prospect of developing vaccines for the prevention and treatment of immunologic diseases including autoimmune disorders, transplantation rejection, and allergic diseases. Thus, in a very short time medical scientists have been handed the major challenge of learning to manipulate the immune system to vaccinate against diseases where the immune system itself causes damage to the host.

NIAID Research: Working Toward New and Improved Vaccines

The NIAID is the lead Federal agency for vaccine research and development. With our integrated and comprehensive research program in infectious diseases, microbiology, and immunology, the NIAID is leading research efforts on the development of safe and effective vaccines for the prevention of a variety of diseases. The NIAID is recognized as a principal participant in both U.S. national vaccine policy and in global vaccine programs. In the United States, the NIAID collaborates with other government agencies, including the Centers for

Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), on issues of vaccine research, safety, and national immunization strategies.

Globally, the NIAID participates with other national research agencies in programs such as The Children's Vaccine Initiative (CVI), a global program launched in 1990 at the World Summit for Children. The goal of the CVI is to expedite the development of safe, affordable, and heat stable vaccines that protect children against major infectious childhood killers with few doses given orally early in life by facilitating the development, production, technology transfer, procurement, and introduction of new vaccines.

Advances in Vaccine Strategies to Prevent Disease

***Haemophilus influenzae* type b**

As recently as a decade ago, 16,000 to 25,000 children in the United States developed disease caused by the bacterium known as *Haemophilus influenzae* type b (Hib) each year. Bacterial meningitis, one of the most serious complications of Hib disease, occurred in 60 percent of affected children; 5 percent of all children stricken by Hib meningitis died, while many who survived suffered permanent health consequences ranging from mild hearing loss to mental retardation.

In 1996 there were less than 100 cases of Hib reported in the United States. This remarkable turnaround resulted from the introduction of a Hib vaccine and the subsequent release of an improved Hib vaccine. Developed after decades of independent and collaborative research by investigators supported by the NIAID, other NIH Institutes, and the pharmaceutical industry, the new Hib conjugate vaccines are a prime example of the public health and economic payoff that results from investment in biomedical research. The dramatic reduction in the incidence of Hib diseases has resulted in savings conservatively estimated at more than $400 million per year in costs for treatment and long-term care of children with meningitis and other Hib related diseases.

In another recent discovery, an NIAID-supported study showed that a Hib conjugate vaccine was highly effective in protecting infants from Hib pneumonia and invasive Hib disease. This study is the first to demonstrate the impact of Hib conjugate vaccines on pneumonia prevention and has enormous ramifications for vaccine implementation in developing countries where Hib is the second most frequent bacterial cause of childhood pneumonia.

Pertussis

Since 1934, when a record 265,269 cases of pertussis (whooping cough) were reported in the United States, the incidence of this childhood disease was followed by a steady decline, hastened in 1949 by the release of the first pertussis vaccine. By 1976, widespread use of this vaccine had reduced the number of cases of pertussis to an all-time low of 1,010. Beginning in the early 1980s, however, the number of reported cases of pertussis once again began to rise. This increase has highlighted shortcomings of the pertussis vaccine. The chief problems

associated with the vaccine were the adverse events, such as fever, fussiness, and redness and pain at the injection site. Although quite rare, more serious events including seizures have also been associated with the whole-cell pertussis vaccine. Concern over these side effects led some parents to forgo having their children immunized and this led to an increased incidence of pertussis.

In two large NIAID-supported clinical trials, researchers in Italy and Sweden recently showed that three new acellular pertussis vaccines are more effective in protecting infants against pertussis while demonstrating fewer adverse events than the whole-cell vaccine. These two trials provide direct evidence of the effectiveness of acellular pertussis vaccines used in infants. Widespread use of these new vaccines will have significant public health benefits in the United States and globally, as pertussis is responsible for 350,000 deaths annually worldwide.

Rotavirus

Rotaviruses are responsible for 30 to 50 percent of all cases of severe diarrhea in the world. In developing countries, the toll from rotaviruses is staggering. Each year they are responsible for about 18 million cases of moderately severe or severe diarrhea and the death of more than 870,000 infants and young children under 5 years of age. In the United States, rotaviruses cause more than 1 million cases of rotaviral diarrhea and account for 65,000 hospitalizations of children under 5 years of age each year.

NIAID Intramural Research Program investigators have recently patented rotavirus strains for use in vaccines against rotavirus. Subsequently, a Cooperative Research and Development Agreement was negotiated with a domestic pharmaceutical manufacturer that led to further development and evaluation of a rotavirus vaccine. Clinical trials sponsored by NIAID's industry partner showed that this orally administered vaccine was safe in infants and significantly reduced the incidence of rotavirus diarrhea. In addition, medical visits for rotavirus disease were reduced by 73 to 78 percent in vaccinated infants. In one of these studies, dehydrating illnesses due to rotaviral infection was reduced by 100 percent.

Recently, NIAID Intramural Research Program investigators have designed and tested a vaccine that combines human and animal rotavirus genes. This vaccine was found to be safe, with only mild side effects, and effective in preventing severe rotavirus diarrhea 80 to 90 percent of the time. These results have raised hopes that a licensed rotavirus vaccine may become available in the near future.

Tuberculosis

A significant focus of NIAID tuberculosis (TB) research is the development of an effective TB vaccine. The only currently available anti-TB vaccine, BCG, has several limitations. Its efficacy has been highly variable in clinical trials, ranging from 0 to 80 percent effective and its use interferes with the TB skin test, the most important diagnostic tool available to detect TB infections. Because this vaccine is based on a live, attenuated mycobacterium, the safety of BCG in individuals with weakened immune systems is suspect.

Recently, NIAID-supported researchers have reported encouraging results in the search for a useful TB vaccine. In an early trial, NIAID scientists have demonstrated that vaccination with DNA encoding any one of three mycobacterial proteins stimulates an immune response and protects against *M. Tb.* Protection was equal or better than the protection conferred by the current BCG vaccine. Further development of this so-called "naked DNA" vaccine may lead to a human TB vaccine that improves upon BCG.

Hepatitis B

Hepatitis B virus (HBV) is a persistent infection affecting the liver and causes significant morbidity and mortality. HBV is transmitted parenterally and sexually. Despite the availability of an effective vaccine, an estimated 300,000 new HBV infections occur each year in the United States. Each year HBV accounts for 60,000 hospital admissions and 5,000 deaths in the United States at a total estimated cost that exceeds $800 million.

NIAID scientists found that by supplementing a HBV vaccine with a gene for a molecule that is known to stimulate an immune response, they were able to enhance the immune response in mice. In addition to demonstrating an improvement in the current HBV vaccine, this finding suggests a novel approach for the development of both preventive and therapeutic vaccines against infectious agents in general.

Vaccines Against Tumors

Tumor destruction, like virus clearance, requires that immune cells recognize the tumor as an intruder and mount a response to destroy the tumor. NIAID scientists have manipulated a vaccine by rendering tumor-specific proteins insoluble. Prior vaccines, using soluble tumor-specific proteins have been ineffective as the immune system has failed to recognize them. The new vaccine allows the immune system to detect the vaccine, mount a response, and decrease tumor growth in mice. This finding provides a novel approach for immunization against cancer as well as viruses.

Future Opportunities in Vaccine Development

In 1998, the NIAID will continue to capitalize on opportunities in the vaccine development arena by launching a new initiative, Basic Mechanisms of Vaccine Efficacy, that will provide support for innovative strategies in vaccine development. This initiative will define basic principles of vaccine efficacy, and translate the wealth of recently acquired basic knowledge on immunological mechanisms into novel strategies for vaccination.

The NIAID will launch another vaccine initiative in 1998, Evaluation of Vaccines in the Elderly. This effort will be aimed at advancing our understanding of the immunobiology of aging to assure that older adults and the elderly receive the full benefits of vaccination by evaluating existing and novel vaccines for those infectious diseases that contribute to substantial morbidity and mortality in this population.

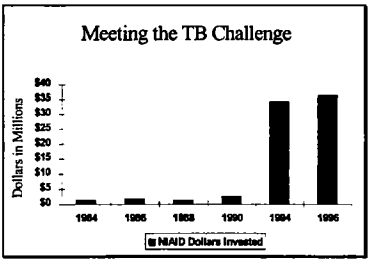
Tuberculosis

Tuberculosis (TB) is the leading cause of death worldwide. More people, over 3 million, died from (TB) in 1995 than in any previous year in history, and 8 million new cases of TB developed. In all, one-third of the world's population is infected with *Mycobacterium tuberculosis* including 15 million people in the United States. Drug resistant strains of TB infect 50 million people worldwide. During the next decade an estimated 300 million more people will become infected with TB, 90 million people will develop active diseases, and at least 30 million people will die from TB. TB is also the leading killer of women, causing more deaths than all other causes of maternal mortality.

A century ago, TB was the leading cause of death in the United States and still remains a matter of grave concern. In 1995, a total of 22,813 cases of TB were reported to the CDC from all 50 states and the District of Columbia. More than 55 percent of active TB cases were reported among Hispanics and African Americans.

The HIV/AIDS epidemic is an important factor in the global resurgence of TB. The World Health Organization (WHO) estimates that by the year 2000, HIV infection will be responsible for 1.4 million cases of TB that would not otherwise have occurred. TB is now the leading cause of death for HIV-infected persons, responsible for over 30 percent of AIDS-related deaths.

NIAID Research Advances are Addressing the Resurgence of Tuberculosis



Because of the need for improved TB drugs, diagnostics, and prevention strategies, the NIAID has dramatically increased its support of TB research. In 1990, we invested approximately $3.5 million for research on TB. By 1996, our investment grew to more than $36 million.

The development of drug resistant strains of TB has created a need for new anti-TB therapies. Several enzymes involved in the synthesis of the cell wall of *Mycobacterium tuberculosis* are being targeted for current and new drugs by NIAID Intramural Research Program investigators. NIAID intramural researchers have identified six of these enzymes and their function. Ongoing work is aimed at understanding each enzyme reaction more thoroughly and identifying any additional molecules involved in the reactions. This information will be useful in the development of new therapies for TB.

Through investigator-initiated research grants, the NIAID has fostered the development and initial animal testing of several new types of potential anti-TB vaccine candidates, including recombinant BCG strains, subunit vaccines, and nucleic acid-based vaccines. The NIAID also

funded a new research initiative in 1997, Basic Research in Human Tuberculosis. This research is directed toward improved understanding of the basic and molecular biology, genetics, immunology, and pathogenic mechanisms of TB.

The Institute also recently collaborated with the United States Agency for International Development (USAID) in jointly awarding several grants for pilot projects in TB research. These research endeavors will further enhance opportunities for U.S. investigators to conduct studies in areas where TB is endemic.

The NIAID also maintains a Tuberculosis Research Unit that encompasses an international, multidisciplinary team of collaborators. These researchers are addressing several important goals for the ultimate translation of basic TB research findings into the clinical arena. Studies are assessing immunologic markers of progressive infection versus protective immunity and microbiologic surrogates of therapeutic and vaccine efficacy in the context of an epidemiological study and clinical trials. A Phase I/II study of *Mycobacterium vaccae* as an immunotherapeutic agent for the treatment of TB in HIV-negative patients is currently underway.

Future Directions in Tuberculosis Research

In 1998, the NIAID will continue its efforts to address the significant public health threat of TB. Support for investigator-initiated TB research will remain a priority. Additionally, we will renew our Tuberculosis Research Materials contract to continue the preparation, purification, and supply of TB research materials and resources to qualified investigators. Integral to this project will be efforts, in cooperation will other interested TB researchers, directed toward identification and evaluation of the major TB antigens associated with protection against TB.

Also in 1998, the NIAID will launch a new initiative on Respiratory Pathogens. This investment will capitalize on, and expand, research opportunities and help meet the research needs relevant to respiratory pathogens, including tuberculosis.

Lyme Disease



The deer tick that transmits Lyme disease

Many important infectious diseases, both classical and newly emerging, are insect or tick-borne. Lyme disease, first recognized in the 1970s, is the most common tick-borne infection in the United States. In 1995, 9,634 cases of Lyme disease were reported in 43 states. The cost for treating early, acute Lyme disease is approximately $60 million annually.

Progress Against Lyme Disease

Much of the progress in understanding Lyme disease has been facilitated by NIAID-supported discoveries. For instance, NIAID-funded studies helped identify the borrelial OspA surface lipoprotein as a vaccine candidate. Phase III clinical trials of Lyme disease vaccines based on OspA, involving more than 10,000 individuals, are nearing completion in Lyme disease-endemic regions of the Untied States. Earlier studies of OspA vaccines have demonstrated the safety and immunogenecity of these vaccines in a smaller number of people in non-endemic areas.

Although most patients diagnosed with Lyme disease are successfully treated with antibiotics early after infection, a small number develop a chronic condition called Post-Lyme Disease Syndrome (PLDS). This syndrome is characterized by persistent musculoskeletal and peripheral nerve pain. Fatigue and memory impairment are also common symptoms of PLDS. This syndrome may be caused by ongoing infection with Lyme disease or another tick-borne pathogen, or perhaps by persistent inflammatory or immune responses; however, the precise pathogenesis is unclear.

Recently, the NIAID initiated a 5 year Chronic Lyme Disease study to address the pathogenesis and treatment of this elusive syndrome. In conjunction with this trial, NIAID intramural investigators are exploring bringing some chronic Lyme disease patients to the NIH Clinical Center for evaluation and treatment. We anticipate that these studies will provide information that will help us move toward the development of effective solutions to this problem.

Future Directions in Lyme Disease Research

Lyme disease research remains a high priority area for the NIAID in 1998. Working with the CDC and the FDA, the NIAID will address critical issues in the recognition and treatment of chronic manifestations of Lyme disease and will continue to assess the current OspA-based vaccine for Lyme disease.

In 1998, we will also launch an initiative on Expanded Research on Emerging Diseases. This initiative will encourage basic and applied research on broad issues relevant to emerging and re-emerging diseases such as Lyme disease.

Sexually Transmitted Diseases



An STD pathogen: The syphilis spirochete. Each year, more than 14 million Americans acquire an STD.

The United States has the highest rates of Sexually Transmitted Diseases (STDs) in the industrialized world. Each year, more than 14 million Americans acquire an STD. These include an estimated 16,500 cases of primary and secondary syphilis; 418,000 cases of gonorrhea; and 4 million cases of chlamydia. Of the 14 million cases of STDs, 63 percent are among people younger than the age of 25. The consequences of these conditions are devastating in both human and economic terms.

From the human standpoint, untreated chlamydial and gonorrheal infections can lead to pelvic inflammatory diseases (PID). PID often causes scarring of a woman's fallopian tubes and life-threatening tubal pregnancies can result. Chlamydia, gonorrheal, and other infections of a woman's upper reproductive tract also cause complications of pregnancy such as fetal wastage, low birth weight, and congenital infection. Treatment of PID in the United States cost an estimated $7.0 billion in 1996[4].

The control of many STDs has been complicated by the frequency of asymptomatic infections; the lack of safe, effective vaccines; the cost and technical difficulty of available diagnostic tests; the expense of single-dose oral therapies; and the absence of effective methods that women can use to protect themselves from STDs.

Reducing the Burden of Sexually Transmitted Diseases

The NIAID has addressed these challenges with a multidisciplinary research strategy that includes basic research, vaccine development, behavioral science, development of topical microbicides, and the development of rapid and inexpensive diagnostic tests. Recently NIAID-supported researchers and their colleagues in industry have shown that a highly sensitive and non-invasive urine test that detects the genetic material of *Chlamydia trachomatis* holds promise for large-scale screening programs to detect both symptomatic and asymptomatic cases of chlamydia.

This type of screening can have a profound effect, as demonstrated by a recent NIAID-supported research study. This trial demonstrated that women who were screened and treated for asymptomatic chlamydia infection were 60 percent less likely than unscreened women to develop PID. Additionally, a recent NIAID Intramural Research study showed that men and women are equally likely to contract *Chlamydia trachomatis* from infected sex partners. Previous studies had suggested that male-to-female transmission of chlamydia occurred more often than female-to-male transmission. The similar rates of infection suggest that thoughts about women being more susceptible to infection may be incorrect.

[4] JAMA 1991. 266: 2564-9.

Prevention of Sexually Transmitted Diseases: Topical Microbicides and Vaccines

Ultimately, safe and effective topical microbicides and vaccines will be the most powerful tool for controlling STDs. Topical microbicides are chemical or physical barriers that women can use intravaginally to inactivate STD pathogens. The NIAID research effort for the development of topical microbicides includes basic research, preclinical product development, and clinical evaluation of existing and new compounds.

A number of vaccine candidates for gonorrhea, chlamydia, and other STDs are in various stages of development. NIAID-sponsored researchers are sequencing the genomes of these pathogens, efforts that will help illuminate the pathogenesis of these infections and help identify new antigens for evaluation as vaccine candidates.

Future Opportunities for Research on Sexually Transmitted Diseases

The NIAID will continue to support its multidisciplinary research approach in reducing the burden of STDs. In 1998, we will renew our Research on Molecular Immunology of STDs program. This initiative will link basic research on the molecular immunology of STDs with existing clinical research that is ongoing in the NIAID-supported STD Cooperative Research Centers program. The goal of this program is to facilitate the movement of basic research on STDs toward applications relating to STD infections in humans. This will further strengthen our capacity to fully study and characterize the molecular nature of immune responses in humans to sexually transmitted disease pathogens. Understanding the human response to these diseases is crucial in the development of safe, effective vaccines for the prevention of these diseases.

Additionally, we will enhance our existing network of STD Cooperative Research Centers by launching an initiative that is devoted to the study of STDs in adolescents. The addition of this Adolescent STD Cooperative Research Center will allow for the development of a systematic approach to assessing the biological and behavioral factors that determine susceptibility to STDs during adolescence. This investment will also allow us to develop effective tools and subsequently develop behavioral and biomedical interventions to control STDs in this high risk population.

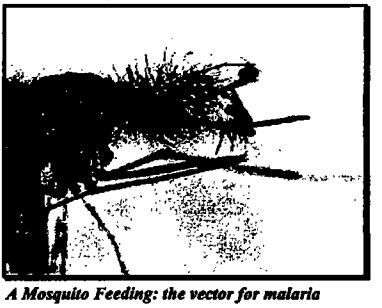
The study of STDs remains a high priority research area for the NIAID since these diseases are inextricably linked to the HIV epidemic. Therefore, efforts to control STDs will play a critical role in fighting HIV and AIDS. Likewise, HIV-related interventions will impact the concurrent epidemic of non-HIV STDs.

Tropical Medicine and Parasitic Diseases

The World Health Organization estimates that approximately 2.5 billion people are at risk for, and 500 million people currently suffer from, the major tropical diseases caused by protozoan and helminth parasites. Malaria and acute diarrheal diseases are among the most common causes of serious morbidity and death in children under the age of 5. Tropical diseases are increasingly recognized as emerging or reemerging health threats in the United States. While exerting their toll mainly on the poor in the tropics, tropical diseases are of U.S. concern as international travel, commerce, immigration, and military activities extend the impact of these diseases.

Progress Against Tropical and Parasitic Diseases

Malaria: Malaria is a significant public health problem in tropical and subtropical regions of the world, where an estimated 200 to 300 million cases occur each year. Of these cases, 2 to 3 million are fatal. Changing environmental and ecological patterns, vector (mosquito) resistance to pesticides, and parasite resistance to drugs have resulted in a dramatic resurgence of malaria in recent years. The etiologic agent of the most severe form of malaria, *Plasmodium falciparum*, is known to feed on the hemoglobin in red blood cells during its life cycle. The parasite's digestion of hemoglobin produces a toxic substance called heme and, through some as yet unknown mechanism, the parasite crystallizes the substance to form a substance called hemozoin. NIAID-supported basic research on the precise mechanism of hemozoin formation has revealed that histadine rich proteins (HRPs) promote hemozoin formation. HRP-mediated synthesis of hemozoin was found to be inhibited by chloroquine, a drug commonly used to treat and prevent malaria. Malaria control efforts are hindered by the widespread development of parasitic resistance to chloroquine. The findings of this study provide further insight into the molecular mechanisms of a key step in malaria pathogenesis. Detailed knowledge of these events may lead to the design of new antimalarials or other strategies to overcome chloroquine resistance.



A Mosquito Feeding: the vector for malaria

Chagas' Disease: Chagas' disease affects millions of people in South and Central America. Currently there is no satisfactory treatment for this parasitic infection. In an NIAID-supported study, scientists were able to block replication of the parasite in mammalian cells *in vitro* and reduce parasite burden in experimentally infected animals by inhibiting the activity of a critical enzyme. The molecular structure of this enzyme was then determined. These findings establish the parasite enzyme as a promising target for drug development and provide valuable information to facilitate such development.

Schistosomiasis: Schistosomiasis is a parasitic disease that is extremely problematic in tropical developing countries. An endogenous immune system molecule called IL-12 is known to have potent effects against schistosomiasis. In a collaborative effort with researchers from Johns Hopkins University, NIAID Intramural Research Program investigators demonstrated that IL-12 was able to boost the immune response to a live vaccine and confer nearly complete resistance to subsequent infection in an animal model. The study also revealed that IL-12 is able to boost antibody responses to infectious agents, a previously unknown function of IL-12. These findings provide a basis for future research into how these antibodies protect against schistosomiasis and for the development of a human vaccine based on the IL-12 boosting strategy.

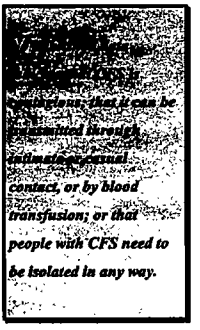
Future Opportunities in Tropical and Parasitic Disease Research

The NIAID will maintain its strong commitment to the study of tropical and parasitic disease research in 1998. We will continue to support our International Collaboration on Infectious Diseases Research program, a collaborative effort between U.S. and foreign investigators. Likewise, we will continue to fund our Tropical Medicine Research Centers and our Tropical Disease Research Units.

Also in 1998, the NIAID will launch a new malaria initiative, Malaria: Immunologic Correlates of Resistance. Through clinical studies, this effort will expand our understanding of human immunity to *Plasmodium falciparum*. We will also launch an initiative on Expanded Research in Emerging Diseases. This initiative will address issues of concern related to emerging diseases, including tropical and parasitic diseases.

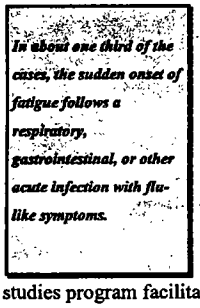
Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is an illness characterized by prolonged, debilitating fatigue and multiple nonspecific symptoms such as headaches, recurrent sore throats, muscle and joint pains, and cognitive complaints. Profound fatigue, the hallmark of the disorder, can come on suddenly or gradually and persists for or recurs throughout the period of illness. Unlike the short-term disability of an acute infection, CFS symptoms by definition linger for at least six months and often for years.



CFS is a poorly understood illness that involves many systems of the body and is diagnosed more frequently in women than in men. Despite multidisciplinary studies into the cause of CFS, its etiology remains elusive. Four hypotheses have been proposed for CFS etiology: infectious diseases, immune system dysregulation, neuroendocrine abnormalities, and psychiatric disorders. Despite extensive research seeking an infectious agent association and specific immune dysregulation, no consistent infectious or immunological markers have been found.

NIAID Research: Addressing the Problem of Chronic Fatigue Syndrome

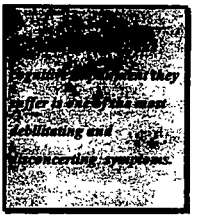


NIAID's commitment to CFS research has grown in the past ten years. To provide an environment for the sustained, multidisciplinary research needed to understand what underlies this complex illness, the NIAID supports a broad based program of research into CFS both in the extramural research community and in our Intramural Research Program. In the extramural research community we support a program of Chronic Fatigue Syndrome Cooperative Research Centers and several investigator initiated research studies.

NIAID-supported scientists at the CFS centers are conducting basic science and clinical investigations into CFS. The centers' pilot studies program facilitates the testing of new theories and observations about the disease. State-of-the-art methods in virology, psychology, and physiology are being used to compare people with CFS with healthy people and with people who have similar symptoms to learn what makes people susceptible to CFS and what causes the symptoms of CFS.

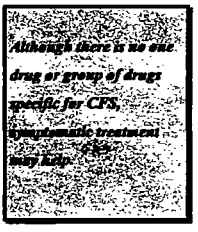
In our Intramural Research Program the NIAID is undertaking several studies on CFS. These studies are aimed at identifying and addressing the clinical features, natural history, pathogenesis, and treatment of CFS and other fatigue disorders that may be related to CFS.

Progress Against Chronic Fatigue Syndrome



Recent reports from Johns Hopkins University suggest that a form of abnormally low blood pressure, known as neurally mediated hypotension, is common among CFS patients. In tests comparing CFS patients with healthy controls, 96.0 percent of CFS patients showed abnormal test responses compared to only 28.5 percent in the control group. Patients were offered therapy with several drugs directed at neurally mediated hypotension. Complete or near complete resolution of symptoms was reported in 39.0 percent of the patients.

In collaboration with Johns Hopkins researchers, NIAID intramural investigators have established a clinical trial of fludrocortisone, a synthetic steroid that mimics the actions of some adrenal hormones, including their ability to raise blood pressure to assess the efficacy of this therapy. If successful, it could provide a major benefit to CFS patients.



In another Intramural Research Program study, the NIAID is assessing whether CFS may be related to a defect in the hypothalamic-pituitary-adrenal axis. A clinical trial using hydrocortisone therapy is underway. Preliminary results from this study showed that some improvement was afforded by this drug. These results may provide important insights on the mechanisms of CFS pathogenesis.

Future Investment in Chronic Fatigue Syndrome Research

The NIAID will continue to support research directed toward defining the role of infectious agents and immune alterations in the etiology and pathogenesis of CFS, responding to opportunities suggested by new findings. We will also continue to support research on CFS prevalence in economically and ethnically diverse populations. Particular emphasis will be placed on studying CFS in minority populations. The NIAID will foster creative new investigator-initiated approaches and multidisciplinary studies through primary support of a trans-NIH program announcement on CFS Pathophysiology. This multi-NIH institute announcement will encourage research proposals from medical disciplines previously not involved in CFS research.

NIAID research will continue to provide new insights into CFS, testing rationale hypotheses concerning etiology, natural history, and the pathogenesis of CFS. This investment will provide a better understanding of this syndrome and will lead to improved diagnosis, intervention, and treatment strategies for this debilitating illness.

Asthma & Allergic Diseases

An estimated 7 percent of all children aged 18 and younger have asthma, one of the most common chronic diseases of childhood. The most common cause of asthma is allergy, and both are currently among the major causes of illness and disability in the United States. Despite improved treatments, asthma-related illnesses and deaths have increased in the United States, particularly in minority populations. The economic costs associated with asthma are enormous. In 1990, total economic costs associated with asthma were approximately $6.2 billion. Although asthma is often thought of as a mild, chronic disease, 43 percent of the economic impact was associated with emergency room use, hospitalization, and death. The largest single economic cost associated with asthma was $1 billion for decreased productivity due to lost school days.

Reducing the Burden of Asthma and Allergic Diseases

Research supported by the NIAID continues to decrease the burden of asthma and allergic diseases. The disturbing trends in asthma morbidity and mortality underscore the importance of the NIAID's research into understanding, preventing, and treating asthma.

Inner-City Asthma Study: Over the past 6 years, investigators supported through the NIAID National Cooperative Inner-City Asthma Study have identified factors involved in the increase in asthma prevalence, and designed new strategies to reduce asthma morbidity and mortality. Some very promising findings are now emerging from the first two phases of this study, conducted at sites across the United States. The first phase of the study enrolled over 1,500 children and discovered a number of factors to be associated with asthma severity. These factors included high levels of indoor allergen, particularly cockroach allergen; high levels of smoking among family members and caretakers; and exposure to high levels of nitrogen dioxide, a respiratory irritant. Additionally, over half of the participants found it difficult to get follow-up care for their asthma.

In the second phase of the study, more than 1,000 high risk children and their families were assisted by a nurse practitioner in managing the child's condition and in instituting environmental controls, such as the removal of cockroach allergens from their homes. Over 90 percent of enrolled families complied with this intervention strategy, which led to a marked reduction in asthma symptoms, an improved quality of life, better school attendance, and a striking 30 percent decrease in asthma-related hospitalizations and unscheduled physician and emergency room visits for asthma. The NIAID has recently funded a continuation of this study to extend and disseminate the very promising results achieved thus far. This model of asthma intervention in the inner city, if adopted nationwide, could result in a substantial reduction in emergency room visits, hospitalizations, and significantly reduce health care costs.



An asthma case manager assists a young patient

Asthma, Allergic, and Immunologic Diseases Cooperative Research Centers: The NIAID supports 15 extramural programs in its Asthma, Allergic, and Immunologic Diseases Cooperative Research (AAIDCRC) program. We also support one Intramural research center within the NIAID to link the basic and clinical aspects of this program. The AAIDCRC program is designed to support basic and clinical research on mechanisms of, intervention in, and prevention of asthma, allergic, and immunologic diseases. A major purpose of this program is to accelerate the development and application of fundamental knowledge of the immune system through support of investigators studying immune system-mediated diseases. In addition to concentrating on traditional basic and clinical research, all of these centers conduct a variety of demonstration and education activities. The NIAID renewed this program in 1997, and will concentrate on research aimed at interventions in asthma and allergic diseases in defined populations, particularly underserved populations such as inner city African-Americans, Latino-Americans, Asians, Native-Americans, the elderly, and women.

Other Advances in Asthma & Allergy Research: Allergies are commonly treated with a class of medications called antihistamines. "Allergy shots," technically called immunotherapy, are another treatment option for allergies. In addition to being inconvenient to the patient due to the frequency of treatment, immunotherapy works inconsistently and can be dangerous due to the small risk of inducing a severe allergic reaction. DNA vaccines could potentially reduce this risk, eliminate the need for repeated treatments, and generally provide a more potent and consistent treatment than immunotherapy.

NIAID-supported scientists have demonstrated that DNA vaccines are capable of stimulating an immune response that may abate allergy symptoms. Studies are ongoing to assess the value of DNA vaccines for allergic diseases.

Future Investment Opportunities in Asthma and Allergy

In 1998, the NIAID will launch an initiative on Inflammation in Allergy and Asthma to support studies of the underlying mechanisms of inflammation in asthma and allergic diseases. The goal of this expanded effort is to promote innovative research to identify factors responsible for initiation and maintenance of inflammation in asthma and allergic diseases. Emphasis will be placed on innovative research in areas of opportunity such as allergic mechanisms, non-allergic mechanisms, and combined allergic and non-allergic mechanisms of asthma and allergic diseases. The NIAID also plans to vigorously pursue research on asthma by fostering individual investigator-initiated research studies.

Transplantation

Today, over 19,000 organ transplants are performed each year in the United States. Kidneys are the most commonly transplanted organ worldwide. In the United States, nearly 10,000 people, including approximately 500 children, receive a kidney each year, and more than 1,000 children are on transplant waiting lists. Children usually undergo kidney transplants to correct congenital defects or diabetes-related complications. In 1993, there were 217,479 Americans with end stage renal disease (ESRD) requiring treatment with dialysis or transplantation. Reimbursements for all treatment modalities for ESRD beneficiaries totaled approximately $11.1 billion. Approximately $8.3 billion of this cost was borne by Medicare and $1.8 billion was borne by third-party payers.



A patient undergoing dialysis treatment

Long-term medical costs associated with a successful kidney transplant are much lower than the costs of chronic kidney dialysis treatment. In addition, the quality of life for patients receiving transplants is improved compared with that of patients undergoing dialysis. Children, however, have poorer graft survival than adults because their immune systems respond differently to immunosuppressive therapies developed for use in adults. Even though surgical techniques and immunosuppressive therapies have made transplantation a daily occurrence, 10 to 50 percent of transplanted organs and tissues fail within the first year following transplantation. Even in a "best case" scenario, nearly 30 percent of transplanted kidneys are lost within 3 years, primarily because of graft rejection.

Advances in Transplantation Technology

Transplant rejection occurs when the recipient's immune system identifies the donated organ as a foreign invader and initiates a response to rid the body of the transplanted organ. Specific molecules on the surface of cells are responsible for this immune response. These molecules, called major histocompatibility antigens (MHA), are uniform throughout the body. In order for a transplanted organ to be accepted, the donor's MHAs must match the recipient's MHAs. Occasionally, a transplant will be rejected even when the donor and recipient MHAs match precisely. Other molecules called minor histocompatibility antigens (MiHA) are thought to be responsible in such cases. After 40 years of arduous research, scientists have located the gene for one of these molecules. Current studies are underway to determine if a therapy can be devised to prevent transplant rejection by blocking the recognition of MiHA.

In addition to histocompatibility antigens, other molecules on the surface of cells contribute to transplant rejection by recognizing foreign organs and tissues and initiating the immune response. NIAID-supported investigators have identified one such molecule on the surface of critical immune cells called B lymphocytes. This molecule was found to be necessary

for the induction of transplant rejection in mice and may provide a new target for the development of strategies to prevent transplant rejection.

In addition to these discoveries, the NIAID is undertaking several projects addressing the complexities associated with organ transplantation. We are funding investigator-initiated research targeted at further identifying MiHA systems involved in graft rejection and research targeted at understanding how to induce and maintain specific transplant tolerance.

Given the important economic and human impact of this problem, we have renewed our Cooperative Clinical Trials in Transplantation program and our initiative on Immunopathogenesis of Chronic Rejection. The NIAID is also sponsoring a national study to improve the characterization of MHAs in the African-American population. Finally, in collaboration with the NIH Office of Research on Minority Health, we are sponsoring similar studies in Native-American and Latino populations.

Opportunities for the Future

In 1998, the NIAID will renew its Cooperative Clinical Trials in Pediatric Transplantation. This study will examine new treatments to prevent rejection of transplanted kidneys in children. We will also invest in a new initiative to study the immune response to antigens present on the tissues and organs from other species, and study the immune response to infectious agents that may be introduced by xenotransplantation.

In 1998, NIAID Intramural Research Program investigators will continue studies on the structure of an immune cell protein that may be a useful target for drugs that aid tissue transplants. Investigator-initiated basic research proposals will also remain a high priority in 1998.

Autoimmune Diseases and Immune System Disorders

Allergic and immunologic diseases are among the leading causes of illness and disability in the United States. More than 1 out of every 10 persons are reported to have a condition related to immunologic illness. Several of these diseases such as asthma, rheumatoid arthritis, and diabetes affect millions of individuals. Other immunologic conditions such as scleroderma, primary immunodeficiency syndrome, and Wegner's granulamatosis, occur less frequently. However, when viewed collectively, even these less prevalent diseases constitute a significant disease burden within the U.S. population.

Basic Research: The Key to Discovery



The immune response involves a complex mixture of interactions between molecules and cells. Some of these interactions stimulate the immune response, while others suppress the immune response. A balance between the stimulatory and suppressive effects controls the immune response such that it is neither so intense that it harms the body nor so passive that invading germs take over the body. One way to determine whether a specific molecule has a suppressive or stimulatory effect is to genetically engineer a "knock out" mouse that is unable to produce the molecule in question. NIAID-supported researchers have created a "knock out" mouse for a specific cell surface molecule and have found that this molecule is essential for survival. This molecule helps maintain the essential balance by suppressing the immune response, and in mice lacking this molecule, immune cells multiplied unchecked, infiltrated and destroyed organs, and this rapidly led to death. The apparent influence of this molecule makes it a promising target for therapeutic strategies to treat autoimmune diseases and prevent transplant rejection.

Application of Basic Research Findings

Multiple sclerosis (MS) is a disabling autoimmune diseases that affects 250,000 to 350,000 people in the United States. Using an animal model of MS, NIAID-supported scientists delineated the specific roles of two receptors on cells thought to be involved in the inflammatory response that triggers relapses that are characteristic of MS and other autoimmune diseases. The study found that the receptors were activated at different times during the disease process. More significantly, the study also found that one of the receptors actually had a substantial inhibitory effect on the inflammatory response and, as a consequence, a role in forestalling clinical relapse. In clarifying the roles of these two important receptors, this research discovered a potential target for the development of therapies for MS.

In another study using a mouse model of MS called experimental allergic encephalomyelitis (EAE), NIAID-supported scientists have discovered that a specific interaction between two types of critical immune cells is associated with the symptoms of EAE and MS. Moreover, they found that blocking this interaction was able to prevent EAE in mice, and it dramatically improved the symptoms in mice that already had EAE. These important findings suggest a new approach for alleviating symptoms of MS in humans.

NIAID-supported researchers have also identified the function of the product for some of the genes that cause primary immunodeficiency disease. As an example, NIAID-supported researchers have located the gene for Wiskott-Aldrich Syndrome, a hereditary disease that causes abnormal immune function, on a specific chromosome. This information will allow specific strategies to be developed for gene therapy to replace defective genes and treat, or possibly cure, Wiskott-Aldrich Syndrome.

NIAID Intramural Research Program investigators are tackling another of these diseases, chronic granulomatous diseases (CGD). They have shown that the immune system molecule interferon gamma improves the function of the white blood cells called neutrophils in patients with CGD, reducing infections by 70 percent.

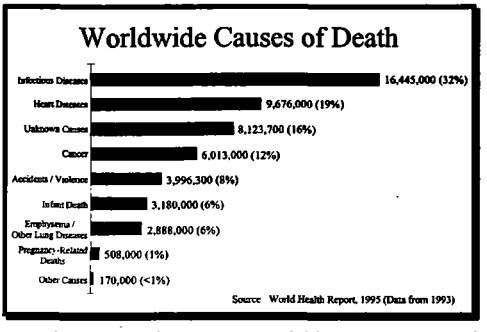
Autoimmune/lymphoproliferative Syndrome (ALPS) is a newly recognized pediatric disease characterized by an immune system attack on various organs systems with massive accumulation of immune cells called lymphocytes. NIAID scientists in our Intramural Research Program have found that ALPS patients have a mutation in a gene called Fas. The normal function of this gene is to regulate lymphocyte numbers by signaling them to commit suicide. Without such "programmed cell death", lymphocytes over-accumulate and this leads to an attack on the body's own organs in ALPS patients. Our scientists also found that the mutations in Fas were inherited. These findings identify a target for gene therapy of ALPS and suggest a potential cause of other autoimmune diseases such as diabetes, rheumatoid arthritis, and multiple sclerosis.

Future Investments in Research on Immune System Disorders

In 1998, scientists in NIAID's Intramural Research Program will continue to investigate a recently discovered immune disorder in children that involves the overproduction of an unusual class of immune cells. This disease results in a susceptibility to repeated, severe infections with bacteria such as streptococci, pneumococci, and *Haemophilus influenzae*. Continuation of these studies will further our understanding of the mechanisms of B lymphocyte development and the treatment of immunodeficiency diseases.

Also in 1998, the NIAID will launch an initiative to establish a Primary Immunodeficiency Diseases Registry. A registry for primary immunodeficiency diseases is an inexpensive way to improve access of investigators to patients for basic and clinical studies, gather current clinical and mortality data for use in clinical settings, and improve access for affected individuals to advances in treatment and the latest therapies.

Economic and Public Health Benefits of NIAID-supported Research

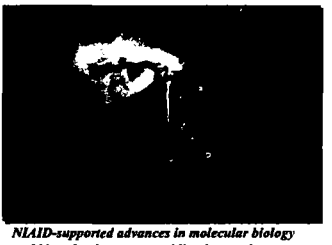


From both a public health standpoint and economic perspective, the diseases within the purview of the NIAID place a heavy burden on society. Infectious diseases are the leading cause of death worldwide and the third leading cause of death in the United States. The medical care costs and lost productivity associated with infectious, allergic, and immunologic illnesses can be reduced through the development of new and better strategies for preventing and controlling these diseases. Toward this end, basic and clinical research supported by the NIAID continues to advance our knowledge of the pathogenesis, diagnosis, treatment, and prevention of infectious diseases and immune system disorders.

By their very nature, infectious and allergic diseases can strike large numbers of people. Sexually transmitted diseases, influenza, and asthma, to name just a few, are examples of diseases that affect millions of Americans. In addition, diseases such as AIDS, Lyme disease, ebola hemorrhagic fever, and hantavirus pulmonary syndrome have been newly identified in the past 20 years; and ancient diseases, including tuberculosis, cholera, and malaria, have re-emerged as significant health problems.

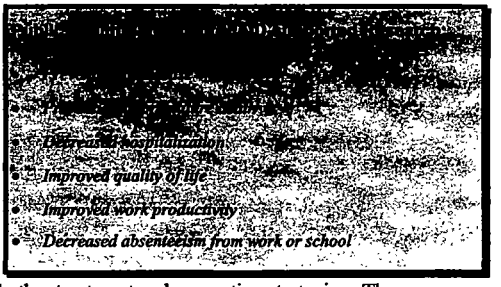
NIAID Research: Developing Innovative Strategies to Fight Disease

Biomedical innovation is a continuous process in which new products are developed, modified, refined, and improved. NIAID research serves as a catalyst of biomedical innovation, bringing forth new or improved vaccines, diagnostics, and therapeutics. These advances in biotechnology not only lead to improvements in public health, but also are a major source of economic growth, promoting increased efficiency in our health care system and creating new jobs in the biotechnology industry and in industries related to product development and commercialization.



NIAID-supported advances in molecular biology and biotechnology are providing innovative approaches to developing and improving vaccines against a wide variety of diseases.

NIAID Research: Improving the Public's Health



NIAID-supported research has a wide-ranging influence on the public's well-being. By expanding the breadth and depth of our understanding of infectious diseases, which place a heavy burden on our Nation's health care system and often disproportionately affect minorities, women, and children, NIAID-funded research has paved the way for the discovery of new vaccines, diagnostics, medications, and other treatment and prevention strategies. The widespread use of these products has, in turn, produced enormous public health and economic benefits.

New public health tools made possible by NIAID research also help foster a healthier economy. Effective strategies for preventing and treating illness reduce the incidence of premature death and disease-related disability, as well as the need for health care services, enabling people to lead healthier, more productive lives.

NIAID Research: Maintaining the Nation's Preeminence in Biomedical Research



NIAID is committed to recruiting minority investigators and academic institutions to its basic and clinical research programs.

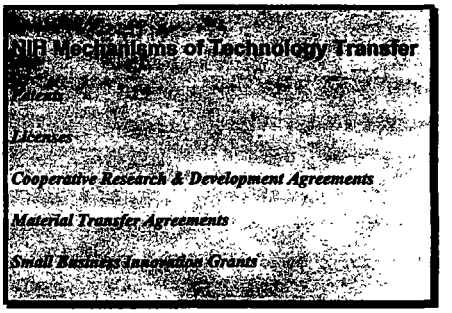
NIAID grants and contracts have also created many jobs and have improved the research infrastructure at academic institutions throughout the Untied States. NIAID funding supplements institutional funds for infrastructure development and enhancement, research equipment and supplies, hiring of research assistants, associates, and postdoctoral students, and support for principal investigators at universities and teaching hospitals in all regions of the country. This support has a significant impact on the research and educational endeavors of these institutions and is a critical element of the Nation's research enterprise.

Investment in higher biomedical education is vital if America is to continue to compete successfully in the international biotechnology arena. Building a foundation for the future while maintaining our preeminence in biomedical technology demands a balance of support between new and established investigators. Each new generation of talented young investigators brings

new ideas and renewed energy to the process of scientific discovery, the wellspring of our ability to compete in the global marketplace.

NIAID Research: Collaborating with Industry to Improve Public Health

Scientific advances from research performed in Government-sponsored laboratories not only improves health care but also results in commercial products and the creation of new jobs. The NIAID has developed a significant technology transfer portfolio that involves interaction with industry and academia, and the transfer of the Institute's technology to the private sector for commercialization. These collaborative efforts lead to marketable products that benefit the public health.



The implementation and use of the various mechanisms of technology transfer from Government to industry and academia is a great benefit to all parties, allowing the U.S. biomedical industry to become more competitive in both domestic and international markets. Through commercialization licenses, NIAID patent holders agree to share their rights with private companies that guide the invention through the steps to develop, test, and market a product.

NIAID Research: Providing Biomedical Materials for Research and Commercialization



NIAID scientists use biotechnology techniques to create strains of mice that mimic a broad range of human allergic and infectious diseases.

NIAID intramural and extramural researchers have developed resources and reagents that are used by scientists worldwide for basic research and for research aimed at developing commercial products such as new medications and vaccines. Some of these materials have been patented by NIAID-funded scientists or are available to other researchers through Cooperative Research and Development Agreements or other licensing agreements. Many of these research reagents and resources have been placed in NIAID-sponsored repositories, where they are available for use by other researchers.

By making the fruits of federally funded research widely available, NIAID-sponsored repositories ensure that as many investigators as possible can contribute to the development of better health care products, foster cooperation and collaboration among researchers, and help the research community get the best value from every Federal research dollar. These research benefits, in turn, bring forth public health and economic benefits. The various research repositories facilitate the development and evaluation of treatments and diagnostics for a wide range of public health problems.

The ready availability of shared research resources and materials helps researchers develop these products as cost effectively as possible. The products themselves then create further economic benefits through decreased health care costs and greater worker productivity.

NIAID Research: Addressing Global Health Problems & Expanding International Markets



NIAID-supported research helps improve the health and productivity of people throughout the world by supporting research aimed at preventing or curing diseases that may be rare in the United States but that are common overseas. In doing so, scientists are better able to respond to newly emerging diseases and to domestic public health threats that originate in other countries.

NIAID's international research also is vital for maintaining and expanding the international market for products derived from U.S. biomedical technology. These overseas efforts provide a point of entry into emerging foreign markets for U.S. health care products and biomedical technology. The development of better and less expensive products is central to our Nation's success in the international marketplace and depends on the continuous biotechnological innovation that is made possible by NIAID-funded basic research.

NIAID Research: Providing Economic and Public Health Benefits

To help counter the multiple adverse consequences of disease, NIAID research brings forth myriad public health and economic benefits. From strengthening our Nation's research infrastructure and ensuring the preeminence of U.S. biomedical research, to developing treatment and prevention strategies for costly infectious and allergic diseases, NIAID-supported research has a wide-ranging impact on the health of our citizens and on the health of our economy. By continuing to expand our understanding of disease, NIAID basic and clinical research will lead us to still greater opportunities for reducing the human and economic costs associated with disease.

Challenges for the Future

The advances and research endeavors described herein, and many others, are a cause for great optimism. However, we must keep our sights aimed on the many challenges that lie ahead. The global HIV epidemic is exploding and new infectious diseases continue to emerge, and old foes such as TB and diarrheal diseases continue to have a significant impact on human health. We also face an unprecedented crisis caused by the emergence and spread of drug resistant microbes.

We cannot overemphasize the intrinsic value of basic research in our quest for research results that have immediate application to persons afflicted with disease. Basic research is the key to developing public health tools. Basic science has contributed to the dramatic growth in our understanding of disease and disease processes and is essential to discovering new treatment and prevention strategies. The information gleaned from fundamental research provides the basis for fashioning clinical and biological interventions. Investments in NIAID research will ultimately result in improved health and quality of life by improving the diagnosis, treatment, and prevention of diseases.

In 1998, the NIAID will continue to foster basic research to reveal new methods of immune intervention and to unmask new approaches for treating and preventing human autoimmune, allergic, and inflammatory diseases. Basic research conducted by NIAID-supported scientists in molecular structure and function, host/pathogen interaction, genetics, and physiological and biochemical processes of bacteria, viruses, fungi and parasites will lead to increased understanding of the body's protective needs. In addition, we will continue funding studies on microbial pathogens to gain knowledge needed for identifying specific protective factors and examining mechanisms of emergence, infection, pathogenicity, and virulence.

Our battle with disease must be fought on several fronts and with an unwavering commitment to basic and applied research. The NIAID has developed a comprehensive research program that will enhance the ability of our Nation to detect and control infectious diseases. Concurrently, we are working to reduce the burden of known diseases with new and improved treatments and vaccines. Only such a sustained commitment to basic research will lead to new drugs, vaccines, and other interventions that will benefit the health of this and future generations as we begin to enter the next millennium.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	1,146	$270,684,000	1,133	$273,987,000	1,258	$311,267,000
Administrative supplementals	(110)	14,496,000	(51)	6,867,000	(51)	6,867,000
Competing:						
Renewal	149	38,154,000	189	51,040,000	154	42,493,000
New	240	48,955,000	308	64,384,000	262	55,871,000
Supplemental	0	82,000	0	0	0	0
Subtotal, competing	389	87,191,000	497	115,424,000	416	98,364,000
SBIR/STTR	54	10,134,000	67	12,857,000	72	13,976,000
Subtotal, RPGs	1,589	382,505,000	1,697	409,135,000	1,746	430,474,000
Research Centers						
Specialized/comprehensive	3	3,300,000	3	3,422,000	3	3,490,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research centers in minority institutions	0	0	0	0	0	0
Subtotal, Centers	3	3,300,000	3	3,422,000	3	3,490,000
Other Research						
Research careers	122	9,853,000	125	10,518,000	125	10,728,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	680,000	0	725,000	0	740,000
Other	25	576,000	39	1,597,000	39	1,628,000
Subtotal, Other Research	147	11,109,000	164	12,840,000	164	13,096,000
Total, Research Grants	1,739	396,914,000	1,864	425,397,000	1,913	447,060,000
Training	FTTPs		FTTPs		FTTPs	
Individual	92	2,527,000	92	2,582,000	92	2,634,000
Institutional	556	15,823,000	556	16,977,000	556	17,316,000
Total, Training	648	18,350,000	648	19,559,000	648	19,950,000
Research & development contracts	65	51,911,000	67	55,545,000	67	57,515,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	579	81,742,000	579	85,749,000	579	87,047,000
Research management and support	427	22,702,000	427	22,700,000	427	22,700,000
Cancer prevention & control	0	0	0	0	0	0
Construction	0	0	0	0	0	0
Total, ICD	1,006	571,619,000	1,006	608,950,000	1,006	634,272,000
(Clinical Trials)		(39,159,000)		(40,725,000)		(42,354,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Allergy, Immunology and Transplantation	---	174,047	---	186,462	---	195,176	---	8,714
Microbiology and Infectious Diseases	---	293,128	---	314,039	---	329,349	---	15,310
Subtotal, Extramural research		467,175		500,501		524,525		24,024
Intramural research	579	81,734	579	85,749	579	87,047	---	1,298
Research management and support	427	22,702	427	22,700	427	22,700	---	---
Total obligations	1,006	571,611	1,006	608,950	1,006	634,272	---	25,322
Unobligated balance lapsing		8		---		---		---
Total, Budget Authority	1,006	571,619	1,006	608,950	1,006	634,272	---	25,322

Note. Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Summary of Changes

1997 Estimated budget authority	$608,950,000
1998 Estimated budget authority	634,272,000
Net change	25,322,000

	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$36,426,000		+523,000
b. Annualization of January 1997 pay increase		36,426,000		+303,000
c. January 1998 pay increase		36,426,000		+782,000
d. Legislative proposal, 1.51% increase in the CSRS rate		36,426,000		+114,000
e. Service and supply fund		3,620,000		+96,000
f. Increased cost of laboratory supplies, materials, and other expenses		29,456,000		+764,000
Subtotal				+2,582,000
2. Research Management and Support:				
a. Within grade increase		15,138,000		+224,000
b. Annualization of January 1997 pay increase		15,138,000		+126,000
c. January 1998 pay increase		15,138,000		+325,000
d. Legislative proposal, 1.51% increase in the CSRS rate		15,138,000		+47,000
e. Service and supply fund		1,037,000		+26,000
f. Increased cost of laboratory supplies, materials, and other expenses		3,046,000		+80,000
Subtotal				+828,000
Subtotal, Built-in				+3,410,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Summary of Changes--continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	1,133	280,854,000	+125	+37,280,000
b. Competing	497	115,424,000	-81	-17,060,000
c. SBIR/STTR	67	12,857,000	+5	+1,119,000
Total	1,697	409,135,000	+49	+21,339,000
2. Centers	3	3,422,000	---	+68,000
3. Other research	164	12,840,000	---	+256,000
4. Research training	648	19,559,000	---	+391,000
5. Research and development contracts	67	55,545,000	---	+1,970,000
	FTEs		FTEs	
6. Intramural research	579	85,749,000	---	-1,284,000
7. Research management and support	427	22,700,000	---	-828,000
Subtotal, program		608,950,000		+21,912,000
Total changes				+25,322,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Object

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:				
Full-time employment		1,006	1,006	---
Full-time equivalent of overtime and holiday hours		1	1	---
Average ES salary		$114,000	$119,000	5,000
Average GM/GS grade		10.8	10.8	---
Average GM/GS salary		$50,000	$52,000	2,000
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)		$79,000	$82,000	3,000
Average salary of ungraded positions		$29,000	$31,000	2,000
	Personnel Compensation:			
11.1	Full-Time Permanent	28,010,000	29,263,000	$1,253,000
11.3	Other than Full-Time Permanent	6,625,000	6,917,000	292,000
11.5	Other Personnel Compensation	1,802,000	1,881,000	79,000
11.8	Special Personnel Services Payments	5,535,000	5,779,000	244,000
11.9	**Total Personnel Compensation**	**41,972,000**	**43,840,000**	**1,868,000**
12.0	Personnel Benefits	9,552,000	9,972,000	420,000
13.0	Benefits for Former Personnel	40,000	42,000	2,000
	Subtotal, Pay Costs	**51,564,000**	**53,854,000**	**2,290,000**
21.0	Travel & Transportation of Persons	997,000	997,000	0
22.0	Transportation of Things	174,000	174,000	0
23.1	Rental Payments to GSA	940,000	987,000	47,000
23.2	Rental Payments to Others	541,000	552,000	11,000
23.3	Communications, Utilities & Miscellaneous Charges	1,902,000	1,940,000	38,000
24.0	Printing & Reproduction	92,000	92,000	0
25.1	Consulting Services	95,000	95,000	0
25.2	Other Services	13,331,000	12,894,000	(437,000)
25.3	Purchase of Goods & Services from Government Accounts	30,730,000	29,981,000	(749,000)
25.4	Operation & Maintenance of Facilities	1,150,000	1,173,000	23,000
25.5	Research & Development Contracts	50,213,000	52,059,000	1,846,000
25.6	Medical Care	632,000	663,000	31,000
25.7	Operation & Maintenance of Equipment	643,000	643,000	0
25.8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**96,794,000**	**97,508,000**	**714,000**
26.0	Supplies & Materials	7,467,000	7,467,000	0
31.0	Equipment	3,375,000	3,543,000	168,000
32.0	Land and Structures	4,000	4,000	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	444,956,000	467,010,000	22,054,000
42.0	Insurance Claims & Indemnities	139,000	139,000	0
43.0	Interest & Dividends	5,000	5,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**557,386,000**	**580,418,000**	**23,032,000**
	Total Budget Authority by Activity	**608,950,000**	**634,272,000**	**25,322,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$28,010,000	$29,263,000	$1,253,000
Other Than Full-Time Permanent (11.3)	6,625,000	6,917,000	292,000
Other Personnel Compensation (11.5)	1,802,000	1,881,000	79,000
Special Personnel Services Payments (11.8)	5,535,000	5,779,000	244,000
Total Personnel Compensation (11.9)	**41,972,000**	**43,840,000**	**1,868,000**
Civilian Personnel Benefits (12.0)	9,552,000	9,972,000	420,000
Benefits to Former Personnel (13.0)	40,000	42,000	2,000
Subtotal, Pay Costs	**51,564,000**	**53,854,000**	**2,290,000**
Travel (21.0)	997,000	997,000	0
Transportation of Things (22.0)	174,000	174,000	0
Rental Payments to Others (23.2)	541,000	552,000	11,000
Communications, Utilities and Miscellaneous Charges (23.3)	1,902,000	1,940,000	38,000
Printing and Reproduction (24.0)	92,000	92,000	0
Other Contractual Services:			
Advisory and Assistance Services (25.1)	95,000	95,000	0
Other Services (25.2)	13,331,000	12,894,000	(437,000)
Purchases from Govt. Accounts (25.3)	23,686,000	22,813,000	(873,000)
Operation & Maintenance of Facililties (25.4)	1,150,000	1,173,000	23,000
Operation & Maintenance of Equipment (25.7	643,000	643,000	0
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**38,905,000**	**37,618,000**	**(1,287,000)**
Supplies and Materials (26.0)	7,452,000	7,452,000	0
Subtotal, Non-Pay Costs	50,063,000	48,825,000	(1,238,000)
Total, Administrative Costs	**101,627,000**	**102,679,000**	**1,052,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Significant Items in the House and Senate Appropriations Committee Reports

FY 1997 House Appropriations Committee Report Language (104-659)

Item

Asthma - The House in its report (page 69) stated -- "The Committee urges the NIAID to continue to make minority and children-related asthma research a high priority, and requests the Director to provide an update on these efforts, and the NIAID's National Cooperative Inner City Asthma study, at next year's appropriations hearings."

Action Taken or To Be Taken

The National Cooperative Inner City Asthma Study comprises eight centers studying asthma in minority children living in the inner city. In Fiscal Year 1996 the NIAID renewed this program for five years. The continuation of this study includes educational programs aimed at physicians and focuses attention on the relationship between the environment and asthma morbidity in minority children.

The NIAID also co-sponsored a workshop on "Asthma and the Environment" in collaboration with the National Heart, Lung, and Blood Institute; the Fogarty International Center; the Environmental Protection Agency; the National Institute of Occupational Safety and Health; and the Centers for Disease Control and Prevention (CDC). The workshop brought together basic scientists, clinicians and epidemiologists to evaluate the potential association between environmental pollution and asthma and to identify critical questions to be addressed to facilitate future progress in this area.

Item

Tuberculosis - The House in its report (page 69) stated -- "NIAID researchers have begun to understand multi-drug resistant tuberculosis and hope to develop methods to quickly determine which drug therapy is appropriate for multi-drug resistant strains, so a patient can begin an appropriate treatment therapy immediately, thus reducing the risk of transmitting the disease to others. The Committee encourages further work in this area."

Action Taken or To Be Taken

The NIAID supports research focusing on the development of improved diagnostics, treatment and vaccine strategies to control and prevent Tuberculosis (TB).

NIAID research also includes studies directed toward improved understanding of basic and molecular biology, genetics, immunology and pathogenic mechanisms of M.tb. The identification of factors associated with the transmission and emergence of drug-resistant forms of tuberculosis is also a high priority area. The development of drug resistant strains of TB has created a need for new anti-TB therapies. Several enzymes involved in the synthesis of the cell wall of *Mycobacterium tuberculosis* are being targeted for current and new drugs by NIAID Intramural Research Program investigators. NIAID intramural researchers have identified six of these enzymes and their function. Ongoing work is aimed at understanding each enzyme reaction more thoroughly and identifying any additional molecules involved in the reactions. This information will be useful in the development of new therapies for TB.

Item

Liver Disease - The House in its report (pg. 70) stated -- "The Committee is pleased that NIAID and NIDDK will sponsor a consensus development conference on chronic hepatitis C and encourages the involvement of other NIH institutes, as appropriate."

Action Taken or To Be Taken

The NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) will co-sponsor a consensus conference in 1997 focusing on chronic hepatitis C. Recently, the NIAID awarded four new, four-year research grants focusing on hepatitis C. One of these new awards was co-funded with NIDDK. These projects are designed as multidisciplinary, collaborative research units each focused on the prevention and treatment of hepatitis C viral infection. In addition, NIAID has recently issued two program announcements, "Enteric and Hepatic Infectious Diseases: Research Needs" and "Expanded Research on Emerging Diseases," with the goal of further enhancing the Institute's hepatitis C portfolio.

Item

Hemophilia - The House in its report (pg. 70) stated -- "The Committee is pleased with NIAID efforts to maximize funding support of the HIV/AIDS clinical trials for persons with hemophilia through the treatment centers network and expects that this program will continue to provide access to these newly available drugs including protease inhibitors."

Action Taken or To Be Taken

The NIAID will continue to provide access to HIV/AIDS clinical trials and newly available drugs for hemophilia patients using existing networks of hemophilia treatment centers.

Item

Cervical Cancer - The House in its report (pg. 70) stated -- "The Committee encourages the NIAID (with the NCI) to collaborate in sponsoring basic and clinical research on human papillomavirus diagnosis, screening and prevention, and the identification of women at high risk of cervical cancer."

Action Taken or To Be Taken

The Institute currently pursues several areas of research on human papillomavirus (HPV), which is causally associated with cervical cancer. In Fiscal Year 1996, the NIAID in collaboration with the NCI participated in a consensus development conference on cervical cancer. The NIAID also participated on a trans-NIH working group on HPV. In Fiscal Year 1998, the NIAID plans to release an RFP titled "Therapeutic Strategies for Papillomavirus Infections," which integrates *in vitro* and animal model evaluations of efficacy and studies of the mechanism of action of experimental therapies for HPV infections.

Item

Microbicides - The House in its report (pg. 70) stated – "The Committee acknowledges the progress that NIAID has made in funding research on microbicides for STD/HIV prevention. It encourages NIAID to continue its commitment to funding the major areas of microbicide research including basic research, product development, clinical evaluation, and behavioral research."

Action Taken or To Be Taken

The NIAID supports a broad range of projects focused on the development of topical microbicides. Through these efforts, the NIAID continues to provide support for the development and evaluation of formulations of topical microbicides. Our future plans include the expansion of existing models for viral infections, development of new animal models for bacterial infections, and strengthening the capabilities for toxicity screens.

Item

Women's Interagency HIV Study (WIHS) - The House in its report (pg. 70) stated -- "The Committee urges funding for this study so that women can be followed prospectively to obtain the information critical to treatment and prevention efforts. The Committee believes that it is important to maintain geographical representation and to continue the study's broad scope in addressing a variety of women's health issues."

Action Taken or To Be Taken

The NIAID continues to support the WIHS ensuring that the Institute enrolls an appropriate number of women in the study and that the Institute achieves appropriate geographical representation.

Item

Primary Immune Deficiency Diseases (PIDD) - The House in its report (pg. 70) stated -- "The Committee is encouraged to learn that NIAID has entered into a collaborative agreement with a private foundation to support gene-transfer research grants to isolate and characterize the defective genes that cause all of these diseases and to develop techniques to correct the defects. The Committee encourages NIAID to maintain its focus on these devastating childhood diseases and supports its innovative approach to funding this research."

Action Taken or To Be Taken

The NIAID will continue to support research focused on identifying the causes of PIDD and potential therapeutic techniques. The Institute recently awarded three grants in this area and looks forward to continued interaction with the Modell Foundation.

Item

Fanconi Anemia - The House in its report (pg. 71) stated -- " The Committee encourages the Institute to pursue additional research opportunities into this disorder."

Action Taken or to be Taken - The National Heart, Lung, and Blood Institute (NHLBI) has a very active and promising research program to determine the clinical efficacy of using umbilical cord blood transplantation to treat several genetic diseases, including Fanconi anemia, as well as certain acquired diseases. Recently, the Institute established a network of transplant centers, which will follow common protocols in transplanting cord and progenitor cells in treating adults and children with unrelated donor umbilical cord blood for high risk leukemia, bone marrow failure syndromes (for example, Fanconi anemia), immunodeficiency states, and inborn errors of metabolism. A coordinating center will manage donor searches, facilitate the distribution of cord blood units for transplantation, and collect and analyze data from this research. Several Institutes at NIH will continue to support related research, which will help continue and extend the excellent progress that is taking place.

Item

Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) - The House in its report (pg. 71) stated -- "The Committee encourages NIAID to support extramural grants focused on investigations which seek to identify the etiological agent(s) and

markers for, and the pathophysiology of, chronic fatigue and immune dysfunction syndrome (CFIDS)."

Action Taken or To Be Taken

The NIAID continues to support intramural and extramural efforts into the causes and most effective treatments for Chronic Fatigue Syndrome (CFS). Recently, in collaboration with eight other NIH Institutes and Centers, NIAID released a program announcement titled "CFS Pathophysiology," that is designed to lead to an improved understanding of the mechanisms CFS pathogenesis.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Significant Items in the House and Senate Appropriations Committee Reports

FY 1997 Senate Appropriations Report (104-368)

Item

Liver Disease - The Senate in its report (pg. 88), stated -- "The Committee is pleased that NIAID and NIDDK will sponsor a consensus development conference on chronic hepatitis C in 1997 and urges the involvement of other NIH institutes, as appropriate. In view of the rapid growth of hepatitis C, the Committee urges hepatitis C to be made a research priority as an emerging infectious disease and that NIAID give consideration to supporting additional hepatitis C cooperative research centers."

Action Taken or To Be Taken

The NIAID and the NIDDK will co-sponsor a consensus conference in 1997 focusing on chronic hepatitis C. Recently, the NIAID awarded four new research grants focusing on hepatitis C. One of these awards was co-funded with the NIDDK. These projects are designed as multidisciplinary, collaborative research units each focused on the prevention and treatment of hepatitis C viral infection. In addition, NIAID has recently issued two program announcements, "Enteric and Hepatic Infectious Diseases: Research Needs" and "Expanded Research on Emerging Diseases," with the goal of further enhancing the Institute's hepatitis C portfolio.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
			>	$589,391,000	>	$614,322,000
National Institute of Allergy and Infectious Diseases	Title IV Part C, Subpart 6	42§285f et seq	Indefinite		Indefinite	
Research Regarding Tuberculosis	Section 447(b)	42§285f - 2(b)	*Such Sums* as Necessary		*Such Sums* as Necessary	
National Research Service Awards	Section 487(d)	42§288(d)	a \	19,559,000	b \	19,950,000
Total, Budget Authority				608,950,000		634,272,000

a\ Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104 - 208).

b\ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Appropriation History

Fiscal Year		Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation	1/
1989		$435,084,000 2/	$732,453,000 3/	$758,352,000	$744,152,000	
1990		442,596,000 4/	854,523,000	847,112,000	843,745,000	5/
1990	Sequester				(10,768,000)	6/
1991		886,875,000	944,965,000	904,010,000	906,251,000	
1991	Sequester				(12,000)	7/
1992		976,711,000	972,830,000	965,952,000	959,914,000	8/
1993		1,010,845,000	990,055,000	989,055,000	979,471,000	
1994		1,065,583,000 9/	1,065,583,000 10/	1,065,583,000 10/	1,063,704,000	10/
1995		542,864,000	535,847,000	535,847,000	535,847,000	
1995	Rescission				(648,000)	
1996		557,354,000 9/	1,169,628,000	549,246,000 9/	1,169,628,000	
1996	Rescission				(676,000)	
1997		584,362,000 9/	1,256,149,000	595,016,000 9/	1,256,659,000	11/
1998		634,272,000				

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ The 1989 request excludes funds for AIDS research ($310,268,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
3/ Excludes $13,537,000 in NRSA training programs not considered.
4/ The 1990 request excludes funds for the National HIV program ($400,116,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
5/ Excludes enacted administrative reductions of $2,573,000.
6/ Excludes enacted administrative reductions of $26,986,000.
7/ Excludes enacted administrative reductions of $11,197,000.
8/ Excludes enacted administrative reductions of $12,334,000.
9/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research.
10/ Excludes enacted administrative reductions of $569,000.
11/ Excludes enacted administrative reductions of $575,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	150	150	150
Division of Intramural Research	579	579	579
Division of Extramural Activities	92	92	92
Division of Allergy, Immunology, and Transplantation	16	16	16
Division of Acquired Immunodeficiency Syndrome	117	117	117
Division of Microbiology and Infectious Diseases	52	52	52
Total, NIAID	1,006	1,006	1,006

	Average GS/GM Grade
1993	10.5
1994	10.7
1995	10.7
1996	10.8
1997	10.8
1998	10.8

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	1	1	1
ES-5	4	4	4
ES-4	5	5	5
ES-3	3	3	3
ES-2	0	0	0
Subtotal	13	13	13
Total - ES Salary	$1,430,000	$1,493,000	$1,559,000
GS/GM-15	109	109	109
GS/GM-14	102	102	102
GS/GM-13	85	85	85
GS-12	116	116	116
GS-11	119	119	119
GS-10	1	1	1
GS-9	67	67	67
GS-8	26	26	26
GS-7	76	76	76
GS-6	44	44	44
GS-5	15	15	15
GS-4	23	23	23
GS-3	4	4	4
GS-2	8	8	8
GS-1	7	7	7
Subtotal	802	802	802
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	28	28	28
Senior Grade	12	12	12
Full Grade	25	25	25
Senior Assistant Grade	2	2	2
Subtotal	67	67	67
Ungraded	177	177	177
Total permanent positions	826	826	826
Total positions, end of year	1,059	1,059	1,059
Total full-time equivalent (FTE) employment,end of year	1,006	1,006	1,006
Average ES level	4	4	4
Average ES salary	$110,000	$114,000	$119,000
Average GS/GM grade	10.8	10.8	10.8
Average GS/GM salary	$48,000	$50,000	$52,000

THURSDAY, FEBRUARY 27, 1997.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

WITNESSES

KENNETH OLDEN, PH.D., DIRECTOR
SAMUEL H. WILSON, M.D., DEPUTY DIRECTOR
CHARLES E. LEASURE, JR., ASSOCIATE DIRECTOR FOR MANAGEMENT
LAURIE JOHNSON, BUDGET OFFICER
HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH
BILL BELDON, [DIVISION DIRECTOR, OFFICE OF DEPUTY ASSISTANT SECRETARY] BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We're pleased to welcome Dr. Kenneth Olden, the Director of the National Institute of Environmental Health Sciences, for his testimony. Dr. Olden, would you introduce the people who are with you and then proceed.

INTRODUCTION OF WITNESSES

Dr. OLDEN. To my far left is Ms. Laurie Johnson. She's Director of the Budget Office. The Deputy Director, Dr. Sam Wilson; Mr. Charles Leasure, and you know Dr. Varmus, and Mr. Bill Beldon is on the end representing the Department.

OPENING STATEMENT

Mr. Chairman and members of the committee, I welcome the opportunity to appear before you today to discuss the important work of the National Institute of Environmental Health Sciences. The development of environmental regulatory policy is one of the most problematic areas of Congressional responsibility. This is a problem area, because there's too little scientifically sound information on which to base decisions.

When there is too little information, there can be no satisfactory solution to the complex issues surrounding human exposure to environmental pollutants and health outcomes. In my testimony today, I want to outline a vision for environmental health science research that will transform environmental health decision making. A vision based on four critical areas of science. Areas where major information gaps exist, areas where reasonable research questions can be formulated, areas where technologies are available, and areas where understanding offers the potential to significantly improve public health and regulatory policy.

First, research is urgently needed to determine the basis for the wide variation and individual responsiveness to exposures to envi-

ronmental toxicants. To address this problem, NIEHS proposes to expand its molecular genetics research to identify susceptibility genes for environmentally induced diseases through a new Environmental Genome Project. This genome project will be a broad multi-center effort to obtain information about DNA sequence diversity for the U.S. population on all the environmental susceptibility genes identified to date.

Second, there is an urgent need to develop new approaches for toxicological testing, to cut costs and to increase timeliness. If we are going to work our way through the thousands of chemicals to which humans are exposed, we must develop bold new screening strategies. Technologies are now available to develop new high through-put technologies to screen that are less costly and more relevant to predicting human health. And they should be more timely in terms of generating the information. Identification of carcinogens and other toxicants can be reduced from years to days.

Third, investigation of the mechanism of the health effects of mixtures is another area where lack of scientific information is a problem. The current toxicologic data bases were developed using single chemicals in animal bioassays. As we all know, humans are exposed to a variety of chemicals in the form of mixtures. Depending on the assumptions made regarding the nature of the interaction between components of the mixture, risks may be either seriously over or under estimated with dire economic and public health consequences. NIEHS proposes to develop high through-put biologically based screening procedures to address this problem.

And lastly, a major challenge is to strengthen the links between environmental science, toxicology, epidemiology and public health. To achieve this objective, NIEHS proposes to monitor human exposure to specific chemicals in our environment by measurements in body tissues such as blood and urine. Such real world exposure assessment would be far more useful than the estimation of exposure based on the EPA toxic release and production information as is currently done. Estimation of exposure based on toxic release and production information is at best only a reflection of the potential for human exposure.

In conclusion, progress in the four areas of research emphasized offers real world answers to the quagmire of indecision and discontent as a consequence of having too little information. Our vision of a more science-based environmental health regulatory decision system is achievable, given today's technology. The President's budget request for NIEHS is $313,583,000. I would be happy to answer any questions that you might have.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Environmental Health Sciences

Mr. Chairman and Members of the Committee, I am pleased to appear before you today to discuss the important work of the National Institute of Environmental Health Sciences.

Virtually all diseases have both a genetic and an environmental component. Thus both environmental health research and human genome research are vital for fulfilling the public health mission of this Nation.

The opportunity to make a difference in the environmental health sciences has never been greater. The discipline has undergone a rapid transition and, coupled with advances made in genetic research, we are nearing a breakthrough in the "bottleneck" currently encountered when we try to identify environmental hazards that contribute to human illness. We are now poised to make enormous progress to prevent, diagnose, and treat the environmental components of diseases. Although we cannot yet say which environmental or genetic factor is the most important contributor to a specific disease, nor which individual is most likely to develop a particular disease, that day is not far off. When that day arrives, policy makers can more rationally determine the best, most cost-efficient ways to protect public health without unnecessarily sacrificing economic vitality.

Efforts to control environmentally-caused illness must be based on the understanding of human-environment interaction at the molecular level. Many of the common diseases such as cancer, Alzheimer's, Parkinson's, osteoporosis, and asthma appear to arise from the complex interplay between inherited genetic alterations and the environment. So, before we can prevent or improve the treatment of such diseases, we need a better understanding of the individual function of genes involved in the growth and development of humans and the ability of environmental agents to interact with, and damage, these genes.

In considering future research needs and opportunities, we have focused on areas of fundamental knowledge and practical issues relevant to understanding the role of the environment in the etiology of human illness. The areas of emphasis represent issues where major information gaps exist, where reasonable research questions can be formulated, where technologies are available, and where understanding offers the potential to significantly improve public health and regulatory policy.

Today, I would like to talk about some of the critical research needs and plans for the upcoming year.

First, we need to continue our effort to develop new and better carcinogenicity and toxicity test systems. While we have greatly improved test methods, they are still too costly and too time consuming for use in screening the thousands of natural and synthetic environmental chemicals requiring toxicity assessment. Opportunities now exist to develop alternative testing methods by incorporating knowledge of molecular and cellular mechanisms associated with the toxic or carcinogenic process.

Second, environmental health research can also capitalize on recent developments in molecular and cell biology to develop a mechanistic understanding of the toxic action of environmental agents. Under this scheme the actual biological events that lead to toxicity will be determined. Insights into molecular mechanisms of diseases will: 1) provide a more rational basis for assessing human risk based on data obtained in animals; 2) suggest new laboratory procedures for use in epidemiologic studies to more precisely identify the causes of human illnesses; 3) increase understanding of the wide person-to-person variation in risk to disease; and 4) provide the basis to develop molecular medicine strategies to prevent, detect, and treat various diseases.

Third, knowledge of mechanisms is also a prerequisite for prevention/ intervention using molecular medicine approaches. The field of environmental toxicology has historically limited its prevention efforts to eliminating or reducing environmental exposures. While this remains the most pragmatic approach, elimination or reduction of environmental exposures is not possible in some cases because the causative agent cannot be readily controlled. Although much progress is being made in the laboratory in defining the environmental basis of disease and dysfunctions, this knowledge and technology is not being effectively translated into the practice of medicine. The recent creation of the clinical program within the NIEHS underscored the importance of translating discoveries made in the laboratory to benefit individuals and populations in terms of improved health status and reduced health care costs.

Fourth, research is needed to determine the genetic, behavioral, and developmental basis for the wide variation in individual responsiveness to exposures to environmental toxicants. There are indications that differences in responsiveness can be related to age, gender, lifestyle, or genetic predisposition. These differences could be important for human risk assessment.

NIEHS proposes to greatly expand its molecular genetics research on susceptibility genes for environmentally-induced diseases through a new Environmental Genome Project. This genome project, which makes use of technology developed by the human genome research efforts, will acquire a population database on the sequence diversity for the environmental disease susceptibility genes.

Genetic approaches used in the past have identified many susceptibility genes for environmental diseases. An individual with a defect in such a gene has an elevated risk of becoming ill after an environmental exposure. The molecular mechanisms of

susceptibility are not well understood; however, we are now able to categorize many of the susceptibility genes into five broad classes: Genes controlling the distribution and metabolism of toxicants; genes for the DNA repair pathways; genes for the cell cycle control system; genes for metabolism of nucleic acid precursors; and genes for signal transduction systems controlling expression of the genes in the other classes. The NIEHS Environmental Genome Project will be a broad, multi-center effort to obtain information about DNA sequence diversity for the U.S. population on all of the environmental disease susceptibility genes now recognized, which number greater than 200. The Project will be expanded as additional susceptibility genes are discovered.

The availability of a population database on environmental disease gene diversity will allow us to conduct more focused molecular epidemiology that relates environmental exposures and disease to individual susceptibility genotype. Ultimately, information from such medical genetic epidemiology will allow us to greatly enhance public health through better prevention strategies for environmental diseases.

The Environmental Genome Project will provide information for future research on molecular mechanisms of susceptibility gene products. The project will also foster development of new high, through-put technology for the application of genetics in medical epidemiology as a function of environmental exposure.

Fifth, investigation of the mechanisms and health effects of mixtures is another area where lack of information is a serious problem. The data on exposure and toxicology of mixtures is inadequate for assessing health risk. The current toxicologic databases were developed using single chemicals in animal bioassays, whereas humans are exposed at a variety of levels to large numbers of chemicals either concurrently or sequentially via multiple pathways. Mixtures of chemicals are ubiquitous in ground and surface water, and in air, food and soil. For example, 700 organic chemicals have been identified in the drinking water supply of the U.S., 40 of which are possible carcinogens; 320 toxic industrial chemicals are released into ambient air, of which 60 are possible carcinogens; and approximately 380 pesticides are applied to food sources, 66 of which have been identified as actual or potential carcinogens. Furthermore, the problem of mixtures is not limited to chemical interactions since health outcome may also be influenced by physical or biological agents. For example, risk of radon-induced lung cancer is increased in cigarette smokers and people infected with hepatitis B virus are more susceptible to aflatoxin-induced liver cancer. Thus, our inability to say whether agents act in an additive, synergistic, or antagonistic fashion creates real problems in health risk assessment.

Sixth, research is needed to develop methods for screening environmental pollutants and natural products for endocrine-disrupting effects and for assessing the health effects of these exposures. Although the possibility for human health effects of these hormonally-active agents remains hypothetical, their pervasiveness and persistence in the environment make this an area of significant public health concern. These

chemicals can potentially alter the balance of physiological systems whose coordination is controlled by delicately balanced neuroendocrine mechanisms.

Animal studies have demonstrated that exposure of the fetus to endocrine-disrupting chemicals can profoundly disturb organ development. Field studies have shown an association between exposure to endocrine-disrupting chemicals in the environment and developmental anomalies in fish, birds, reptiles and other wildlife species. These anomalies include feminization of male fish, birds and mammals; decrease in reproductive potential, and under-developed genitalia. Human exposure to synthetic estrogen (e.g., diethylstilbestrol) during early development caused reproductive organ dysfunction, abnormal pregnancies, cancers of the reproductive tract, and decreased fertility in females.

Given the large numbers of hormonally-active chemicals released into the environment over the past 50 years, more research is needed concerning the health consequences associated with chronic exposure to low doses of mixtures of endocrine-disrupting chemicals during the various stages of development. Exposure during the development of the embryo, fetus, and neonates is of particular concern because the consequences may be both more striking and permanent.

Lastly, a major challenge is to strengthen the links between fundamental science, toxicology, epidemiology, and risk assessment. To make environmental health research findings more applicable to human risk assessment, monitoring of human exposure to specific chemicals must be undertaken using improved and highly sensitive analytical procedures. NIEHS-supported scientists continue to generate novel and innovative biomarkers of environmental exposure that could be incorporated into a national survey to assess to what extent people absorb or retain the chemicals in their environment. This more "real world" assessment would greatly strengthen our capability to conduct risk assessment policy that reflects actual, rather than putative, exposures. To be most useful, this survey would include information concerning the nature of the exposure, estimated numbers of persons exposed, and demographic information such as age, gender, socioeconomic status, race or ethnicity, and geographic region.

In summary, environmental health policy decisions are only as good as the scientific foundation upon which they are founded; that is, the data and models used in assessing the risk, and the assumptions made in the absence of facts. The guiding principal should be good science for good decisions. Health risk assessment policy decisions affect millions of lives and involve hundreds of billions of dollars. Such an investment is worth doing and worth doing well.

The budget request for FY1998 is $313,583,00. I would be pleased to answer any questions.

FUNDING INCREASE

Mr. PORTER. Dr. Olden, thank you for your excellent statement.

I notice that the rate of increase for your institute is higher than the rate of increase for NIH generally. I assume you think that is a very good sign.

Dr. OLDEN. I'm very pleased with that.

Mr. PORTER. My question is, does this reflect expenditures on the new screening procedures that you described in your testimony, or is this apart from that?

Dr. OLDEN. Well, if I may go back a bit, it probably reflects a number of things. And certainly the resources that we are requesting will at least in part be used to address the new issues. And these are new issues for NIEHS. And we think they are extremely important. I think we've convinced Dr. Varmus that these are important new initiatives and I guess that's at least one of the explanations for why we are enjoying a good budget increase recommendation.

But let me say, over the years, the Institute has not fared as well as some of the other institutes. So in fact, maybe it's at least in part a recognition on Dr. Varmus' part of the important public health problems that this Institute must address. Other institutes have important problems as well, but the point is, to deal with these issues I just mentioned. It creates problems for Congress in making decisions about what is the appropriate standard. I think we have to do the science in order to answer these questions to put risk assessment on a solid scientific foundation.

Mr. PORTER. Dr. Varmus, would you like to comment also?

Dr. VARMUS. Just briefly, since we've been talking about priority setting. The fact that one institute happens to be a half percent or a quarter percent or even 1 percent above some of the others, does not represent an evaluation of that institute or an attempt to remedy what may be perceived as past inequities. Because almost every institute feels it's been penalized at some point in the past.

It represents a decision by me and my colleagues to place money on initiatives which are frequently trans-institute in nature. And what I try to avoid is getting into a discussion of the pecking order of institutes based on hundredths of a percentage point difference and instead, look to support new initiatives, of which the NIH has many good ones this year. And that may account for NIEHS being slightly above the others.

Mr. PORTER. Yes, sir. My question was, does this reflect the cost of the new screening procedures? I wasn't suggesting anything different at all. And I simply wanted to know whether that was included in this budget figure, which obviously is a high priority.

Dr. OLDEN. Yes, absolutely. The Environmental Genome Project is a high priority. And we will make the investment with it in 1998.

Mr. PORTER. And you didn't skirt around Dr. Varmus and talk to the President directly to get this?

Dr. OLDEN. No, we did not. [Laughter.]

VITAMIN D AND PROSTATE CANCER

Mr. PORTER. Last December, researchers at your Institute reported that men with a particular vitamin D receptor appeared to have only a third the risk of developing prostate cancer requiring surgery. How does vitamin D play a role in prostate cancer?

Dr. OLDEN. Well, vitamin D is protective. And that's been known for some time. And what the investigator at NIEHS demonstrated was that, depending on the level of activity, whether the receptor was active or inactive, it increased the susceptibility to prostate cancer. In other words, if one had an inactive receptor, then the protective effect was not observed.

Mr. PORTER. No matter how much vitamin D you might absorb or take?

Dr. OLDEN. Exactly. It could not be metabolized. So this is an example of the kind of research that I had in mind when I talked about looking at differences in susceptibility. And that's just one of them.

MIXTURES

Mr. PORTER. In January, NIEHS scientists reported that three existing tests used in combination provide a rapid assessment of whether chemicals have estrogen-like qualities. This topic of environmental estrogens has been hotly debated in the past year. What can these new tests contribute to the debate that was unavailable previously?

Dr. OLDEN. Well, that gets at the issue of mixtures. And I said, we don't know whether agents in mixtures—estrogens or otherwise—act additively, synergistically or even antagonistically. In the papers that were reported by scientists who used to work at NIEHS, but did not at the time we reported those studies, it was determined that estrogens, in the particular yeast assay systems that they used, acted synergistically. In other words, the response together was elevated by more than a thousand-fold.

Potentially, that was very significant. Because of the threat that even low level exposures to a mixture of estrogens could be a significant health effect. Last year, I testified before this committee that my impression was that the low level exposures to synthetic or man-made chemicals would probably be dwarfed by exposures to natural estrogens, and that my opinion was that man-made chemicals probably did not represent a health threat.

But if their observations were found to be correct, then that would be a very significant and important finding. However, I must point out that a number of other investigators, using different yeast systems, have been unable to repeat that observation in other systems. We are bringing all of the investigators together at our Institute in the near future to try to resolve the differences in the observations between the one laboratory and many others who were unable to get the same results. But admittedly, in different yeast systems.

So I guess the answer is, we don't know what it means. Because that may be simply a unique or artifactual observation for that one system.

ENDOCRINE DISRUPTORS

Mr. PORTER. The Environmental Protection Agency by statute is required to evaluate the risk of chemicals to the endocrine system. In addition, EPA is funding a two-year National Academy of Sciences study on the health impact of synthetic and natural substances that have estrogen-like effects. Has EPA taken the lead role in this area of science, and how does your research on endocrine disruptors mesh with their research portfolio?

Dr. OLDEN. Well, EPA has not taken the lead role. We've been involved in this research area for over 20 years. What EPA is doing mainly is two things. Most of their estrogen-related research is directed towards ecology, for one. And the other is to develop risk assessment methodologies. Our research is coordinated at two levels, or at two official and formal levels. First is through the Environmental Health Policy Committee of the Department of Health and Human Services, which is chaired by the Assistant Secretary. In fact, we met on Tuesday of this week with the Assistant Secretary, EPA, to discuss the Government estrogen-related research.

So it is coordinated through the Environmental Health Policy Committee. It is also coordinated through the CENR, which is the Committee for Environment and Natural Resources of OSTP. There is a subcommittee of CENR that deals specifically with estrogens. And we co-chair that subcommittee with EPA and the Department of Interior. And again, the purpose of the subcommittee is to coordinate estrogen research across the Federal Government. We've done an inventory of the research in the Federal Government, so it is closely coordinated formally through those two committees.

Now, when EPA recently funded their estrogen grants, they consulted with us to make certain that they were not funding research that we were already funding. In some cases we agreed that we had not funded adequate research because of limitation of resources. And they are co-funding some projects with us as a consequence of that consultation.

So the research is very closely coordinated, not to mention that the Health Effects Laboratory is right down the street from NIEHS in Research Triangle Park. And so there is also informal interaction to make certain that there is synergy between the two programs.

CONGRESSIONAL VISIT

Mr. PORTER. Speaking of Raleigh-Durham, we are attempting, as you are aware, Dr. Olden, to get our subcommittee, as many members as can do so, to come down and visit you. Because you're off there by yourself and we want to have a chance to see what you're doing. And if the other facilities are nearby, maybe that would work out very well.

Dr. OLDEN. Thank you very much. We are looking forward to your visit.

Mr. PORTER. Both of us have to talk to Dr. Varmus about this.

Dr. OLDEN. Dr. Varmus has been down recently, and we enjoyed having him.

NEW TESTING METHODOLOGIES

Mr. PORTER. Tell us more about your Beat the Mouse experiment in which researchers are testing alternative methods to predict whether 30 chemicals cause cancer before the results are available from a series of standard rodent tests. Has anyone crossed the finish line yet?

Dr. OLDEN. No, but they will, the results will be reported out soon. In our November meeting of our advisory committee, the results will be revealed, and we'll see. We are anticipating that we will have at least 30 chemicals that have been tested through the traditional classical two-year rodent bioassay and have also been tested through our transgenic animal models in a period of six months at a reduced cost. And we are hopeful that the results will demonstrate that the transgenic animal models are just as effective in identifying carcinogens, both genotoxic and non-genotoxic, as the two-year rodent bioassay.

Mr. PORTER. Assuming that's true, how many increased chemicals can you test in, let's say, a year, with this faster procedure, if that's factual?

Dr. OLDEN. Well, we haven't, I can't tell you what the costs for the transgenics are exactly. We are testing about 10 in the rodent bioassay now. We think with the same dollars, we could test about 40 new ones.

Mr. PORTER. Four times as many?

Dr. OLDEN. That's what we think. Now, let me say that the tests that I just described in my testimony, the high through-put technologies, we are very excited about those. We've had discussions with people in pharmaceutical industries. The technologies are available so that we should be able to screen, if we make the investment into the technologies, we should be able to screen a hundred or more chemicals per year for the same dollars. So it's mind-boggling, what the potentials are. It is simply the fact that we've never made the commitment to develop these new tests. And we are excited about them.

During my tenure as Director of the Institute, I am confident that I can come back here and report exciting results about these new tests. And we've consulted people in the scientific community, and they are eager and excited, and tell us that these things can be done. But for the first time, we will be asking them to do them.

ENVIRONMENTAL GENOME PROJECT

Mr. PORTER. Before I call on Mrs. Lowey, I wonder if you would explain to us more about the environmental genome project that you mentioned in your testimony.

Dr. OLDEN. I present it to you somewhat prematurely, let me say that. I have had brief preliminary discussions with Dr. Varmus. This is in a sense a trans–NIH effort. And what we are going to do, as a matter of fact, is we have a date I think some time in March, to meet with Dr. Varmus, Dr. Collins and Dr. Klausner, and some other staff to talk about this project. We are confident that it doesn't overlap activities going on in the Human Genome Project or in NCI. But we want to make certain of that. We think there is synergy between the two projects.

The Human Genome Project is identifying disease genes, but not the ones that interact and are affected, influenced by, the environment. In our case, an individual could inherit an environmental susceptibility gene and not have a disease at all. In fact, the only way that that person would be at increased risk would be in a certain or specific environment, that is, when exposed to a specific environmental agent.

For example, recently one of our investigators demonstrated that individuals who have either none or very low levels of a detoxifying enzyme called glutathionine-s-transferase, cannot detoxify certain toxic chemicals. Those individuals then are at increased risk. But they are only at increased risk if they are exposed to the chemicals that glutathionine-s-transferase detoxifies.

We also reported that one of our grantees recently reported that individuals differ in their susceptibility to organophosphate. We were interested in it and reported it to you because it's a component of nerve gas, Sarin. It is also a component of a lot of pesticides. One of our grantees demonstrated that there is an enzyme that detoxifies the lethal form of the organophosphate pesticides. And individuals who have a defect in that enzyme are more susceptible to nerve gas, because the organophosphates nerve gases inhibit choline esterase. So they inhibit nerve transmission.

So these are the kinds of genes, that we will go after. There's roughly 200 identified to date. What we will try to do is sequence those 200 or so genes and ask what is the variability in the population, and can that account for the differences in susceptibility.

Now, when we have that kind of information in hand, then we can begin to protect people based on individual differences in susceptibility, not on the basis of an average person to an average exposure. The absence of that information really creates a problem for risk assessment. That information is being obtained now at a slower rate. We want to enhance the rate at which we do that. And make that a major initiative. I would say the four things that I've presented here, even though I've presented seven or eight in my written submission, the four things that I've presented here will revolutionize environmental health decision making. And those are the Institute's and my top priorities. And these are things that I would like to be the legacy for my tenure as Director of the Institute.

Mr. PORTER. Dr. Olden, I can see how you convinced Dr. Varmus. [Laughter.]

Dr. OLDEN. Thank you.

LINK BETWEEN SCIENCE AND PUBLIC HEALTH

Mr. PORTER. Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman.

And I do apologize, Dr. Olden, as you know, with our schedules, it's hard to be in three places at the same time.

But I want to assure you that I am extremely interested in the work of your Institute. And I think there is rising concern and rising interest in almost every area of the country about the impacts of the environment on health. And we're all struggling to gain additional knowledge about the impact of the environment on the health of women, children, families.

I have had scientists come to me and express concern about the research that is being done involving human subjects versus research on animal subjects. Research in the lab versus beast research on actual populations. Could you discuss this with me and your view of this and the dollars that are being spent?

Dr. OLDEN. In my opening statement——

Mrs. LOWEY. And I do apologize if I missed it.

Dr. OLDEN. I said there are four priorities. And one of those is creating the linkage between basic laboratory science, epidemiology, toxicology and public health. We're very much concerned that the science that we do is linked to public health. Now, at least three or maybe all four of the projects I talked about are population based studies.

For example, I talked about exposure assessment. Now, we propose to do the exposure assessment with EPA and CDC. And we already have a pilot study going now with CDC. And what we really need to know is exactly, of all the chemicals in the universe, in the U.S., which ones should we really be worried about. And the way to make that determination is to decide exactly which ones are we taking up in our bodies. Which chemicals are humans actually exposed to. Not based on some potential. But really exposed to.

And we can do this by taking samples of blood, of urine. And we can find and identify, either by biomarkers or chemical markers, and we can come back in a matter of years and say to the American people, these are the 40 or so chemicals out of the thousands or so that we really should be worried about. Because these are the ones that people are indeed being exposed to.

That's a public health initiative. That's why we're involving CDC. We already are funding such studies. The money's been transferred to CDC to do this for us. Because they have the technologies. And we want to expand that effort.

The Environmental Genome Project is population based. And we will sample maybe 10 different populations, maybe 100 individuals. And again, we will have information that's relevant to public health. So we are doing that.

But in addition, we have some human studies. We have a study that I discussed here before, looking at developing a treatment for lead poisoning in the range of 20 to 45 micrograms per deciliter of blood, a project devoted to children. We also have a project that we're funding, that is being conducted in China, to look to see if we can use the biomarker of oltipraz as an agent that we've demonstrated from basic research that will prevent aflatoxin-induced liver cancer.

Well, now we have a trial going on in China to see if we can indeed prevent the formation of an adduct between aflatoxin and albumen in the blood. And what we've demonstrated, at least preliminarily, is that if we treat individuals with oltipraz that indeed we prevent the formation of aflatoxin albumen adducts. And that's an intermediate bit of information to say that we can prevent aflatoxin-induced liver cancer. And that's the next phase of the study.

So we are supporting human studies. But I think all of our, at least my four priority areas, are oriented toward public health.

ENDOCRINE DISRUPTORS

Mrs. LOWEY. Thank you. And I also know that NIEHS has been a pioneer in conducting research on the health effects of endocrine disruptors.

Dr. OLDEN. Yes.

Mrs. LOWEY. And I'd like to know how your agency is coordinating its research with other Federal agencies, particularly in light of these new directives, and what is your best estimate of how long it will be until we have definitive answers about the threat to public health posed by endocrine disruptors?

Dr. OLDEN. Well, I am personally spending a lot of time talking with everybody who's concerned and has research programs dealing with environmental endocrine disruptors, not only estrogens, but other hormone mimics. We have collaborations with EPA, I mentioned earlier, we are co-funding projects with EPA. Every three months, we meet in the Department to talk about the research going on in the Federal Government, not just in the Department, because EPA, Agriculture and other departments participate, to make sure that we are indeed coordinating the research. It's coordinated also through the Committee for Environment and Natural Resources.

I have also reached out to industry. I have met with chemical manufacturing industries that are responsible for making many of these estrogens. And we believe that we are going to be able to develop a partnership with the chemical manufacturing industry to pursue the research to make certain that we leverage our dollars which you provide us to have an impact that's much larger than the amount of money that we're devoting to this project.

So we are in touch with and coordinating our research efforts with everybody, not only other Federal agencies, but with private industry, because private industry, the ones that make more than 95 percent of all the estrogenic-like chemicals in the United States, are represented through the chemical manufacturing industry.

COLLABORATION WITH INDUSTRY

Mrs. LOWEY. I'm delighted you brought that up. Because recently, I attended a conference, and one of the participants was a representative from DuPont. And I'm aware of the fact that they've invested quite a bit of money and done a good deal of research, because they understand it's in their own interests.

Dr. OLDEN. Right. And we had discussions with them about that at the outset. And they are part of the chemical manufacturing industry.

Mrs. LOWEY. Actually, if the Chairman would approve, I wonder if you can enlighten us as to cooperation from other corporations. I mean, they are spending enormous amounts of money, making enormous profits, and to what extent are they investing in this kind of research, as DuPont seems to be doing?

Dr. OLDEN. Significantly. The project that I mentioned about developing the transgenic animal models, new alternative models that are faster and cheaper, well, that project is an industry–Government collaboration. There are 35 industry groups participating

in the partnership. EPA is participating, and FDA and the NIH. So this is indeed a Government-industry partnership.

Now, we got everybody to the table because when I first became Director, I went around and met with the industry, DuPont, Dow Chemical, Proctor and Gamble, and I discovered that they have exactly the same problems that we have in the National Toxicology Program. They need models that are faster and cheaper, because they have to provide information to EPA, FDA and regulatory agencies to get their products approved.

So we then convinced them that it was in their best interests for all of us to pool our intellectual and economic resources to address these problems collectively. We have now had several meetings. We meet regularly in Research Triangle Park, around the table just like this, and we discuss these issues. We decided together what body of science was necessary to convince the American people that indeed, these new models are valid. In other words, will they identify a carcinogen? And that's what we're focusing on at the present time, just carcinogens.

And they were eager to do this, because if these tests cost the Government $2 million to $6 million per chemical, it costs them the same amount of money. So they are interested in the same issues we are, saving money and saving time and getting products to the market sooner. So we have that partnership, and we are very proud of that.

Mrs. LOWEY. Well, thank you very much. In light of budget realities, I would encourage you to continue to encourage the private sector to continue to invest in these areas.

Dr. OLDEN. We are.

Mrs. LOWEY. I thank you.

Dr. OLDEN. Thank you very much.

GULF WAR SYNDROME

Mr. PORTER. Thank you, Mrs. Lowey.

Dr. Olden, has your Institute been involved in any of the ongoing evaluations of whether there is a true Gulf War Syndrome? We seem to be caught between the President's panel, which doubts its existence, and a series of studies published in January in the *Journal of the American Medical Association,* which assert that the syndrome is real.

What's your personal assessment of the available evidence?

Dr. OLDEN. Well, Mr. Porter, actually I had it in my opening statement, but it would have made it a bit too long, so I cut it out. I simply was going to say that the Gulf War veterans' illness is a prime example of what I said, of having too little information to make a decision. And that's the problem. It's a problem for you, it's a problem for the American people. And in this case, there's too little information about multiple chemical sensitivity, or chronic fatigue syndrome, or fibromyalgia, and those three at least probably have some similarities in terms of underlying mechanism.

There's too little information about susceptibility. Again, from what I read in the newspapers, and it was just in the newspapers today, that some of the veterans were indeed exposed to Sarin. Sarin is a nerve gas. We know what the components are, organophosphates. We know that if you expose 10,000 people, there

are going to be ranges of susceptibility. Some are going to be susceptible and others aren't. And we understand now why that is the case.

So there's too little information about susceptibility, and there is also too little information about mixtures. Clearly, from what I read in the newspaper, indeed the veterans were exposed to mixtures. There were pesticides. And pesticides often contain as many as 100 different chemical components. There was possibly the nerve gas exposures also.

So I would say, Mr. Porter, there's too little information about multiple chemical sensitivity. There is too little information about mixtures. And there's too little information about differences in susceptibility for us to ever figure out what happened. And what we need to do, and my recommendation has been, when we've had these discussions on one occasion in the Department, is that we do what I've asked be done here, and that is, let's focus on doing the science to answer the basic fundamental questions that we need to do intelligent human risk assessment, irrespective of whether there is a war here or there. Because the American people have the same kinds of exposure. They are exposed to mixtures. We don't know about differences in susceptibility. We have the same kinds of problems. If we had solved these problems for civilians, then we would not be in this quagmire about what to do about the Gulf War.

So, I don't think we'll have a satisfactory solution, because there's inadequate science.

Mr. PORTER. It kind of indicates a problem, perhaps, also with our legal system. Because let's assume this was not a Government, but a private party, and the burden of proof would be on the plaintiff to prove that this was a cause and effect. And what you're telling me is, in a situation like this, it's probably impossible to prove.

Dr. OLDEN. That's what I think.

Mr. PORTER. Yes. And that means that maybe we need some method apart from the traditional methods to compensate people who are injured, and not worry about the cause of the injury or even the causor of the injury. A total aside.

Dr. OLDEN. Right.

ARTIFICIAL SWEETENERS

Mr. PORTER. At the time of its initial approval concerns were expressed by some about the safety of the artificial sweetener, aspartame, and its possible links to brain cancers. In the intervening years, has your Institute or anyone else supported research providing further answers to this question?

Dr. OLDEN. Aspartame has been nominated for testing on several occasions. We've discussed the nominations with FDA on each occasion, once during my tenure. And we will discuss them with FDA officials, tomorrow. I have a 10:00 o'clock meeting tomorrow to discuss aspartame again.

And the reason that we keep coming back to aspartame is, first of all, and there are other sweeteners among these——

Mr. PORTER. That's my next question.

Dr. OLDEN. There is increased usage in terms of sweeteners in sodas, for example. We're very much concerned about increased exposure for children, in one example.

Also, aspartame was tested in the early 1970s when test standards and methodologies were very different from what they are today. And although we've reviewed that data critically, we don't see anything flawed about it. But we have to admit if it was tested today, it may test differently, in other words, positive.

But there is a problem, and I understand FDA's reluctance to go back and test any chemical that we tested 20 years ago. The reluctance is, once you open that can of worms, that's a slippery slope. Because there are a lot of chemical agents that are in the marketplace that were tested using 1970s technologies and standards. So why single out aspartame and other sweeteners? Are we going to get petitions to test all the others? We believe, the American people are very concerned about sweeteners, there is tremendous exposure and increased usage in sodas and other things that children are exposed to recently.

So we are concerned about it. We are going to express our concerns to FDA tomorrow morning, as we have done in the past. And based on that discussion, we will decide whether we want to reevaluate aspartame in a two-year rodent bioassay.

Mr. PORTER. Being a major user of the product, I think you should do that. [Laughter.]

Dr. OLDEN. Well, that's what we hear. NutraSweet, is the trade name, commercial name.

Mr. PORTER. A new artificial sweetener already used in Canada called Sunett is being considered for approval in this country for soft drinks, and again, safety concerns are being raised about possible links to tumors. Do you plan to conduct studies on this sweetener?

Dr. OLDEN. It's included in the discussion tomorrow. There's two. And that's the other one. It's been nominated for testing and fits into the same category. Both were tested in the early 1970s. Same kind of test procedures, same problems. And we're going to discuss it with FDA tomorrow morning at 10:00 o'clock.

NANOFABRICATION

Mr. PORTER. Last year, we briefly discussed the technology of nanofabrication. Your justification indicates that this field has matured to the point of application in environmental health. Can you give us some examples of possible uses of nanofabrication in your Institute's work, and do you have any plans to support this technology?

Dr. OLDEN. Well, I must say, thanks to you, I really gave it a lot of thought and looked into it. And it is a very rapidly developing technology. It developed as a consequence of the computer industry, and informatics industry, and it is important. And it is being used now for environmental monitoring and assessment, mainly in the defense industry.

Right now, my prediction is that nanoscale tests will be developed some time in the future. Right now, the tests that I've talked about, the new tests, the fast through-put technologies, are going to be done on a microscale, not necessarily a whole animal. But we're talking about a microscale, much smaller. And I think with time, we will be doing tasks that are fast through-put on the nanoscale dimension.

So yes, I am interested. The Institute is very interested in new technologies. And we have scheduled, in fact, to bring a few people in to talk about this technology and its potential for some of these fast through-put screening tests that we want to develop. But right now, as we perceive it, we will be working at the microscale level. But in a matter of years, we will be at the nanoscale level, and the technologies will be highly relevant.

But they could also be very important for exposure assessment, individual exposure assessment. They are relevant, highly relevant, to what we do in NIEHS. And we are exploring.

CONTRACT MECHANISM

Mr. PORTER. Your budget continues to emphasize the use of the contract mechanism, 22 percent of the total compared to an NIH average of 6 percent. You have testified in previous years that you were trying to increase the share of your budget allocated to research project grants. Does that continue to be an interest for you, or have you found that the nature of your work requires you to heavily use the more directed mechanism of contracts?

Dr. OLDEN. Well, I'm clearly interested in getting more money into the grants mechanism, in part because I think we buy better science. So that's the motivation.

During my tenure, we have dramatically decreased the amount of money that, dramatically may be an overstatement, sir, but we have decreased the amount of money that we spend via the contracts mechanism. For example, many of the NTP studies now we are doing on a grant mechanism. And I can just cite two.

There was the National Academy report about two to three years ago about the health effects of pesticide exposures on children. And it turns out that we just had no studies any place to address any of those issues. Most pesticide exposure experiments are done with an adult animal.

We are now doing studies involving in-utero exposure to pesticides and to estrogens. It seems that the critical time for exposures to estrogens at low levels may not be during adulthood, but may be during development. And there's lots of studies to suggest that is the case. And those studies are NTP studies that are being done via a grant mechanism, R01 grant mechanism. We advertised RFAs, we took the very best grant applications that we had and we funded those.

So that is the trend, and we will continue to do that. But in the end, for some work that we do through the National Toxicology Program we simply have to use the contract mechanism. I mean, they are kind of routine kind of screening activities that we would not get a scientist to invest time and effort to do. And you don't need a university professor to do. I mean, these are just studies that are kind of assembly line things, same activity day after day after day for two or three years.

So unfortunately, that's where we are. I can get it down, and I've gotten it down. But in the end, I won't be able to reach the NIH average.

Mr. PORTER. Thank you, Dr. Olden.

Mrs. Lowey.

ASTHMA

Mrs. LOWEY. Thank you, Mr. Chairman.

And I just have two follow-up questions. Dr. Olden, you talked about your focus on public health problems. In recent years, there has been an increased number of children being admitted to the emergency room as a result of asthma. Could you give us some insight as to the work you are doing in that regard? Especially in our cities.

Dr. OLDEN. Yes. We created one new program, and it's called the Five Cities Study, to specifically address that problem. Then we collaborated with the National Institutes of Allergy and Infectious Diseases on another project called the Inner City Asthma Project that Dr. Fauci may have described to you this morning. The Inner City Asthma Project is an effort to look at indoor allergens, cockroach dust, and dust mites on asthma in inner city children. These are kids who are mostly minority and also economically disadvantaged.

Since the Inner City Asthma Project focused on indoor air, and it is at the point now of being an intervention study, we created a new project this year called the Five Cities Study, to look at the effects of outdoor air pollution on asthma admission rates to emergency rooms. And so those are the two major projects that we initiated specifically to address those issues.

But let me say, we go way back. We have 24 city studies, the 6 city studies, and in fact, the bulk if not all of the data that's being used to debate the new EPA-proposed air standards for ozone and particulate matter in the air, that data was generated through NIEHS grant mechanisms by Doug Dockery and collaborators at Harvard. So we've been in this business a long time. And I would say have made the major contribution to that area.

RETESTING OF CHEMICALS

Mrs. LOWEY. Just one last follow-up question to the Chairman's question. If I heard correctly, you mentioned that you were concerned about retesting aspartame because there would be, I don't remember what you said, thousands, many petitions to retest other products.

Dr. OLDEN. Right.

Mrs. LOWEY. Now, what immediately came to mind were the advance in science, with all the new information, how do you make determinations on which products, which additives you should retest? If something is passed 15 years ago, there's a good deal of new information since then. How do you set your priorities and how do you make those determinations?

Dr. OLDEN. Well, that's going to be very difficult. Because even the test, the rodent bioassay that we're using today, I hope that that becomes obsolete. That's what we're working for. Everything that we're testing today will be obsolete in 20 years in terms of the test standards. And do you want to go back and test the things that we're testing today that we believe in?

So that is what we're faced with. And obviously, I can't make that decision alone. I have to have a number of people who are more expert than I to give us advice on what we should do. And

in the end, it's not only a scientific issue, it's a social issue. Do we want to make that kind of investment, because we've never tested about 80 percent of the agents—chemicals, man-made chemicals—that are in use commercially today. About 80 percent have never, ever been tested in a single assay. We've only tested about 20 percent of them.

Now, do we want to spend our money retesting or do we want to go forward and test new things that may pose a health hazard. This is a dilemma. And that is FDA's position, or it has been, and we'll find out if it still is tomorrow. And I don't have a lot to combat that. We'll present it, we have advisory councils, and I will take the discussion tomorrow back to my advisory council, and it's made up of scientists, industry people, and lay people, and we'll present it and get their input.

Mrs. LOWEY. I'd be interested in hearing more from you in that area. It certainly seems to me roughly, well, I imagine there are thousands, of chemicals and additives that are part of foods and products. And right now, you're saying that if a product's been tested 15 years ago, it's safe, it's off the agenda, is that correct?

Dr. OLDEN. I'm saying that that is a position. And do we want to go back and retest those? Because once you start that, there's an awful lot of things that we tested over the last 20 or 30 years. And the test standards and methodologies were different. The things we're testing today, we will have sophisticated, better tests 20 years from today. And so it's kind of a never-ending issue.

So I guess what we'll do is present it to our Council and we'll get a feel for how comfortable people are with data that was generated 20 years ago. The artificial sweeteners are obviously of concern, because 60 Minutes featured them in a 20 minute segment one evening about a month ago. And I get a lot of letters, and FDA gets a lot of letters about it. And the public is very concerned, as Mr. Porter said. Well, all of my friends who saw 60 Minutes immediately the next morning came to us and asked us, what are you doing, can you assure us of safety.

So these are the issues. And our council and board of advisors will have the same kind of reservation.

Mrs. LOWEY. Well, thank you. I frankly didn't watch the 60 Minutes, and I'm much more concerned today than I was yesterday as a result of your question. [Laughter.]

Mrs. LOWEY. So I certainly look forward to continuing this dialogue. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mrs. Lowey. I think there's a difference between those things that we voluntarily ingest and believe are okay and those that we might be exposed to involuntarily or unknowingly. And with the volume of use of artificial sweeteners like aspartame now in our society, it seems to me that looking at children, who would probably be at greatest risk on these things, it's probably a wise thing to do, if it otherwise seems to point in that direction.

Dr. OLDEN. Yes. And that we can do.

AIR QUALITY STANDARDS

Mr. PORTER. Speaking of coordination between agencies, there is considerable discussion in Congress about whether EPA air quality standards are based on sound science. You know there are new regulations.

Dr. OLDEN. Yes.

Mr. PORTER. Has your Institute provided any data to EPA to aid in this debate?

Dr. OLDEN. Yes in part. In my answer to Congresswoman Lowey, I mentioned that the data that is being used to decide what the new standard is, and in fact, the reason it's being debated at all, was the result of the 24 city study that was done by Doug Dockery at Harvard. He found that particles, and he called them particle size ten, which are very small particles, he discovered and demonstrated in his epidemiologic study that the mortality rate was increased by something like 23 percent and that translates into a life expectancy decrease of 2 years. He found that that was true for the most polluted cities compared to the least polluted cities.

It is exactly that data that EPA is now using to advance a new regulatory policy. And in fact, we've been in discussion with EPA and Congress, as a matter of fact, in the last week or two, about that data. So the data from these studies is being used for documentation. And the reason that there is a concern, even going way back to the Middle East oil crisis, has to do with work that the NIEHS supported.

Mr. PORTER. So you, I can conclude that you believe that the science on which EPA based their regulations is sound science?

Dr. OLDEN. Well, I think, as I understand it out of the newspaper, both EPA and industry are not, people aren't refuting the science. The question is, EPA and industry both agree that more data is needed. I think where they disagree is, should you regulate, err on the side of safety now and put in place a regulation, or should you wait until the science is in. I think that's the debate.

So it's not about the need for more science. I think EPA would like to see more science in place. Industry would like to see more science in place. So this again is an example of where there's inadequate information. And probably, no matter what decision is made, it's going to be problematic. People aren't going to be satisfied with the decision without the additional information which we do not have today.

So the data that's been presented is fine, but there are gaps. And that's the problem, and that's what the debate is about, those gaps. EPA acknowledges those gaps.

SMOKING

Mr. PORTER. Dr. Olden, I thought we had planned our time quite well, but Ms. DeLauro just arrived. Ms. DeLauro, would you like to ask questions of Dr. Olden? You can proceed if you want.

Ms. DELAURO. One question, because I just came from the Agriculture subcommittee where we were talking about tobacco.

I've been a strong advocate for trying to get at kids to stop smoking. We have something called the Kick Butts Connecticut campaign, where we're working with middle school kids. We've got this

army of middle school kids, about 50 or 60 of them in the district, who are going to the elementary schools and talking to their peers about not smoking. It's a great effort.

But what I wanted to ask about is your initiatives in terms of dealing with a link between cigarette smoking, disease and cancer. That effort in terms of what that body of research is, and getting that information out to deal with the issue of children and adolescent smoking. If you could just comment on that.

Dr. OLDEN. Over the years, the National Cancer Institute and NIEHS, and I would say more even the years before I got there as Director, made long-term commitments and investment in basic, fundamental research, on the health effects of chemical agents in cigarette smoke. And it's that long-term commitment to the basic fundamental research that demonstrated the epidemiological association between cigarette smoking and cancer. And many of the chemicals were subsequently indentified, not only by NTP assays, but also by the bioassay program conducted by the National Cancer Institute.

We played a major role in it, and we continue to look at some aspects of lung cancer. I did not say one of our other susceptibility gene discoveries in the past few years was one that enhances the susceptibility to lung cancer if exposed to 925 cigarette smoke carcinogens.

So we continue to do research in that area. But so does the National Cancer Institute. And they are clearly much more active, I would say, than we are in the outreach component in terms of public education.

Ms. DELAURO. They are more active on the outreach component than you?

Dr. OLDEN. That's what I would guess. We do have an information service. But I would say we probably get no questions on that issue. And NCI has, as you know, an information service and community outreach that's focused on smoking cessation. So I would say that the bulk of that work is being sponsored and supported by the NCI, although we certainly have played a major role over the years and will continue to.

Ms. DELAURO. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Ms. DeLauro.

Dr. Olden, thank you very much for your good testimony, your forthright answers to our questions, and for the fine job that you're doing at NIEHS. And we look forward to coming down and visiting you and seeing things up close in April.

Dr. OLDEN. Thank you. We look forward to your visit.

AUTISM

Mr. PORTER. Thank you.

Now, as Dr. Snow comes to the table, I want to ask a question of Dr. Varmus. I want to keep you a little busy here, Dr. Varmus.

Many of us on the subcommittee have been visited this past week by parents of autistic children who are concerned about the level of support that NIH research provides with respect to this disease. I wonder if you could tell us which institutes are involved, do you have an estimate of how much is being spent, has the

money been constant or has it been rising or falling, and what are the prospects for research into autism in the years ahead?

Dr. VARMUS. Thank you for the question, Mr. Porter.

As you may have read, the NIH is taking a dramatically increased interest in autism for a number of reasons that I'll come to. At the moment, there are roughly four institutes that do research in this area: NICHD, NINDS, NIMH and NIDCD, which is at the table with me now.

The level of funding as of 1996 was approximately $14 million. I can give you the exact number if you like. And there was a very substantial increase for 1997 of about $4 million. And we expect to have that increased a little further in 1998.

In addition, we as a result of my request for initiatives to support with my 1 percent transfer authority, we have decided to put together a package of $4 million that will go for the study of the genetics of autism, to be sponsored by the Institutes to my left, NIDCD, NIMH and NICHD.

Now, let me say a word or two about autism. This is obviously a devastating illness for the child and for the family. And for many years, it was marginalized, in my view. But for a number of reasons, it's become more central and more accessible to research. And now it's positioned itself in the middle of the technological advances that are revolutionizing our view of neuroscience. It's approachable by neuroimaging, it's approachable by genetics, approachable by neurophysiology.

It's become recognized as a disease that is likely developmental in origin, with subtle anatomical changes. It's been changed by the perception that it's not really one disease. It's a range of diseases, at least four, possibly five, discrete syndromes, that can be fairly well recognized. And that is changing our notion of how to go about approaching the disorder.

There is already underway a fairly extensive attempt to understand the genetics of autism. In particular, the NIMH has assembled a large cohort of families. Recently published work suggests that it's possible to exclude a fair amount of the genome as the site of genetic lesions that contribute to autism. That's helpful to narrowing down this ever-engaging search for the loci involved.

As you might appreciate, since there seem to be several syndromes that go under the general term of autism, it's important to have clear criteria for deciding what disorder you're looking at. And recently, the four institutes that are involved in the study of autism have gotten together and agreed to try to work out some common defining principles, so that the genetic information that we're assembling can be made more useful.

In addition, there have been recent reports that suggest that it's possible to develop an animal model for at least one sub-form of the disease. And that's based on evidence from a small number of autopsy patients who seem to lack what are called the nuclei for some of our cranial nerves. What that suggests to developmental neurobiologists is that the developmental lesions in at least some cases of autism occur about the time of the closure of the neural tube during development.

By using known developmental anomaly-inducing agents, one in particular called valproic acid, which happens to be a drug that's

used in the treatment of epilepsy and schizophrenia, using that drug in a rat model, it's been possible to reproduce some of the anatomical defects that are seen in at least an occasional case of autism.

So all those things combined, I don't want to go on longer, it's clear there are a lot of new things to do. I'm sure you're aware that about two years ago, we had an important workshop on the NIH campus. It was very widely attended, I was there myself to hear many of the talks. I think that had the effect that I like to see when we think about funding at increased levels in an area. That is, people were there from a number of fields that had not participated actively before. We were drawing new talent to a field instead of simply putting more money into the pockets of those who were already working on the problem.

And the synergy among the neurobiologists, geneticists, and clinical and behavioral students of autism, was very obvious. One of the reasons that there was a lot of enthusiasm among my outside advisors for supporting the work on autism that was proposed for the 1 percent transfer authority was the fact that in response to the RFA that Dr. Snow and Dr. Alexander put together, applications of very high quality were received in excess of the ability of those institutes to support them.

Mr. PORTER. Thank you, Dr. Varmus.

[The following questions were submitted to be answered for the record.]

SUPERFUND

Mr. Porter: Provide a five-year table of funds received from Superfund, broken down into research and worker training.

Dr. Olden: The following table provides a five-year history of funds received by the National Institute of Environmental Health Sciences (NIEHS) from EPA for carrying out our Superfund responsibilities:

NIEHS
SUPERFUND
(Dollars in Thousands)

Area	FY 1994 Actual	FY 1995 Actual	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Research	$32,913	$35,769	$32,000	$32,527	$25,500
Worker Training	19,998	22,993	20,500	24,000	23,000
TOTAL	52,911	58,762	52,500	56,527	48,500

NATIONAL TOXICOLOGY PROGRAM

Mr. Porter: Identify FY '96-98 funding for the National Toxicology Program from all agency sources.

Dr. Olden: The following table identifies the FY 1996-98 funding for the National Toxicology Program from all agency sources.

NATIONAL TOXICOLOGY PROGRAM AGENCY SOURCE
(Dollars in Thousands)

Agency	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
NCTR	$ 1,858	$ 1,642	$ 916
NIEHS	84,745	88,472	91,987
NIOSH	4,810	4,011	4,011
TOTAL	91,413	94,125	96,914

NEW TEST METHODOLOGIES

Mr. Porter: You have been working for sometime on a report on developing better toxicological test methods to determine the safety of chemicals. What are your

major conclusions about the most promising alternatives to the standard two-year rodent exposure study?

Dr. Olden: The traditional approach for identifying cancer-causing chemicals in the environment, workplace, and food has been to conduct long-term bioassays in rodents. These studies have been valuable to regulatory agencies, but they are costly, time-consuming, and often give equivocal results. Because of their costs, we can only start about 10 chemicals per year on these two-year bioassays. The NIEHS has been working hard to develop, validate, and achieve regulatory acceptance of alternatives to the two-year bioassay as part of our mandate from the National Institutes of Health (NIH) Revitalization Act of 1993. To fulfill this mandate, we formed an interagency committee to work with all interested stakeholders. A copy of the report entitled "Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the Ad Hoc Interagency Coordinating Committee on Validation of Alternative Methods (ICCVAM)" will be provided under separate cover. More specifically, we are working with other regulatory agencies and industry to determine if transgenic mice could be used to replace the two-year bioassay. Transgenic mouse studies are about one-fifth as expensive as two-year bioassays and can be completed about five times faster. These validation studies are going well, and we expect to develop recommendations which will be peer-reviewed in an open public meeting in late 1997. Likewise, we are using the tools of molecular biology and computational capacities to develop molecular screens for rapidly identifying agents which could pose health risks. Results from these studies are becoming critical determinants in how we set priorities for use of our resources.

AIR QUALITY STANDARDS

Mr. Istook: In response to a question about air quality standards and the Environmental Protection Agency (EPA), the NIEHS director indicated that the Institute had been involved in research used by the EPA to promulgate a new air quality standard. Please answer the following questions for the record:

Was the Institute involved in research regarding particulate matter (PM) national ambient air quality standard (NAAQS)?

Dr. Olden: Yes, the Institute supports research on health effects of air particulates.

Mr. Istook: Was NIEHS involved, consulted, or asked to assist in the process of developing the new NAAQS standard?

Dr. Olden: No, NIEHS was not directly involved in developing the actual standards themselves. However, NIEHS scientists participated in the review of the scientific literature, particularly the scientific findings based on research supported by NIEHS, that was an important part of the scientific basis for the standard-setting process.

Mr. Istook: If NIEHS has supported the new PM standard the EPA is promulgating, please provide a statement of why NIEHS supports the EPA's proposal to tighten the PM standard. (Please include the basis for NIEHS' support for the new NAAQS standards.)

Dr. Olden: As a basic research agency, it is not within the purview of NIEHS to take official positions for or against the actions of a regulatory agency such as the EPA. NIEHS can indirectly provide EPA, through the scientific literature, with the best available environmental health science for use in its risk management decisions, but NIEHS does not take an official position on the decisions themselves.

Mr. Istook: Please provide a copy of any correspondence with the EPA regarding their NAAQS (letters and email).

Dr. Olden: There has been no correspondence with EPA regarding NAAQS.

PARTICULATE MATTER

Mr. Istook: Please provide a listing of any NIEHS research projects, completed or ongoing, regarding particulate matter.

Dr. Olden: The following list shows the NIEHS' research projects regarding particulate matter.

NIEHS RESEARCH PROJECTS ON PARTICULATE MATTER

TITLE:
PROJECT NUMBER:
PRINCIPAL INVESTIGATOR:
LOCATION:
SUBJECT PERCENT:

COMPLETED RESEARCH GRANTS:

The Effects of SO_2 and Respirable Particles on Health
5-R01-ES01108
Dockery, Douglas W.
Harvard University
100 Percent

ONGOING RESEARCH GRANTS:

Inhaled Pollutants--Mechanisms of Injury and Adaptation
5-K04-ES00256-04 (M 0000)
Gordon, Terry
New York University
50 Percent

Ozone Chemistry and Chemical Carcinogenesis
5-R37-ES01984-18
Murray, Robert
University of Missouri - St.Louis
50 Percent

Toxic Effects of Particles and Oxidants on Lung Function
5-R01-ES02679-16 (M 0000)
Utell, Mark J.
University of Rochester
100 Percent

Epigenetic Mechanisms of Toxicity of Environmental Metal
5-R01-ES03543-08
Chou, Iih-Nan
Boston University
25 Percent

Silica and Asbestos Effects on Macrophage Function
5-R01-ES04804-06 (M 0000)
Holian, Andrij
University of Texas Hlth. Sci. Ctr. Houston
100 Percent

Mechanisms of Particle Induced Lung Injury
5-R01-ES04872-08 (M 0000)
Oberdoerster, Guenther
University of Rochester
100 Percent

Acid Aerosol--Respiratory Effects in Infants and Mothers
5-R01-ES05410-07 (M 0000)
Leaderer, Brian P.
John B. Pierce Laboratory, Inc.
100 Percent

White Cell Responses to Environmental Toxins
5-R01-ES05859-06 (M 0000)
Soberman, Roy J.
Massachusetts General Hospital
100 Percent

Asthma and Air Pollution-Aeroallergen Interactions
5-R29-ES06214-05 (M 0000)
Delfino, Ralph J.
San Diego State University
100 Percent

Effects of Acid Aerosols and Ozone on Urban Populations
5-R01-ES06239-04 (M 0000)
Dockery, Douglas W.
Harvard University
25 Percent

Grain Dust, Endotoxin, and Airflow Obstruction
5R01-ES06537-04 (M 0000)
Schwartz, David A.
University of Iowa
100 Percent

Role of Ozone in Modulating Chromium-Induced Lung Immunotoxicity
5-R01-ES06783-02
Schlesinger, Richard B.
New York University
25 Percent

Ambient Air Pollution and Cardiovascular Morbidity
1R29ES07204-01A2
Morris, Robert D.
Medical College of Wisconsin
25 Percent

Biological Determinants of Environmental Airway Injury
5-R01-ES07498-02
Schwartz, David A.
University of Iowa, Iowa City, Iowa
100 Percent

Inner City Cockroach Allergen Reduction Trial
1R01ES07527-01A1
Eggleston, Peyton A.
Johns Hopkins University
100 Percent

P53 in Asbestos Induced Lung Disease
1R29ES07856-01
Morris, Gilbert F.
Tulane University of Louisiana
50 Percent

COFUNDED RESEARCH GRANTS:

Environmental Agents--Asthma Development and Severity
5-R01-ES07456-02
Leaderer, Brian P.
John B. Pierce Lab, New Haven, CT
50 Percent

Molecular Regulation of Allergic-Immune Inflammation
5-U01-AI34567-02
Saxon, Andrew
University of California, Los Angeles, CA
100 Percent

National Cooperative Inner-City Asthma Study
1U01AI39761-01
Shapiro, Gail G.
University of Washington
50 Percent

Trial of Interventions to Reduce Asthma Morbidity
1U01AI39769-01
O'Connor, George T.
Boston University
50 Percent

Data Coordinating Center for NCICAS II
1U01AI39776-01
Mitchell, Herman E.
New England Research Institutes, Inc.
25 Percent

National Asthma Inner City Study--Tucson Field Center
1U01AI39785-01
Morgan, Wayne
University of Arizona
50 Percent

Team Targeting the Environment and Asthma Management
1U01AI39900-01
Crain, Ellen F.
Yeshiva University
50 Percent

National Cooperative Inner City Asthma Study
1U01AI39901-01
Kattan, Meyer
Mount Sinai School of Medicine
50 Percent

Chicago Inner City Asthma Study
1U01AI39902-01 420864 102063
Richard, III, J. Evans
Children's Memorial Hospital (Chicago)
50 Percent

CENTER GRANTS:

Occupational and Environmental Health
5-P30-ES00002-34 (S 0038)
Monson, Richard
Harvard University
100 Percent

Research in Environmental Health Sciences
5-P30-ES00260-34 (C 9009)
Schlesinger, Richard
New York University
100 Percent

Research in Environmental Health Sciences
5-P30-ES00260-34 (C 9010)
Lippmann, Morton
New York University
100 Percent

Trace Contaminants as Environmental Health Hazards
5-P30-ES01247-22 (S 0063)
Oberdoerster, Guenter
University of Rochester
100 Percent

Trace Contaminants as Environmental Health Hazards
5-P30-ES01247-22 (S 0064)
Utell, Mark J.
University of Rochester
100 Percent

Environmental Health Sciences
2-P30-ES05605-06AL (M 001)
Merchant, James M.
University of Iowa
50 Percent

Mr. Istook: Please provide a bibliography of research (pro & con) on the effects of particulate matter, and their possible effect on the human population.

Dr. Olden: The list of references provided represents results of key studies on air particulates and health effects/mortality in human and animal populations. It is not a comprehensive list, but it includes some of the most important publications on this issue. Since these are research studies, the citations present research results only and are not amenable to analysis on an individual basis about whether they support or refute a given air quality standard level arrived at through a separate risk assessment/risk management process.

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AIR QUALITY STANDARDS

Mr. Istook: Please provide a copy of studies that were provided by NIEHS, or may have been used by EPA to establish their new NAAQS standards.

Dr. Olden: No studies were directly provided by NIEHS to EPA. Copies of 57 studies that may have been used by EPA to establish their new NAAQS standards will be provided under separate cover.

SECONDHAND SMOKE

Ms. Northup. Please provide for me a listing of any activity your agency is doing on the effects of secondhand smoke.

Dr. Olden: The following is a listing of grants *directly related* to secondhand smoke:

Title	Project Number	Principal Investigator	Location	Dollars
Induction of Squamous Cell Markers in Airway Epithelium	5-ROI-ES06230-04	WU, Reen	University of California, Davis	$134,716
Passive Smoking During Pregnancy--Cognitive Development	5-R29-ES06259-03	Mactutus, Charles F.	University of Kentucky	$105,974

NIEHS has a number of research activities relevant to environmental tobacco smoke (ETS). Epidemiological studies suggest that "involuntary smokers"exposed to ETS are at risk to develop lung cancer, and in animals exposed to secondhand smoke there is doubly the incidence of lung tumors. In a number of other studies, ETS is evaluated as a confounding variable in the study of adverse health effects resulting from exposure. For example, in each of the three radon studies, in the Five-Cities Study -- ozone effects, acid aerosol, and particulate matter on inner-city children -- and the continuation of the inner-city asthma study, all include ETS as a confounding variable, rather than the main focus of the study.

Ms. Northup: I noticed in the budget justification that there has been new research on P53. Please go into deeper detail on this research.

Dr. Olden: NIEHS-supported scientists have confirmed the link between P53 expression and DNA damage by environmental agents. Normally when DNA is damaged, synthesis of new DNA is halted until the DNA is repaired. If it is not halted, newly synthesized DNA is at risk for genetic errors, which could lead to malignancies. P53 is particularly important as it is the most commonly mutated gene in human cancer. Also, the gene has been identified which is directly triggered by P53. These observations are important because they indicate that this gene plays a role in the cell processes that eventually lead to cancer. In a recently reported article in *Science*, NIEHS-supported investigators described the novel finding that a carcinogenic

metabolite commonly found in ETS binds preferentially at P53 in lung cancer cells. These results suggest that this specific binding is responsible for the P53 mutations in lung cancer and provides a direct link between a carcinogen and human cancer. This work has profound consequences for our understanding of tobacco smoking and lung cancer.

BUDGET

Ms. Northup: Why does the budget request support one less competing RPG when you are seeking an increase of 3.7% over last year's funding?

Dr. Olden: Although the number of competing grants decreased by one over last year, the total number of research project grants funded actually increased since the number of noncompeting grants increased by ten from FY 1997 to FY 1998.

Ms. Northup: Why has your agency's budget increased by 3.7% when the entire NIH budget only increases by 2.6%?

Dr. Olden: I believe the increase is a result of the recognition of the importance of environmental factors in a variety of diseases and disorders. It also reflects a role for NIEHS in many of the areas of research emphasis that Dr. Varmus selected for enhanced funding this fiscal year.

TOXICITY TEST SYSTEMS

Ms. Northup: In mentioning test methods you stated that current methods are too costly and time consuming for use in screening large populations. Please be more specific on the costs currently and your efforts to improve these costs.

Dr. Olden: Lifetime bioassays for rodents cost approximately three million dollars and take several years to complete. Likewise, well-conducted epidemiological studies take several years, cost several million dollars, and often give results that are not definitive because of confounding factors. We are working on several methods which are faster, less expensive, and will provide data which will strengthen the science base for risk assessments by improving dose relationships and identifying sensitive subpopulations. The new tests range in costs from several thousand dollars to $500,000. A combination of new tests will be required, but we expect that there will be considerable savings if our strategy is accepted by regulatory agencies. For example, we could possibly provide a cancer evaluation for approximately one-fifth the cost of a lifetime bioassay.

CLINICAL PROGRAM

Ms. Northup: How can the clinical program be used to better understand how research can translate into the practice of medicine. Under your agency what types of clinical programs are being undertaken?

Dr. Olden: Two of the major goals of the NIEHS Clinical Program are to translate advances in understanding the environmental causes of disease into prevention/ intervention strategies and to translate basic research in genetics and molecular biology into a greater understand of the underlying mechanisms and environmental causes of human diseases. Both of these goals are requisite components of the process of translating research results into the practice of medicine.

Translation of basic research into clinical studies of disease prevention and intervention is crucial to the ultimate goals of research at the NIEHS, and to effecting a discernible improvement in human health. New research advances are being extended not only into molecular medicine -- from bench to bedside -- but also into disease prevention -- from bench to longer, healthier lives. The NIEHS applies multidisciplinary approaches to understand the contributions of environment agents to human diseases and dysfunction, and the underlying mechanisms of environmentally associated diseases.

Clinical programs undertaken by the NIEHS include the following:
Lead Clinical Trial. The Treatment of Lead-exposed Children (TLC) trial is a large, clinical trial already in place. This is a randomized trial to test the use of the drug, Succimer, as a treatment for the prevention of lead-induced alterations in growth, behavior, and development in children.

Role Of Platelet Derived Growth Factor In The Pathogenesis Of Idiopathic Pneumonia Syndrome In Patients With Primary Breast Cancer Treated With High-Dose Combination Chemotherapy And Autologous Bone Marrow Transplantation. This pilot study seeks to understand the molecular biology of the lung complications following chemotherapy so that appropriate therapy can be initiated prior to the onset of clinical symptoms to avert fatality in these women.

Epidemiological studies. Current epidemiological studies focus on the impact of environmental toxicants on human health. They include examinations into genetic and environmental risk factors in cancers, factors that affect fertility and pregnancy in humans, effects of environmental estrogens on humans, and associations of genetic damage with smoking. These studies can lead to better understanding of mechanisms underlying environmentally-induced diseases, leading to improved preventative methods.

EPA

Ms. Northup: What is the coordination between your agency and the EPA? Are you working to ensure that the EPA is not duplicating research which is undertaken at your agency?

Dr. Olden: The NIEHS/NTP takes special care to coordinate research efforts with the EPA, both to ensure there is no duplication or overlap of efforts and to ensure that research designs are developed to achieve the maximum benefit to the environmental health community. The most formal, ongoing mechanism is through the NTP Executive Committee, of which both NIEHS and EPA are members. There are, however, multiple projects throughout any given year in which NIEHS staff coordinate their efforts with staff at the EPA. For example, a joint conference with EPA and NIEHS/NTP recently was held to review risk assessment plans of the EPA and to explore ways in which the research efforts of both agencies could be used in complementary ways to strengthen risk assessment methodology. When the endocrine disruptor issue became a major national initiative, the NIEHS extramural division had discussions with program staff at EPA. Some of the grant solicitations on this effort are being co-funded by EPA and NIEHS. NIEHS has also been working both with NCI and EPA on the Agricultural Health Study, a large-scale epidemiologic study of pesticide applicators and their families that examines cancer, birth defects and other reproductive outcomes, asthma, immunological effects, lactation, neurological outcomes, childhood development, and kidney disease.

SUPERFUND

Mr. Obey: I understand the President's request for EPA would cut by 22% the funding for the long range Superfund research conducted by NIEHS which is heading into the last year of a five year grant commitment. Can you describe the nature of this research and the potential impact of this cut?

Dr. Olden: The Superfund Amendments and Reauthorization Act (SARA) of 1986 established a university-based grants program of basic research within the NIEHS. The Program receives funding from EPA through an interagency agreement using Superfund Trust monies. It provides funding to 69 universities and institutions throughout the United States to expand the base of scientific knowledge, reduce the amount and toxicity of hazardous substances, and ultimately, prevent adverse human health effects.

The exciting research efforts being pursued focus on the risk to humans from hazardous waste exposure and the development of innovative technologies to remediate contaminated sites in the future. This a truly multidisciplinary research program, bringing together biomedical researchers, engineers, ecologists, and hydrogeologists. The Program provides critical exposure and health effects information, and develops cost-effective cleanup technologies. The proposed cut in FY 1998 would reduce the overall research effort. The Program would then be cut by about one-third since FY 1995 when this round of funding was started and these new research efforts initiated. The proposed level of cuts would mean that some on-going grants would have to be terminated or there would have to be reduced funding to all programs.

CLINICAL PROGRAM

Mr. Obey: Your testimony indicates that NIEHS has recently started a clinical program. Can you tell us about some of the research being conducted in this setting?

Dr. Olden: We currently have two clinical trials plus epidemiological studies and two additional clinical studies are planned.

Our current trials are:

(1) Treatment Of Lead-Exposed Children (TLC) Trial. Inner-city children who reside in old buildings are at particular risk for lead poisoning. The TLC trial is designed to determine if the drug Succimer, which can help remove lead from the body, can prevent lead-induced alterations in growth, behavior, and development.

(2) Environmental Intervention In The Primary Prevention Of Asthma In Children (The EIPPAC Study). In children, asthma is a major, chronic disease afflicting 8-12% of the population with a disproportionately high prevalence among minorities and persons of lower socioeconomic status. This study seeks

to reduce the prevalence of asthma in children by environmental intervention in the homes of at-risk children. This contract is currently being competed.

In addition to the clinical trials, the Epidemiology Branch of the NIEHS Division of Intramural Research studies the impact of environmental toxicants on human health. This work focuses primarily on environmental and molecular epidemiological studies on effects of potential environmental toxicants, such as radon, pesticides, electromagnetic fields, and lead, on human health, the effects of the environment on human reproduction and development, and examinations of exposure-specific mutations of critical target genes.

Our planned studies are:

(1) A Pilot Study To Investigate Human Germ Line Effects From Zidovudine And Other Didoynucleosides. HIV-1 infection is a serious public health problem. In the United States, where nearly 4 million health care workers are at risk of exposure to blood and body fluids each day, about 10% of hospital employees have experienced needlestick injuries while at work. Zidovudine (AZT) given together with the new class of drugs called protease inhibitors comprises state-of-the-art treatment. The purpose of this study is to determine the effect of AZT treatment on chromosomes and germ cells of otherwise healthy adults who receive treatment following accidental exposure to HIV-1 virus.

(2) Role Of Platelet Derived Growth Factor In The Pathogenesis Of Idiopathic Pneumonia Syndrome In Patients With Primary Breast Cancer Treated With High-Dose Combination Chemotherapy And Autologous Bone Marrow Transplantation. Women with breast cancer and 10 or more positive lymph nodes, an indication that cancer has already spread, are at great risk for developing widespread metastatic disease and death. Following chemotherapy, however, nearly 40% of women develop lung complications which are fatal to some women. This pilot study seeks to understand the mechanism of the lung complications so that appropriate therapy can be initiated prior to the onset of clinical symptoms to avert fatality in these women.

IMPROVING THE HEALTH OF MINORITIES

Mr. Stokes: African Americans and other minorities continue to suffer disproportionally from a tremendous number of diseases and disorders -- from cancer to cardiovascular diseases to AIDS to diabetes. It is thought that fuller participation of minorities in the biomedical research enterprise -- from the conduct of research to research training to research decision making on the front-end, would help to dramatically close this long standing gap in health status. What is the Institute doing to increase minority representation in the field of environmental health sciences?

Dr. Olden: I agree with your assessment and I am pleased to report to you some of our recent activities in this regard. NIEHS has achieved substantial success in fostering the careers of minority faculty as well as attracting talented minorities into environmental health sciences and mentoring their careers development. I also want to assure you that the NIEHS will continue working very hard to recruit African-American and other minorities into research careers. The Institute has intramural and extramural programs that focus on these populations at all points in their educational experience. In the intramural programs we have been very active in recruiting summer students into our laboratories and have reached out to numerous predominantly minority institutions in and around the Research Triangle Park. In the extramural arena, we have very active programs that reach beyond the bounds of the Institute and offer opportunities for minority students and scientists throughout the country. These include the Individual NRSA Predoctoral Fellowship for Minority Students, Research Supplements for Underrepresented Minorities, Short-term Training for Minority Students and the Minority Scientist Development Program.

One specific example regards a faculty member at an HBCU. In this case, NIEHS staff worked with this individual and arranged a research collaboration at an NIEHS center. As a result of this effort, the faculty member was able to obtain funding for his project, and is now preparing a NIH application to continue this work at his institution. Additionally, as a direct result of our short-term training program, we have seen evidence of an increased recruitment of talented minorities into our Ph.D. training programs. I believe that the efforts over the past few years by NIH and NIEHS are now beginning to bear fruit, and we will soon realize an impact of our efforts on the participation of minorities in environmental health sciences.

ENVIRONMENTAL JUSTICE

Mr. Stokes: Socioeconomically disadvantaged populations continue to have greater health problems -- many of which are attributed to their increased likelihood of living in environmentally degraded areas. Recently, the issue of "environmental justice" has received a lot of attention. In fact, House report language continues to express serious concern regarding this matter. Would you bring the subcommittee up-to-date on the progress that the Institute is making in this area, and on collaborative efforts that are underway and/or planned with NCI?

Dr. Olden: NIEHS, in conjunction with NCI and other federal agencies has funded and supported the Institute of Medicine Study on Environmental Justice: Research, Education and Policy Needs. This independent scientific study began in September, 1995 to assess medical science and health issues related to environmental justice and set priorities for medical research. NIEHS, NCI and the Environmental Protection Agency are also working on a major study of farmers and agricultural chemicals. In addition, NIEHS and NCI supports the Intercultural Cancer Coalition in their efforts to promote research, education and training, and preventative and treatment clinical approaches to address the cancer problems of minorities and underserved populations. NIEHS and NCI also support the Biennial Symposium on Cancer, Minorities and the Medically Underserved scheduled for April 22-27, 1997, and at which there will be special sessions addressing environmental justice issues.

Mr. Stokes: What NIEHS activities are planned for FY 1998?

Dr. Olden: Increasing scientific evidence indicates that socio-economically disadvantaged populations continue to have greater health problems, some of which are attributed to their increased likelihood of living in areas of higher environmental contamination. In response, NIEHS, in partnership with the Office of Research on Minority Health, has been an active participant in the emerging agenda of research, education and training on environmental justice. I co-chair the HHS Environmental Health Policy Committee's Subcommittee on Environmental Justice through which the Department's Environmental Justice Strategy has been developed and implemented. A broad number of research grants and contracts are being funded, including: clinical trials for the prevention of lead-poisoning in inner city children and other research on lead poisoning; a multiagency effort to understand the role of farm chemicals on farmworker health; studies of outdoor air pollution and asthma in inner cities; epidemiological studies devoted towards understanding diseases in minority populations; and grants in the specific area of environmental justice and community-based prevention and intervention research.

Mr. Stokes: How does the amount of funds proposed for FY 1998 compare with the FY 1997 appropriation funding level?

Dr. Olden: The funding level for research related to environmental justice in FY 1997 is $ 10,822,000. Anticipated funding for FY 1998 is $ 9,427,000. This decrease reflects no lesser activity, except that the Treatment of Lead-exposed Children (TLC) clinical trial is coming to a close.

Mr. Stokes: In your professional judgement, is the level of funding included in the FY 1998 budget request adequate to do the job?

Dr. Olden: This level of funding for environmental justice will allow NIEHS to continue high priority on-going projects.

CLINICAL RESEARCH

Mr. Stokes: Clinical research is a critical component of the research continuum, as its findings are one of the most important means of determining what constitutes appropriate medical care or treatment. What portion of the Institute's budget is invested in clinical research and how does this compare with the basic research investment?

Dr. Olden: The clinical research budget of NIEHS is $23.8 million. For comparison, the total NIEHS research budget is $277 million, and the total basic research budget is $123 million.

Mr. Stokes: Obviously, the relevance of clinical research findings are greatly enhanced when the study group is representative of the nation's population as a whole. What is the Institute doing to ensure minority representation in its clinical research programs?

Dr. Olden: The NIEHS completely supports the PHS requirement that research projects involving human subjects must include women and minorities in the study population. All of our investigators are aware of this requirement and are expected to fulfill it unless they are able to show inclusion of these groups would be inappropriate. So far, about 90% of the participants in the Treatment of Lead-exposed Children (TLC) trial are from minority populations.

The "Environmental Intervention in the Primary Prevention of Asthma in Children" (The EIPPAC Study) is an NIEHS clinical trial currently under review which is aimed at the primary prevention of asthma in children. This study will target children from low-income residences in North Carolina. To ensure participation of minority patients in the asthma study, representatives from the Office of Research on Minority Health-NIH, National Medical Association, Office of Institutional Development-NIEHS, and the North Carolina Office of Minority Health were invited to provide advice on the study and accrual of minorities. Over 50% minority representation is expected.

KNOWLEDGE "BOTTLENECK"

Mr. Stokes: In your opening statement, you refer to the problems of identifying environmental hazards that contribute to human disease and illness as a bottleneck in our knowledge base. What are the most significant "bottlenecks in our knowledge base," and what are the health implications? What must be done to eliminate them?

Dr. Olden: There are multiple bottlenecks at the moment. Much more information is needed in the area of the fundamental biology of toxicity. Mechanism-based toxicology studies now being emphasized by NIEHS offer much more powerful insight into eventual exposure screening and prevention strategies for improving public health. But, perhaps the most significant bottleneck is our need for more information on the

relationship between individual genetic susceptibility, low-level environmental exposure, and disease.

Genetic approaches used in the past have identified a number of susceptibility genes for environmental diseases. An individual with a defect in such a gene has an elevated risk of becoming ill after an environmental exposure. Hence, genetic susceptibility and environmental exposure are primary determinants of disease risk.

While rare, highly penetrant genetic susceptibility may be identified from family clusters of disease (e.g., BRCA1), less penetrant susceptibility genes cannot be identified from family clusters. Despite the low penetrance, common genetic variants of susceptibility genes may account for a much larger proportion of disease than their rare high penetrance counterparts. This may particularly be the case for genes that control susceptibility to environmentally-associated diseases. Here the disease risk may be evident only in a genetically susceptible population. While a host of environmental susceptibility genes have been identified, polymorphisms in such genes are not systematically sought, identified, or reported.

The NIEHS' Environmental Genome Project will partially solve this information bottleneck. Knowledge of susceptible subpopulations, which will be generated through this initiative, will allow us to conduct far more focused epidemiological studies than before, relating environmental exposures and disease to individual susceptibility genotype. Ultimately, information from such medical genetic epidemiology will enhance public health through better prevention strategies for environmentally-associated diseases and dysfunctions.

The Environmental Genome Project will also provide information for future research on molecular mechanisms of susceptibility gene products and of their gene expression responses to stress. The Project will also foster development of new high-throughput technology for a broader application of molecular genetics in epidemiology as a function of environmental exposure.

Enhancing research on prevention strategies is also a critical bottleneck. For example, we know that low-level exposures to such agents as allergens, lead and some other metals, and some organic chemicals can cause disease. However, our knowledge of how to effectively reduce such exposures across the population is lacking. The NIEHS is sponsoring many research programs on the translation of toxicological information to address these needs toward enhancing public health. Some of these programs are being sponsored in partnership with other federal agencies.

Mr. Stokes: To what extent will the FY 1997 appropriations allow the Institute to address the "knowledge bottleneck" problem, and how much is included in FY 1998 budget request for such? In your professional judgement, is the proposed funding level adequate to address the "knowledge bottleneck", explain?

Dr. Olden: All of the NIEHS research programs are designed in one way or another to overcome the knowledge bottleneck problem as detailed above. The 1997 appropriations allows us to attack these problems more comprehensively than before. The key new areas of research opportunity highlighted in my testimony can be initiated under the 1998 budget request. Partnerships with other NIH institutes, with federal agencies, with foundations, and with the private sector are being pursued to enhance the research impact of these new NIEHS programs.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists' cloning of adult sheep. These articles expressed excitement with regard to opportunities for advances in medical treatments, and concern with regard to misuse of the technology and the possibility of human cloning. This is another area where we must now be certain to examine and address the ethical, legal, and social issues of research on the front-end. As a leading researcher and as an Institute Director, what is your professional opinion of this technology and what are your most serious concerns?

Dr. Olden: I think this technology could have important uses medically, but it also raises a number of ethical concerns which need to be addressed in a forthright and public manner. President Clinton has asked the National Bioethics Advisory Commission to review the issues and to prepare a report on the matter. I think this was a very good decision on his part.

Mr. Stokes: With regard to the diseases and disorders studied by your Institute, what are the most significant benefits that the cloning technology would yield for your major areas of research?

Dr. Olden: I can envision some new approaches to environmental health research diseases that would be made possible by this technology. However, I think we need to have much more public debate and a resolution on the ethical issues involved in advance of moving any of these ideas to the laboratory.

ENVIRONMENTAL HEALTH HAZARDS

Mr. Stokes: Environmental health research is critical to helping policy makers develop effective strategies for protecting the American people from environmental hazards. What major research is needed to bridge the gap between science and policy as it relates to environmental health?

Dr. Olden: One of our most critical information gaps is in the area of exposure assessment for hazardous substances. Improved methods and survey programs to quantify the chemical exposure burden of the population are needed. Research in this area is under development in cooperation with the National Center for Environmental Health, CDC. Research on human exposure to an actual effective dose (bioavailability)

of a hazardous substance is also required. These two points, exposure and bioavailability, represent key information gaps that must be filled in order for us to enhance risk assessment.

COLLABORATIONS

Mr. Stokes: What collaborative research activities are underway between NIEHS and NCI, and what progress do you have to report to the committee in this area?

Dr. Olden: NCI and NIEHS have several collaborations that I would like to tell you about. First and foremost is a cooperative effort in breast cancer. One in eight women will develop breast cancer. The cause of this disease is still uncertain after many years of research, but their is no doubt that the environment and environmental exposures play an important role. Therefore, the two Institutes have begun a series of studies to investigate exposure to pesticides, polychlorinated biphenyl compounds (PCBs), hazardous and municipal waste, water and air pollution, electromagnetic fields, dietary issues and certain reproductive variables as risk factors in developing breast cancer. The studies are known as the North Eastern Mid-Atlantic Breast Cancer Program and the Long Island Breast Cancer Study Project. These multi-center, multi-disciplinary projects are being funded and developed jointly by NCI and NIEHS and will provide much needed information in the search for the causes of breast cancer.

In the area of prostate cancer, NIEHS, NCI, and NIDDK co-sponsored a Request for Applications and co-funded 5 molecular epidemiology grants. The grants are investigating the possible roles of DDT and PCB exposure as well as fatty acids and other risk factors for prostate cancer. Other areas of interest are genetic susceptibility, biomarkers for genetic damage in prostate tissue, other environmental exposures and family history of prostate cancer. NIEHS and NCI also co-sponsored developmental grants for researchers to initiate prostate cancer research programs. Two that were funded have pilot projects which deal with occupational and environmental exposures and their link to prostate cancer development.

As you know, there is substantial evidence that exposure to pesticides is associated with a wide variety of health effects. Both acute and chronic effects have been observed in test animals and in humans, although long-term health effects have not been well studied in humans. A current collaborative research effort between NCI and NIEHS, known as the Agricultural Health Study, is underway and is designed to address the lack of knowledge in this critically important area. The study is investigating possible links between pesticide exposure and cancer in a group of 75,000 licensed pesticide applicators and their spouses, including a cohort of 1,000 African American farmers. The goal of the study is to identify risks related to specific pesticides and evaluate the influence of other known cancer risk factors. NIEHS investigators will also determine the incidence of diseases and conditions other than cancer including spontaneous abortion, neurologic disorders, degenerative eye diseases, menstrual and reproductive dysfunction, and several chronic diseases. This study is progressing well and results should be forthcoming within the next couple of years.

NIEHS and NCI have recently entered into an Interagency Agreement which will allow an NCI researcher, Dr. Michael Waalkes of the Inorganic Carcinogenesis Section of the Laboratory of Comparative Carcinogenesis, to occupy space in the new F-module laboratories at NIEHS. The presence of Dr. Waalkes will encourage inter-institutional collaboration in the critical area of heavy metal carcinogenesis. This collaboration will also fill an important need at NIEHS for expertise in heavy metals, and will foster day-to-day interactions between NCI and NIEHS in the area of carcinogenesis.

In the area of environmental justice, NIEHS, NCI, and other federal agencies have funded and supported the Institute of Medicine Study on Environmental Justice: Research, Education and Policy Needs. This study, which began in September of 1995, is investigating science and health issues important to environmental justice and will set priorities for research. NIEHS and NCI also support the Intercultural Cancer Coalition's efforts to address cancer in minorities and under served populations. In addition, NIEHS and NCI are supporting the Biennial Symposium on Cancer, Minorities and the Medically Underserved which will be held on April 22-27 and which will have special sessions addressing environmental justice issues.

As you can see, NIEHS and NCI have a great deal of collaborative research going on, but I have only highlighted some of these endeavors. Others include:ÿÿÿ

C Joint sponsorship of Environmental Carcinogenesis sessions at a Central and Eastern Europe Conference

C Joint Request for Applications on biomarkers of environmental disease

C Cosponsorship and organization of the First International Conference on Women's Health: Occupation and Cancer. (Also with the NIH Office of Research on Women's Health and the National Institute for Occupational Safety and Health)

C Collaborations with NCI Cancer Etiology staff on a conference and potential Request for Applications/Program Announcement on mechanisms of metals carcinogenesis

C Joint program announcement on the use of the Geographic Information Survey in environmental epidemiology

C Joint organization of a workshop for breast cancer research principal investigators at NIEHS, September 25-26, 1996

MAJOR GRANT FUNDING MECHANISMS

Mr. Stokes: According to the budget submission, the NIH considers investigator-initiated research project grants its highest priority. How many "new" research project

grants will your Institute support in FY 1997, and how does this compare to the number supported in FY 1996 and proposed for FY 1998?

Dr. Olden: Investigator-initiated research project grants are one of the highest priorities of the Institute. During FY 1996, NIEHS funded 88 "new" research project grants. In FY 1997 it is estimated that the NIEHS will pay 122 "new" research project grants and in FY 1998 the request contains an estimate of 112 "new" grants.

Mr. Stokes: In total, how many research project grants do you plan to fund in FY 1997, and how does this compare to FY 1998 proposed funding level?

Dr. Olden: During FY 1997 the NIEHS expects to fund 473 research project grants. During FY 1998 the Institute estimates that 482 awards will be made.

Mr. Stokes: What is the amount of funding allocated for RPGS in FY 1997 and at the budget request level?

Dr. Olden: During FY 1997 the NIEHS will allocate $107,078,000 for RPGs and in FY 1998 this amount will be $113,396,000.

SUCCESS RATE

Mr. Stokes: What is the NIEHS' grant success rate?

Dr. Olden: The NIEHS success rate for FY 1998 is expected to be 20.2%.

Mr. Stokes: In your professional judgement, how much is needed to bring NIEHS' grant success rate at least up to that of the NIH average?

Dr. Olden: Given that the NIH average is estimated to be 28.0%, the NIEHS would have to fund an additional 60 grants to reach the NIH success rate. Based on the estimated average cost of $227,000 per grant award contained in the current request, the NIEHS would need an additional $13,620,000 allocated toward grant awards over and above the request level.

Mr. Stokes: Please provide for the record a funding and success rate history table for the period 1989 to the FY 1998 estimate? In addition for FY 1997 and FY 1998, provide a chart that displays grant success rates by Institute in "grant success rate" rank order.

Dr. Olden: The first table shows the number of competing research project grants funded by NIEHS, their level of funding, and the success rate for 1989 through 1998. The second table shows the success rates by institute for FY 1997 and FY 1998.

NIEHS Competing Research Project Grants

Year	Number	Dollars in Thousands	Success Rate
1989	100	$18,124	27%
1990	104	18,841	28%
1991	103	19,186	27%
1992	129	24,207	29%
1993	112	23,741	21%
1994	113	23,639	25%
1995	94	19,130	16%
1996	131	28,066	21%
1997 Estimate	147	32,609	21%
1998 Estimate	146	33,139	20%

NIH Success Rates

ICD	FY 1997 Estimate	FY 1998 Estimate
NCRR	48%	45%
FIC	42%	40%
NEI	39%	37%
NIDCD	35%	36%
NIGMS	35%	35%
NIAID	33%	33%
NHGRI	27%	31%
NIA	34%	28%
NHLBI	30%	27%
NIDDK	29%	27%
NIDA	24%	27%
NINR	33%	26%
NINDS	25%	26%
NCI	26%	25%
NIMH	25%	24%
NICHD	22%	24%
NIDR	25%	23%
NIAMS	20%	22%
NIEHS	21%	20%
NIAAA	19%	20%

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are currently underway, and what are the expected benefits to be achieved from this investment?

Dr. Olden: There are two clinical trials currently underway at the NIEHS. Lead Clinical Trials. The Treatment of Lead-exposed Children (TLC) trial is a large, clinical trial already in place. This is a NIEHS-sponsored, four-center, placebo-controlled randomized trial to test the use of the drug, Succimer, as a treatment for the prevention of lead-induced alterations in growth, behavior, and development in children. The TLC trial was started in 1994 and is expected to be completed in 1999. Inner-city children who reside in old buildings are at particular risk for lead poisoning. The TLC trial is designed to determine if the drug Succimer, which can help remove lead from the body, thereby decreasing the adverse developmental and behavioral effects of lead on millions of children.

The Environmental Intervention In The Primary Prevention Of Asthma In Children (The EIPPAC Study). In children, asthma is a major, chronic disease afflicting 8-12% of the population with a disproportionately high prevalence among minorities and persons of lower socioeconomic status. This clinical trial is aimed at the primary prevention of asthma in children by environmental intervention in the homes of at-risk children. This trial will target children from low-income residences in North Carolina. An anticipated benefit of this study will be the reduction of the prevalence of asthma in children, thereby decreasing the economic burden of health care to the children's families and to the nation.

Mr. Stokes: What major clinical trials that are ready to be implemented will the FY 1998 budget request allow the Institute to pursue, and what are the expected benefits to be achieved?

Dr. Olden: No major trials are currently ready to pursue in FY 1998. However, with the arrival of our new Clinical Director this spring, NIEHS expects to expand our clinical studies research.

BUDGET FORMULATION

Mr. Stokes: Can you outline for the committee what NIEHS' budget request was at each state in the development and formulation of the FY 1998 budget?

Dr. Olden: All of the FY 1998 budgets were submitted in total by NIH until the OMB submission. The NIEHS non-AIDS OMB submission was for $302,279,000. The President's request is for $313,583,000.

AIR QUALITY

Mr. Stokes: Last year the committee urged the Institute to convene a national scientific summit on air quality issues. What is the status of that effort?

Dr. Olden: NIEHS has supported an effort with the American Lung Association to organize and convene a national scientific summit to address air quality issues during 1997. The summit is a multi-agency effort that will incorporate leadership from science research, federal agencies, environmental groups, at-risk communities, and organizations affiliated with human health effects research. Participants will engage in an open dialogue and scientific review of problems posed by and solutions in response to air pollution, respiratory illness, lead poisoning, and pesticide exposure in inner city neighborhoods.

ASTHMA

Mr. Stokes: Asthma continues to strike African Americans and children disproportionately, as compared to the general population. It appears air pollution and other environmental factors are key risk factors for asthma. Would you bring the subcommittee up-to-date on the NIEHS' asthma initiative?

Dr. Olden: Several important developments have occurred during the past year. First, asthma is a major chronic disease in the U.S. affecting as many as 20 million people and costing an estimated 6.2 billion dollars per year. The prevalence and severity of asthma in children is increasing, with disproportionate morbidity and mortality among Hispanic and African-Americans. A recent NIEHS-supported study has found the following: Childhood asthma is much more prevalent in Hispanics, primarily of Puerto Rican origin, (18.1%) and African-Americans (11.2%) than Caucasians (7%). Hispanic children experienced more severe asthma than African-American or Caucasian children.

Second, in another study, the major objective was to investigate the potential interactive and independent effects of ozone and aeroallergens -- pollens and molds -- on asthma. Key findings have shown that daily ambient levels of total fungal spores had a statistically significant effect on asthma symptom levels. This is the first study to show that outdoor levels of particular groups of fungal spore species, are associated with asthma symptom level and lung function.

Third, I visited the Hunts Point area of the South Bronx in May, 1996. Subsequently, NIEHS awarded a $27,000 supplement to the Mt Sinai Environmental Health Sciences Center to generate preliminary data on the incidence of pulmonary disease in a population of students in Hunts Point. Researchers will establish needed collaborations to develop a curriculum for nurses at Hostos Community College and Lincoln Hospital to enable them to become specialized in pulmonary care. These efforts are a first step toward decreasing morbidity and mortality associated with asthma in this area.

Finally, the NIEHS and the NIAID are co-sponsors and co-supporters of the extension of the National Cooperative Inner-City Asthma Study, now referred to as Targeting the Environment and Asthma Management - TEAM. This cooperative agreement is planned to reduce asthma morbidity among inner-city minority children, by modifying those potentially reversible factors which have been shown to contribute to asthma morbidity.

CANCER

Mr. Stokes: As the budget justification indicates, understanding the environmental components and basic biology of disorders can lead to effective prevention and intervention strategies. What progress do you have to report since you were here last with respect to environmental hazards and cancers in general, and breast and prostate cancer in particular?

Dr. Olden: NIEHS supports a variety of research, prevention and intervention activities focused at reducing the burden of morbidity and mortality from cancer. Environmental exposures are thought to be involved in the complex etiology of many forms of cancer. Reducing levels of these agents in the environment and thereby reducing human exposure can provide sensible strategies for prevention. We have made significant progress that is relevant to environmental hazards and cancers in general and breast and prostate cancer in particular. A few of the highlights include:

Prostate Cancer - Vitamin D has been associated with risk for prostate cancer. NIEHS scientists have found that 20% of men inherit a variant form of the vitamin D receptor and that these men have one-third the risk of developing prostate cancer. The KAI1 metastasis suppresser gene for prostate cancer has also been identified by NIEHS scientists and shown to be commonly altered in prostate, lung, and breast cancers.

Breast Cancer - NIEHS researchers have shown that breast cancers arising in women with hereditary non-polyposis colorectal cancer (HNPCC) possess a genomic instability phenotype. Additionally, the inherited mutation in the mismatch repair gene from these women is homozygously mutant, suggesting that breast cancer is part of the HNPCC syndrome/spectrum. These results implicate defective mismatch repair genes as another cause of inherited breast cancer.

NIEHS, in collaboration with NCI, supports new programs to stimulate research in breast and prostate cancer. A special area of emphasis of these programs is the role of environmental exposures in the risk of cancer in high risk populations. Prevention activities also exist within each of the four breast cancer programs and two prostate cancer programs co-sponsored by the two institutes.

EPIDEMIC OF PULMONARY HEMORRHAGE AMONG CLEVELAND INFANTS

Mr. Stokes: Approximately 90 cases of pulmonary hemorrhage in infants have been reported to the CDC, about a third of the cases have been in Cleveland, Ohio. All

but two of the Cleveland infants were African American, most were male. A CDC investigation has linked the disease to exposure to toxins produced by a mold found in the infants' homes. To what extent is there research underway to help develop rapid methods to detect and quantify airborne toxic fungi? Is there research underway or planned in animal models that would delineate the role of different fungal toxins in producing human disease in infants?

Dr. Olden: At present there does not appear to be a rapid method to detect and quantify these mold toxins, nor is there ongoing research on animal models. However, research grant applications to develop an animal model and to study the disease in humans and to develop a detection method are under consideration at the Institute. One of the aims is to develop a valid biomarker of exposure to toxins produced by this fungus. If this work is successful, it may begin to provide a better understanding of the pathogenesis and pathophysiology of this serious and unfortunate disease in young infants.

BREAST CANCER

Ms. Pelosi: As you know, the San Francisco Bay area has had one of the highest breast cancer rates in the world. You are aware of the great concern that this rate is linked to environmental factors. Report language in the FY 1997 Appropriations bill urges the NCI to work with community groups and the National Institute of Environmental Health on this concern. The NCI's response to this language cites the Long Island Breast Cancer Study Project as an example. The Bay Area studies cited in the response do not focus on breast cancer in the Bay Area and only one, which is not funded by the government, looks at the epidemiology of breast cancer. Does the NIEHS have plans to study the San Francisco Bay Area with regard to the possible environmental links to breast cancer?

Dr. Olden: NIEHS is aware of the high rates of breast cancer in the San Francisco Bay area and has been in contact with staff at NCI. For the past four years, NIEHS has supported a research program focussed on expanding our knowledge base of the relationship between chemical and physical agents commonly found in our environment, such as pesticides, polyaromatic hydrocarbons and radiation--both electromagnetic and ionizing--and breast cancer risk. NIEHS supports epidemiologic research which addresses risks from these exposures in a variety of human populations and fundamental laboratory based research which will help us understand the mechanism of action of these agents on the mammary gland which may lead to cancer.

During this time, NIEHS and NCI have collaborated on some of these initiatives. NIEHS and NCI jointly support 6 studies in the Northeastern - Midatlantic Region of the U.S. in which investigators are measuring organochlorine pesticide levels in the blood of women with breast cancer and comparing these measurements to women without breast cancer. Other risk factors such as other environmental exposures, diet, and lifestyle habits are also being studied. NIEHS is an active partner with NCI in the Long Island Breast Cancer study. In this study research is being conducted to quantify the risk of breast cancer in women associated with exposure to agents such as organochlorine pesticides, electromagnetic field radiation, air pollution, metals and other chemicals in drinking water. NIEHS is not currently supporting any studies of breast cancer in the San Francisco Bay Area. NIEHS would again partner with NCI, if and when NCI takes on new initiatives in this region.

Ms. Pelosi: In the San Francisco Bay Area alone, possible exposure sources to radiation are plentiful: Lawrence Livermore and Lawrence Berkeley Labs both leak tritium and nuclear ships were decontaminated in the San Francisco Bay following World War II. Medical radiation also causes breast cancer. Has radiation, a known carcinogen for breast cancer, been included in NIEHS' studies?

Dr. Olden: In the studies in the Northeastern Region of the U.S., including the Long Island Breast Cancer Study Project and in populations in California and North Carolina several investigators are gathering data on medical radiation. Questionnaires in these studies include items quantifying the number of and indications for medical

radiation over the lifetime of the study subjects. These are very difficult data to collect and subject to misclassification because of problems inherent with recalling one's radiation histories. If women were exposed to radiation as part of their job, this information will be recalled as part of their occupational histories. No other information on sources of environmental radiation is being collected by study investigators.

ENVIRONMENTAL JUSTICE

Ms. Pelosi: Have there been any findings or recommendations in the NCI/NIEHS collaborative Environmental Justice study regarding the linkage between the environment and cancer in low-income and minority communities? If not, when does the committee plan to release its findings?

Dr. Olden: NIEHS, in conjunction with many other federal agencies has funded and supported the Institute of Medicine Study on Environmental Justice: Research, Education and Policy Needs. This independent scientific study began in September, 1995, to assess medical science and health issues related to environmental justice and set priorities for medical research. The Committee has not yet completed its work, and, therefore, there are no results available for review.

The Study committee has completed site visits to locations around the country where environmental justice issues are of concern -- New Orleans, LA; Spokane, Washington; Chicago, IL; and Tucson, AZ. A final committee meeting was held and the draft report is scheduled for completion in early spring. The committee report and recommendations will be subject to a scientific peer review process, and the final report is anticipated to be available to the agencies and the public by the end of 1997.

NATIONAL TOXICOLOGY PROGRAM

Ms. Lowey: The National Toxicology Program issues advisories to the public about chemical hazards. Please provide the number of advisories issued in each year of the program since it was created.

Dr. Olden: The National Toxicology Program is a comprehensive chemical research and testing program performing studies of varying complexity on hundreds of chemicals every year. These studies evaluate chemicals for their potential to cause cancer, reproductive effects, birth defects, neurological disorders, immunotoxicity, and other adverse health effects. Most of these results are published in the peer reviewed scientific literature and are used by regulatory and other agencies as a basis on which to issue guidelines or regulations concerning chemical safety. The NTP also publishes the Biennial Report on Carcinogens, a Congressionally mandated assessment of chemicals, agents or substances either reasonably anticipated or known to cause cancer in humans. Volume 8 is about to be published and contains notifications concerning approximately 200 agents, substances or mixtures. Much of the information on which these entries are based comes from the chronic rodent toxicity and carcinogenicity studies of chemicals performed by the NTP. These studies were the principal program activity when established in 1978. Findings from these studies are peer reviewed and published as technical reports. The number of reports issued through this peer review process follows for each year of the program existence.

YEAR	NUMBER OF REPORTS
1979	11
1980	16
1981	21
1982	16
1983	9
1984	16
1985	22
1986	14
1987	17
1988	23
1989	23
1990	20
1991	26
1992	21
1993	15
1994	19
1995	17
1996	12

BERYLLIUM

Ms. Kaptur: Dr. Olden, last October, the NIEHS published in its *Environmental Health Perspectives Supplements* the proceedings of a symposium the Institute held on beryllium-related diseases. I am particularly interested in this subject since one of our country's major producers of beryllium and beryllium alloys is in my district, and a number of my constituents suffer from chronic beryllium disease (CBD). The participants at that symposium identified a number of areas where additional research is required; however, I understand that NIEHS is not presently conducting any research on beryllium-related diseases.

In a recent letter to me, your predecessor, Dr. Paul Kotin, pointed out four specific areas where he believes research is both timely and needed. These areas are:

1) The documentation of the chemical structure of DNA sites involved in susceptibility to CBD and the demonstration of the mechanism or mechanisms by which it exerts its effects;

2) Development of a test with a high level of specificity and sensitivity capable of identifying individuals who may have an inherent genetic susceptibility to CBD;

3) The standardization of diagnostic criteria and clinical pathologic diagnostic modalities for CBD; and

4) Determination of the physical, chemical and steric properties of beryllium in the work place to determine if the size distribution, the particle number, and/or the particle morphology are critical factors in the production of CBD in the worker.

I would appreciate it if you could report on the status of CBD research at NIH and nationally. Also, please respond to Dr. Kotin's proposals for CBD research. Are they the appropriate direction in which new CBD research should go? Are there other areas you would recommend?

Dr. Olden: Dr. Kotin's proposals are consistent with research directions noted at the November 1994 conference, namely additional studies of the toxicology of beryllium in animal models, the development of biomarkers for CBD that identify hypersusceptible individuals and preclinical disease, and research on prevention. NIEHS as well as other NIH Institutes support considerable research on mechanisms of DNA injury and repair as well as the molecular mechanisms of cell injury and carcinogenesis. Such information is indirectly related to beryllium health effects but is essential background for conducting and understanding specific research on CBD. NIEHS does support some research that is specifically focused on CBD. Some of this research was reported by Dr. Lee Newman of the National Jewish Center for Immunology and Respiratory Diseases and the University of Colorado Medical Center at the NIEHS Beryllium Conference.

Dr. Newman is a recipient of a Public Health Service Physician Scientist Award from NIEHS for studies on Environmental/ Occupational Health, and is a recipient of a basic research award to determine the significance of the blood beryllium lymphocyte transformation test as indicator of CBD.

Ms. Kaptur: What would you propose for a course of research on CBD?

Dr. Olden: The future course of Dr. Newman's research will determine the influence of macrophage-derived interleukin-6 on beryllium-specific T cell responses in humans with exposure to beryllium in order to recognize pre-clinical or sub-clinical stages of the disease. Further studies will determine the value of these immune biomarkers as indicators of disease prognosis and response to therapy.

Ms. Kaptur: What time frame would be appropriate?

Dr. Olden: It is proposed that the planned studies will be completed in 3 to 5 years but completion will depend on findings and how results of the research can be applied to assist workers.

Ms. Kaptur: What budget would you recommend?

Dr. Olden: A major portion of the NIEHS research budget is directed toward molecular biology and mechanisms of toxicity. The budget for specific research on CBD is less that $1 million per year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

FY 1998 Budget	Page No.
Organization chart	2
Appropriation language	3
Amounts available for obligation	4
Justification	5
Budget mechanism table	16
Budget activity table	17
Summary of changes	18
Budget authority by object	20
Administrative costs	21
Significant items in House and Senate Appropriations Committee reports	22
Authorizing legislation	29
Appropriation history	30
Detail of full-time equivalent employment (FTE)	31
Detail of Positions	32

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Organization Structure

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

For carrying out sections 301 and 311 and title IV of the Public Health Service Act with respect to environmental health sciences, [$308,819,000] *$313,583,000.*

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 1997 P.L. 104-208)

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$288,898,000	$308,819,000	$313,583,000
Rescission in accordance with P.L. 104-134	(520,000)	---	---
Reduction in accordance with P.L. 104-208	---	(332,000)	---
Subtotal, Adjusted Appropriation	288,378,000	308,487,000	313,583,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority	(764,000)	0	0
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	(6,051,000)	(6,489,000)	0
Subtotal, adjusted budget authority	281,563,000	301,998,000	313,583,000
Unobligated balance, lapsing	0	0	0
Total obligations	281,563,000	301,998,000	313,583,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1996 - $76,247,000; FY 1997 - $81,000,000; FY 1998 - $81,000,000

Also excludes funding for HIV activities included in the NIH OAR: FY 1998 - $6,324,000

Note: Excludes $130,000 in FY 1996 and $46,000 in FY 1997 for royalties.

Justification

National Institute of Environmental Health Sciences

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended. Reauthorizing legislation will be proposed.

Budget Authority:

FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
640	$281,563,000	640	$301,998,000	640	$313,583,000	0	+$11,585,000

Introduction

This document provides justification for the FY 1998 Non-AIDS activities of the National Institute of Environmental Health Sciences (NIEHS). Justification of NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The NIEHS supports research to identify the role of environmental agents in disturbing normal physiologic processes, leading to human disease. Understanding this relationship will allow us to design prevention/intervention strategies for the benefit of public health. Although direct links between environmental agents and health outcomes have been established for some diseases, there are numerous chronic dysfunctions and diseases where there are minimal scientific data to substantiate a role for the environment in their etiology or progression, despite the plausibility of these hypotheses. Thus the goal of NIEHS is to understand: (1) how environmental exposures affect our health, (2) how individuals differ in their susceptibility to these exposures, and (3) how these susceptibilities change as a function of age. To fulfill this mission and reduce the burden of environmentally associated diseases and dysfunctions, the Institute provides the science that is necessary to understand the impact of the environment on human health, translates this information into prevention and intervention strategies, and communicates this information to the American public.

The mission of the NIEHS, though formidable, is extremely important. Diseases and dysfunctions with an environmental component include cancer, birth defects, infertility, neurological impairments, immune disorders, and lung dysfunctions. Because environmental exposures can be controlled or avoided, they represent one of the most promising means of improving our Nation's health. The potential cost benefits are illustrated by recent national

health expenditures - $949.4 billion in 1994 (Health Care Financing Review, Vol. 17, Number 3, Spring 1996.) - and projected expenditures of $2.2 trillion in the year 2005. (Health Care Financing Review, Vol. 16, Number 4, Summer 1995.) Effective prevention and intervention strategies could significantly reduce these costs.

Improving human health by reducing harmful environmental substances has both health and economic benefits, but these benefits can incur economic costs. The NIEHS will have an increasingly important role as public policy makers struggle to balance human health needs with the economic benefits of commercial development that might endanger that health. Their decisions will only be as good as the science upon which they rest.

Stories of Discovery

Air Pollution: Air pollution caused by energy use, agriculture, and industrial activities is changing the composition of the atmosphere and of the biological systems it supports. NIEHS has a long history of air pollution research, most notably the extensive 6-cities and 24-cities studies that have tracked the health impact of such common air pollutants as ozone, acid aerosols, and particulate matter. These studies have shown that respiratory symptoms from these pollutants are more serious in children. The Environmental Protection Agency (EPA) used these results to develop guidelines for sulfur dioxide and particulate matter emissions.

Research in this area continues. For example, a study has shown that late-stage pregnant and lactating rats are inherently sensitive to lung inflammation caused by ozone. If the same sensitivities occur in pregnant and lactating women, the health implications are tremendous. NIEHS is focusing on identifying the mechanism of this enhanced sensitivity so that its relevance to humans can be assessed. Other research, some in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), is investigating the role of air pollutants and indoor allergens as risk factors in the development and exacerbation of asthma in children. Given that asthma is on the rise as a major chronic disease, affects 20 million U.S. citizens, and costs $6.2 billion every year, the potential benefit of this research to identify new prevention schemes is substantial.

Lead and Its Many Health Effects: The NIEHS has testified to Congress many times on the health effects of lead. At high levels lead is toxic to blood, kidney, and the nervous system. In children, even low levels of lead exposure can be quite harmful. NIH/NIEHS-supported research has shown that at levels previously thought safe, exposed children suffer from lower intelligence scores, poorer coordination, and, as they mature, aggressive and delinquent behaviors. Congress and regulatory agencies responded to this evolving body of knowledge by banning many of the sources of environmental lead. Their actions include the banning of leaded gasoline in the late 1970s, the banning of lead-based paints in 1978, and the continued lowering of "concern thresholds" for blood lead levels. These efforts have resulted in a drop of the percentage of children with blood lead levels (at or above 10 ug/dL) from 89% in 1980 to 8.9% in 1991. (B. Brody, J. Pirkle, and R. Kramer, JAMA 272:277-283, 1994.) These reductions are significant because an estimated 3 - 4 million children in the U.S. have elevated blood lead levels, with treatment costs of $1300 per child and special education costs of $3331 per child. Much work

still remains, because lead exposures continue in the form of flaking paints in old buildings, contamination of soils from paint and gasoline exhausts, and leaching of lead into drinking water supplied through lead soldered pipes. Nonetheless, lead abatement serves as an encouraging illustration of what this Nation can accomplish when good scientific findings are acted upon by legislators and regulators.

Recent research indicates that our continued resolve to reduce environmental lead, in addition to providing improved intellectual development for our children, might well result in future reductions in two major health problems - hypertension and renal failure. High blood pressure, or hypertension, is a leading risk factor for heart disease. A new NIEHS-supported study showed that in a group of middle-aged and older men, bone lead levels were significantly associated with risk for hypertension. Kidney, or renal, damage is another serious health problem, one that can translate into kidney failure, dependence on dialysis machines, and death itself. A recent NIEHS-supported study showed that even low blood lead levels correlated with significant reductions in kidney function as measured by serum creatine concentration. These findings show that lead abatement and treatment programs might serve as new preventive strategies for a host of diseases that were not originally targeted.

Gene-Environment Interactions: Environmental exposures play important roles in our health at every stage of life and our susceptibility to these exposures depends upon our genetic makeup. Thus, superimposed on environmental influences on human health is the fact that each individual differs in his/her susceptibility to these agents. This wide variability in responsiveness has been a major complicating factor in defining the environmental components of disease.

For example, the ability to withstand exposure to the nerve gas, sarin, is in part genetically controlled. The NIEHS-supported researcher who made this discovery was studying the molecular events by which an important group of pesticides - the organophosphates - exert their toxicity. Nerve gases such as sarin are also organophosphates and probably act through the same mechanisms. This researcher was studying paraoxonase (PON1), the enzyme responsible for destroying the lethal forms of organophosphates. He found that the gene coding for the PON1 enzyme comes in different types. Type Q was very good at producing PON1 enzyme and thus in protecting against organophosphates. Type R produces a PON1 enzyme that is inefficient in destroying organophosphate, and thus would render an individual much more susceptible to organophosphate nerve gases and pesticides. Individual inheritance of these genes varies by ethnic group. Caucasians are most likely to have inherited the resistant gene pattern and Asians are most likely to inherit the susceptible gene pattern; African-American susceptibility has not yet been determined.

This work illustrates the sometimes unexpected applications of research that has been supported over many years. Genetic control of detoxification, important in understanding the health consequences of environmental exposures, has been a long-term NIEHS research focus. Although nerve gas exposures were not the original motivation for this research, these findings nonetheless translate into this other arena of environmental exposure.

Another example would be the 30 years of NIEHS research on the detoxification enzyme, glutathione S-transferase, or GST. It is now known that there are many different genetic variants of this enzyme. One, GSTT1, is missing in fifty million Americans. Scientists at NIEHS have now shown that these people are much more likely to get a serious, often fatal, bone marrow disease. The condition, a cancer-like condition of rapid cell growth called myelodysplastic syndrome, or MDS, is not only serious in itself, but also leads to a form of adult leukemia in about 30 % of cases. The individuals missing the gene do so because they inherited this gene defect from both parents; researchers speculate that people missing the gene will prove especially susceptible to a variety of chemical-related diseases.

One of the most novel plans to explore gene-environment interactions is the NIEHS Environmental Genome Project. This project capitalizes on the fact that we are now able to categorize many of the susceptibility genes into five broad classes: Genes controlling the distribution and metabolism of toxicants; genes for the DNA repair pathways; genes for the cell cycle control system, including apoptosis (programmed cell death); genes for metabolism of nucleic acid precursors; and genes for signal transduction systems controlling expression of genes in the other classes. The NIEHS Environmental Genome Project will be a broad, multi-center effort to obtain information about DNA sequence diversity in the U.S. population on all of the more than 200 environmental disease susceptibility genes now recognized. The project will be expanded as additional susceptibility genes are discovered.

The availability of a population database on environmental disease gene diversity will allow us to conduct much more focused molecular epidemiology that relates environmental exposures and disease to individual susceptibility genotype. Ultimately information from such medical genetic epidemiology will allow us to greatly enhance public health through better prevention strategies for environmental diseases.

Of Mice and Men - New Approaches to Toxicologic Testing: The annual cost to industry for regulatory compliance is $115 billion, yet there are still 70,000 chemicals in commerce for which there is little or no toxicologic data. (OTA Report: Research Health Risks, 1993.) This shortfall will continue until there are quicker, more reliable, and less expensive alternatives for conducting these studies. Equally important, these alternative test systems must meet the needs of the regulatory agencies that require them. The NIEHS, under the auspices of the National Toxicology Program (NTP), has been addressing this issue in a variety of ways.

First, new animal models are being evaluated that could reduce the time required for a cancer bioassay from two years to six months. This reduced time would improve timeliness of product delivery, would reduce the costs of these products to the public, and would enhance profits for industry and its stockholders.

Second, the NIEHS/NTP is capitalizing on recent developments in molecular biology to develop a more mechanistically based toxicologic data base. Under this scheme the actual biological events that lead to toxicity would be determined and their relevance could be more rationally extrapolated from rodents to humans. Equally important, chemicals having similar molecular mechanisms could be assumed to have similar toxicities, thus requiring testing of only a few

candidates of a chemical family rather than every single chemical. Incorporated into risk assessment schemes, mechanistic data could lead to more relevant risk assessment determinations, thus ensuring that regulatory standards protect the public health without being needlessly restrictive to economic growth and vitality.

Third, the NIEHS/NTP is actively developing partnerships with all the affected stakeholders - private industry, legislators, regulatory agencies, labor unions, and environmental advocacy groups. Everyone's participation and consensus will be necessary if the regulatory structure is to be changed to accept alternative test models and mechanistic data. In addition to ongoing consensus-development meetings, the NIEHS/NTP is establishing an Interagency Center for the Evaluation of Alternative Toxicological Methods. With industry and federal support, this Center will provide scientific peer review and evaluation of new alternative test methods. The ultimate goal is to lead to the adoption of improved testing methods that will be cheaper, faster, more relevant, and lead to reduction in animal use. This Center will also eliminate duplicative efforts across regulatory agencies, provide a forum for harmonization of testing requirements across the Federal government and internationally, and provide industry with a mechanism for achieving regulatory acceptance of innovative test systems.

Finally, the university-based research community has responded to a recent NIEHS Request for Applications designed to encourage and support the use of transgenic model systems in molecular toxicology. This initiative stimulated innovative, mechanistically-based approaches for elucidating the regulation of gene expression induced by environmental agents in specific target cells and organs, and for determining how this response varies at critical times during exposure. Research supported through this initiative is being directed toward the potential implications of environmental agents in non-cancer disease endpoints as well as cancer-related endpoints.

Hormonally Active Environmental Compounds - Health Effects of Endocrine Disruptors: Endocrine disruptors are environmental compounds that have the ability to interfere with natural hormonal processes. Among the suspected chemicals are pesticides, plasticizers, industrial compounds, and natural products. These compounds have diverse chemical structures and may act through diverse mechanisms.

To date the most compelling evidence for environmental endocrine disruption has been found in wildlife populations. It is possible that effects observed in reptiles, birds, fish and amphibians are an early warning for a human health problem. Human exposures, however, are at much lower levels than that experienced by affected wildlife and it is still unclear if these low level exposures can exert adverse effects on humans. It is an important research question both because of the significant health effects attributed to these compounds and because of their widespread distribution in the environment.

NIEHS is a pioneer in conducting research on the health effects of endocrine disruptors. NIEHS convened international conferences on "Estrogens in the Environment" in 1979, 1984, and 1994 and alerted the research community to this potential health problem. A broad range of studies

continue to explore the various effects of exposure to environmental estrogens and other endocrine disruptors. Examples include:

o Pesticides, pharmaceuticals, industrial chemicals and by-products, incineration products, and natural plant components that are known or alleged to exhibit endocrine disruption action have been under investigation since the 1970s. NIEHS scientists did much of the early work on two notable endocrine disruptors - the pharmaceutical, diethylstilbestrol (DES) and the incineration by-product, dioxin. These and other agents are evaluated for cancer-causing ability, reproductive effects, effects on the immune system, neurologic effects, and effects on the fetus and newborn.

o Investigations are underway to develop and validate biomarkers of estrogen and dioxin exposure. Such biologic indicators are designed to provide early evidence of exposure to endocrine disruptors and to indicate the potential for adverse effects for a given exposure level.

o The mechanisms through which endocrine disrupting chemicals affect reproductive health are being investigated by molecular approaches and the development and use of genetically altered (transgenic) animals. These studies are helping us to more rapidly determine if an agent is linked to an adverse health effect.

o Combinations of test-tube and whole animal assays are being developed and evaluated with the purpose of providing a rapid, informative, and reproducible means by which to determine the estrogenicity or dioxin-like potency of environmental chemicals. These studies will help determine which agents in the environment possess endocrine-disrupting potential.

o NIEHS has made significant contributions in identifying knowledge gaps that create uncertainty in risk assessment for receptor-mediated toxicants and designing research to fill those gaps. These studies integrate basic research, toxicology, epidemiology and biomathematics. Biologically-based dose response models have been developed for receptor-mediated toxicants and comparative studies have been completed on responses to dioxins in experimental systems and people.

o The university-based research community has responded to a recent NIEHS Request for Applications designed to encourage and support research targeted on endocrine disruptors.

o NIEHS will convene the fourth "Estrogens in the Environment" conference in 1997.

Annual Scientific Advances

This past year has shown the fruition of many years of NIEHS-supported research in some of the most promising areas of environmental health. Highlights of these discoveries follow.

Research advances in the area of "New Preventive Strategies Against Disease":

Lowered Intelligence from Fetal Exposure to Polychlorinated Biphenyls: Reduced intelligence is an unfortunate legacy of early exposure to a common group of environmental contaminants, polychlorinated biphenyls (PCBs). These compounds are widely distributed in the environment due to previous uses in electric transformers, paper recycling, and other commercial processes. NIEHS-supported scientists have shown that when the child is exposed to PCBs while in its mother's womb, serious neurological problems can develop. These problems translate later in life into lower I.Q. scores, poor reading comprehension, memory problems, and difficulty in concentration. Although PCBs have long been banned, partly in response to earlier NIEHS study results, they still contaminate many waters and soils. For this reason caution should be exercised in eating fish from contaminated waters; women of child-bearing age and children under 15 are especially advised to avoid this food source.

Optimal Time and Conditions for Conception: NIEHS scientists have discovered that in healthy women, conception is most likely to occur following intercourse during a six-day period up to and including the day of ovulation. This is critical information that can change advice given couples trying to conceive. Another NIEHS study found that the simple practice of douching can reduce a woman's chance of getting pregnant by 30%. Among young women (18 to 24) this reduction was even greater - 50 %. These studies provide women wanting to become pregnant with useful information on practices to avoid that might impede their chance of conception.

Environmental Causes of Birth Defects: NIEHS has a long history of examining the role of environmental agents and birth defects. This work continues today with the recent findings that fever-induced heat during pregnancy can modulate development of the skeleton. The effect of increased heat has been traced to alterations in development that control symmetry - that is the processes ensuring the left and right sides of the body are the same. Since fever-inducing infections are not uncommon during pregnancy, the potential impact of this work is substantial. In a similar line of investigation, researchers have discovered that exposure to the anticonvulsant drug, valproic acid, during pregnancy can cause a variety of craniofacial defects as well as maldevelopment of the somites of the vertebral column in animals. Once the mechanism of these defects is clarified, new therapies can be devised that avoid these side effects.

Prevention/Intervention of Miscarriages: A major cause of pregnancy loss during the first trimester is failure of the neural tube to close, resulting in an open skull and backbone. NIEHS-supported researchers have discovered that this malformation and the resulting pregnancy loss can be prevented by administration of an amino acid, methionine, prior to and during the pregnancy. Methionine intervention/prevention strategies have been successful in animal studies as well as in preliminary studies in humans. Researchers have also developed a test that can determine if a woman is predisposed to miscarriage due to neural tube closure problems.

Research advances in the area of "Genetic Medicine":

Prostate Cancer and Vitamin D: Every year over 300,000 men worldwide are diagnosed with prostate cancer (E. Giovannucci, Cancer 75:1766-1777, 1995.) and it appears that vitamin D is an

important risk factor for this disease. Vitamin D's effectiveness in the body is dependent upon the presence of a critical protein, the vitamin D receptor. People inherit different versions of the gene that codes for this receptor. NIEHS scientists examined men with and without prostate cancer and analyzed their inherited vitamin D receptor genes. They found that 20% of men inherited a particular version of the gene and that these men had one third the risk of developing prostate cancer. These findings suggest further avenues of investigation that could lead to new prevention strategies for this common cancer.

Gene Isolation Shortcut Uncovered: In a process that could speed gene research and help in development of gene therapies, NIEHS scientists have found a way to isolate and clone genes and other chromosome fragments directly. The method bypasses the lengthy, indirect and cumbersome method in current use. This new approach relies on cloning DNA into yeast cells in a process called transformation-associated recombination (TAR). TAR, because it involves less manipulation and less time than conventional methods, is expected to provide opportunities to better understand errors in genetic diseases as well as to aid in the isolation of chromosomal material to be used in gene therapy.

Research Advances in the area of "New Approaches to Pathogenesis":

Novel Signaling Pathways for Estrogen: NIH-supported scientists studying the effects of pesticides on skin cancer in mice unexpectedly discovered that estrogen blockers initiated hair growth and that estrogen itself stopped hair growth activity. Estrogen as a signal for turning off hair growth is a novel discovery. Conventional thinking has focused on testosterone as the hormone most linked to baldness and thinning hair. This new discovery reveals other, possibly more promising. avenues of research for the commercial sector. In a separate study on cell signaling, scientists at NIEHS have shown that growth factor stimulation can mimic estrogen-stimulated uterine growth in a hormone-dependent manner. Studies using an estrogen receptor knockout mouse clearly illustrated that growth factor action required a functional estrogen receptor to complete this signal coupling mechanism. These studies also indicate other areas in which estrogen acts as an important signal for directing cellular events.

Biological Link Between Cigarette Smoking and Lung Cancer: Although epidemiologic studies have long shown an association between cigarette smoking and lung cancer development, the biological underpinnings to demonstrate actual causality have been lacking. New research by NIEHS-supported scientists have come a step closer to this proof. Studying the tumor suppressor gene, *p53*, these scientists showed that the cigarette smoke byproduct, benzo(a)pyrene, when subsequently metabolized in the body to the carcinogen BPDE, preferentially bound to this gene at three sites. These sites are also the exact areas that are found to be mutated in lung cancer cells. These mutational "fingerprints" can serve to link exposure to the carcinogen with the final lung cancer outcome.

DNA Synthesis and Repair: Genetic DNA represents the blueprint upon which biological life is regulated. Environmental agents are able to damage DNA and, through this damage, affect human health. Understanding the basic mechanisms by which the body reproduces and repairs DNA gives important insight into how environmentally-induced damage occurs and can be

corrected. A NIEHS-supported researcher recently presented the first structural information on the mechanism of templating for a nucleic acid polymerase. These studies were the first demonstration that polymerase-beta is responsible for gap-filling DNA repair synthesis in mammalian cells. Knowledge of the detailed mechanism of polymerase-beta activity will enhance our understanding of the molecular basis for DNA synthesis associated with DNA repair.

Molecular Mechanisms of Chromium: Chromium compounds have been shown to be human carcinogens in some epidemiological studies, but little mechanistic information is available. Studies focused on cellular pathways critical to the carcinogenic activity of chromium have found that chromium (VI) undergoes activation by several metabolic pathways, a process which results in different types of DNA damage in different tissues. In addition, results suggest that it may be possible to modulate the level and type of chromium(VI)-induced DNA damage with vitamin therapy leading to preventive protocols which will reduce cancer risk for chromate-exposed populations. In biotransformation studies a major pathway for the generation of intermediates responsible for chromium mutagenesis and carcinogenesis has been found. This work further demonstrates the mechanism by which chromium damages DNA and causes mutations in cells. The spectrum of mutation induced by chromium resembles the spectrum induced by other agents that cause oxidative damage to DNA, suggesting a role for reactive oxygen species in chromium-induced mutagenesis. Others have shown that chromium (III) alters the kinetics and decreases the fidelity of DNA replication by interacting with DNA. These results suggest important consequences for mutagenesis, and lend themselves well to mechanistic studies to be used in molecular intervention.

Tumor Suppressor Expression: The gene, *p53*, is an important tumor suppressor gene that is "turned on" or expressed in response to damage to DNA. An NIEHS-supported researcher has shown that individuals suffering from Ataxia-telangiectasia, a disease that renders them very cancer-prone, are defective in a gene, *GADD45*, that appears critical to activation of *p53*, a necessary step in its ability to exert tumor-suppressive effects. This work is important because it suggests that the *GADD45* gene plays a role in the cell processes that eventually lead to cell division, cell death, and, ultimately, cancer progression.

Research advances in the area of "Computers and Advanced Instrumentation":

Improvements in Translating Rodent Studies to Humans: Structural biology is having a great impact on environmental health research. Over a decade of NIEHS-supported research recently culminated in the ability to present three dimensional models that assess the similarity, or homology, between different toxicant metabolising enzymes. These enzymes represent one of the most important ways in which biological systems convert ingested harmful environmental substances into less toxic, easily excretable compounds. Understanding how similar, or different, these critical enzymes are across species is obviously important in extrapolating the toxicology results in rodents to their relevance for the human condition. These structure-activity studies represent substantial progress toward rationalizing and predicting individual, strain, and species differences in toxicant metabolism. In turn, it may be possible to link such findings to individual differences in susceptibility to toxicants. In addition, knowledge of the structural basis of

metabolizing enzyme specificity may lead to the rational design of inhibitors that modulate this metabolism.

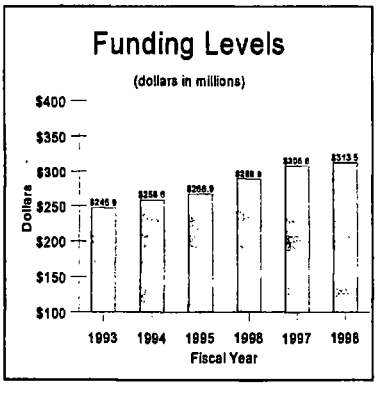
Benefits and Impact of Research

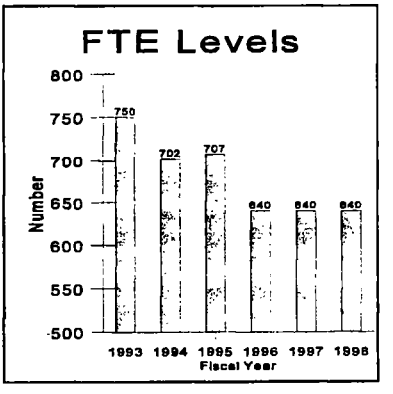
Understanding the environmental components and basic biology of disorders can lead to prevention and intervention strategies that circumvent many adverse health effects. Traditionally these strategies have focused on eliminating or reducing environmental exposures. These approaches will continue to be important parts of the Nation's environmental health programs. NIEHS is working to improve risk assessment methodology so that regulation is not needlessly restrictive, but rather protects both public health and economic vitality.

As we understand the molecular and cellular basis of environmentally associated diseases, prevention and intervention techniques could be developed to treat people following an adverse environmental exposure. These molecular intervention techniques would rely on manipulations of the biological mechanisms underlying environmentally induced diseases, such as detoxifying enzymes, receptors, and other molecular components. They would be particularly useful in dealing with environmental exposures that are ubiquitous or difficult to eliminate. Further, they would have important implications in the pharmaceutical and pesticide industries, which could in the future develop products with maximum effectiveness and minimum side effects.

Budget Policy

The FY 1998 budget request for NIEHS is $313,583,000, an increase of $11,585,000, or 3.7 percent, over the FY 1997 estimate. Seventy-two percent of the budget request would support research grants, training, and contract activities, and 28 percent of the request would support intramural research and research management activities. The FY 1998 request will support 640 full time equivalent positions (FTEs), the same as FY 1997. Total funding and FTE levels for the NIEHS during the last five years are shown below:





Of the increase requested in FY 1998, $8,750,000 is targeted toward special areas of emphasis to highlight NIH initiatives. The NIH areas of emphasis and the corresponding targeted increases include: biology of brain disorders -- $1,500,000, new approaches to pathogenesis -- $1,000,000, new prevention strategies against disease -- $2,250,000, and genetics of medicine -- $4,000,000.

The FY 1998 budget request would support 146 competing RPGs, one less than in FY 1997, and 482 total RPGs, an increase of 9 total RPGs over FY 1997. NIH policy links RPG average cost increases to total program budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for research project grants (RPGs). In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs will increase by up to two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP).

Eighteen environmental health sciences centers and five marine and freshwater biomedical sciences centers would receive $24,137,000 in support from this request, an increase of $473.000 over FY 1997. Other research grants would receive $7,526,000, an increase of $148,000 over FY 1997.

The FY 1998 request would support 500 research trainees at an estimated cost of $12,041,000, an increase of $236.000 over FY 1997.

Contracts to support research and development in toxicity testing and test development, in risk estimation methods. and for other scientific problems in environmental health are projected at $68,575,000. Approximately 114 contracts would be supported, an increase of $3,244,000 and two awards over FY 1997.

The budget request for intramural research is $78,884,000 and 536 FTEs, an increase of $1,166,000 over FY 1997. The request for research management and support is $9,024,000 and 104 FTEs, the same as FY 1997.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	292	$67,612,000	300	$69,368,000	310	$75,031,000
Administrative supplementals	(13)	461,000	(16)	1,345,000	(16)	1,372,000
Competing:						
Renewal	42	12,082,000	24	5,952,000	32	8,112,000
New	88	15,876,000	122	26,607,000	112	24,914,000
Supplemental	1	108,000	1	50,000	2	113,000
Subtotal, competing	131	28,066,000	147	32,609,000	146	33,139,000
SBIR/STTR	18	2,969,000	26	3,756,000	26	3,854,000
Subtotal, RPGs	441	99,108,000	473	107,078,000	482	113,396,000
Research Centers						
Specialized/comprehensive	22	21,722,000	23	23,664,000	23	24,137,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research centers in minority institutions	0	0	0	0	0	0
Subtotal, Centers	22	21,722,000	23	23,664,000	23	24,137,000
Other Research						
Research careers	23	2,743,000	24	3,089,000	24	3,151,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	462,000	0	462,000	0	462,000
Other	29	3,519,000	29	3,827,000	29	3,913,000
Subtotal, Other Research	52	6,724,000	53	7,378,000	53	7,526,000
Total, Research Grants	515	127,554,000	549	138,120,000	558	145,059,000
Training	FTTPs		FTTPs		FTTPs	
Individual	43	1,094,000	46	1,282,000	46	1,308,000
Institutional	457	9,870,000	454	10,523,000	454	10,733,000
Total, Training	500	10,964,000	500	11,805,000	500	12,041,000
Research & development contracts	106	60,968,000	112	65,331,000	114	68,575,000
(SBIR/STTR)	(7)	(1,240,000)	(10)	(1,803,000)	(11)	(1,907,000)
	FTEs		FTEs		FTEs	
Intramural research	536	73,040,000	536	77,718,000	536	78,884,000
Research management and support	104	9,037,000	104	9,024,000	104	9,024,000
Cancer prevention & control	0	0	0	0	0	0
Construction	0	0	0	0	0	0
Total, ICD	640	281,563,000	640	301,998,000	640	313,583,000
(Clinical Trials)		(2,882,000)		(3,526,000)		(619,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Biological Response to Environmental Agents		$86,213		$90,998		$94,460		$3,462
Applied Toxicological Research and Testing		68,526		75,990		81,657		5,667
Biometry and Risk Estimation		10,061		12,799		13,380		581
Resource and Manpower Development		32,686		35,469		36,178		709
Subtotal Extramural research		199,486		215,256		225,675		10,419
Intramural research	536	73,040	536	77,718	536	78,884	0	1,166
Research management and support	104	9,037	104	9,024	104	9,024	0	0
Total obligations	640	281,563	640	301,998	640	313,583	0	11,585
Unobligated balance lapsing		0		0		0		0
Total, Budget Authority	640	281,563	640	301,998	640	313,583	0	11,585

Note Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Summary of Changes

1997 Estimated budget authority	$301,998,000
1998 Estimated budget authority	313,583,000
Net change	11,585,000

	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$36,780,000		$482,000
b. Annualization of January 1997 pay increase		36,780,000		290,000
c. January 1998 pay increase		36,780,000		772,000
d. Legislative proposal, 1.51% increase in the CSRS rate		941,000		203,000
e. Service and supply fund		1,613,000		42,000
f. Increased cost of laboratory supplies, materials, and other expenses		37,200,000		967,000
Subtotal				2,756,000
2. Research Management and Support:				
a. Within grade increase		5,937,000		72,000
b. Annualization of January 1997 pay increase		5,937,000		51,000
c. January 1998 pay increase		5,937,000		125,000
d. Legislative proposal, 1.51% increase in the CSRS rate		215,000		46,000
e. Service and supply fund		105,000		3,000
f. Increased cost of laboratory supplies, materials, and other expenses		1,757,000		45,000
Subtotal				342,000
Subtotal, Built-in				3,098,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences
Summary of Changes--continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B Program:				
1. Research projects grants:				
a. Noncompeting	300	70,713,000	10	5,690,000
b. Competing	147	32,609,000	(1)	530,000
c. SBIR/STTR	26	3,756,000	0	98,000
Total	473	107,078,000	9	6,318,000
2. Centers	23	23,664,000	0	473,000
3. Other research	53	7,378,000	0	148,000
4. Research training	500	11,805,000	0	236,000
5. Research and development contracts	112	65,331,000	2	3,244,000
Subtotal, extramural				10,419,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes			0	0
b. Special emphasis areas			0	0
Subtotal, intramural	536	77,718,000	0	(1,590,000)
7. Research management and support	104	9,024,000	0	(342,000)
Subtotal, program				8,487,000
Total changes				11,585,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Object

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:				
Full-time employment		640	640	
Full-time equivalent of overtime and holiday hours		4	4	
Average ES salary		$118,971	$122,569	$3,598
Average GM/GS grade		10.85	10.85	
Average GM/GS salary		$52,044	$54,386	$2,342
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)		$78,680	$80,883	$2,203
Average salary of ungraded positions		$33,021	$33,946	$925
		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	26,583,000	27,645,000	$1,062,000
11.3	Other than Full-Time Permanent	4,158,000	4,324,000	166,000
11.5	Other Personnel Compensation	663,000	723,000	60,000
11.8	Special Personnel Services Payments	4,510,000	4,916,000	406,000
11.9	**Total Personnel Compensation**	**35,914,000**	**37,608,000**	**1,694,000**
12.0	Personnel Benefits	6,778,000	7,087,000	309,000
13.0	Benefits for Former Personnel	25,000	26,000	1,000
	Subtotal, Pay Costs	**42,717,000**	**44,721,000**	**2,004,000**
21.0	Travel & Transportation of Persons	1,010,000	1,020,000	10,000
22.0	Transportation of Things	224,000	224,000	0
23.1	Rental Payments to GSA	878,000	878,000	0
23.2	Rental Payments to Others	662,000	662,000	0
23.3	Communications, Utilities & Miscellaneous Charges	5,509,000	5,511,000	2,000
24.0	Printing & Reproduction	815,000	815,000	0
25.1	Consulting Services	161,000	161,000	0
25.2	Other Services	6,739,000	6,308,000	(431,000)
25.3	Purchase of Goods & Services from Government Accounts	16,939,000	16,524,000	(415,000)
25.4	Operation & Maintenance of Facilities	4,524,000	4,514,000	(10,000)
25.5	Research & Development Contracts	53,945,000	57,189,000	3,244,000
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	4,967,000	4,967,000	0
25.8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**87,275,000**	**89,663,000**	**2,388,000**
26.0	Supplies & Materials	7,627,000	7,627,000	0
31.0	Equipment	5,378,000	5,169,000	(209,000)
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	149,709,000	157,100,000	7,391,000
42.0	Insurance Claims & Indemnities	186,000	186,000	0
43.0	Interest & Dividends	8,000	7,000	(1,000)
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**259,281,000**	**268,862,000**	**9,581,000**
	Total Direct Obligations	**301,998,000**	**313,583,000**	**11,585,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$26,583,000	$27,645,000	$1,062,000
Other Than Full-Time Permanent (11.3)	4,158,000	4,324,000	166,000
Other Personnel Compensation (11.5)	663,000	723,000	60,000
Special Personnel Services Payments (11.8)	4,510,000	4,916,000	406,000
Total Personnel Compensation (11.9)	**35,914,000**	**37,608,000**	**1,694,000**
Civilian Personnel Benefits (12.0)	6,778,000	7,087,000	309,000
Benefits to Former Personnel (13.0)	25,000	26,000	1,000
Subtotal, Pay Costs	**42,717,000**	**44,721,000**	**2,004,000**
Travel (21.0)	1,010,000	1,020,000	10,000
Transportation of Things (22.0)	224,000	224,000	0
Rental Payments to Others (23.2)	662,000	662,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	5,509,000	5,511,000	2,000
Printing and Reproduction (24.0)	815,000	815,000	0
Other Contractual Services:			
Advisory and Assistance Services (25.1)	161,000	161,000	0
Other Services (25.2)	6,739,000	6,308,000	(431,000)
Purchases from Govt. Accounts (25.3)	5,337,000	5,138,000	(199,000)
Operation & Maintenance of Facilities (25.4)	4,524,000	4,514,000	(10,000)
Operation & Maintenance of Equipment (25.7)	4,967,000	4,967,000	0
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**21,728,000**	**21,088,000**	**(640,000)**
Supplies and Materials (26.0)	7,627,000	7,627,000	0
Subtotal, Non-Pay Costs	37,575,000	36,947,000	(628,000)
Total, Administrative Expenses	**80,292,000**	**81,668,000**	**1,376,000**

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

1997 House Appropriations Committee Report Language

Item

Asthma -- . . . .The Committee encourages the NIEHS to continue its leadership role in studying environmental aspects of asthma and to continue to forge scientific collaborations with NIAID and NHLBI on this important health problem.

The Committee is aware of an unusually high incidence of asthma and other health problems among students of Public School 48 in the Hunts Point area of the South Bronx, New York, where there is a concentration of waste transfer and sewage treatment facilities. The Committee understands that the Director of the National Institute of Environmental Health Sciences has visited the area. met with members of the affected community, and suggested ways that NIEHS might work with state and local public health officials and researchers to determine what environmental factors might be contributing to this asthma cluster. The Committee commends the NIEHS for its involvement and encourages the NIEHS to continue to support the community's efforts to identify and, if possible, mitigate any environmental causes of the Hunts Point asthma problem.

Action Taken or to be Taken

The Director of NIEHS visited the Hunts Point area of the South Bronx in May 1996. Subsequently, NIEHS awarded a supplement to the Mt Sinai Environmental Health Science Center to generate preliminary data on the incidence of pulmonary disease in a population of students in Hunts Point. Researchers will establish needed collaborations to develop a curriculum for nurses at Hostos Community College and Lincoln Hospital to enable them to become specialized in pulmonary care. Researchers will also hold a series of workshops for community leaders, selected by the Hunts Point Awareness Committee, about scientific research and the role of citizens in reducing environmental pollution and associated disease. These efforts are a first step toward decreasing morbidity and mortality associated with asthma in this area.

Item

Parkinson's disease -- The Committee is pleased that the September 1995 workshop on the link between Parkinson's and other neurodegenerative disorders and the environment was well-attended and productive. The Committee also notes that the report on the August 1995 NIH-wide Parkinson's research planning workshop concluded that the environment is likely to play a role in the cause of Parkinson's. As a result, the Committee encourages the NIEHS to increase its focus on the environmental link to Parkinson's, using the findings of its September 1995 workshop and the August 1995 research planning workshop as a guide.

Action Taken or to be Taken

As a result of the research needs cited by the workshops, NIEHS is cooperating with NINDS, NIA and NIMH in a solicitation for applications through a program announcement on the role the environment plays in Parkinson's and other neurodegenerative diseases. In FY 1997 and 1998, NIEHS is planning to fund several new grants in this area of biology of brain degeneration research as part of its involvement in this field.

Item

Nanofabrication -- The Committee is interested in the promise for improving the detection, prevention and remediation of environmentally related illnesses by the incorporation of cell and molecular biology into techniques of nanofabrication-which is the synthetic preparation of materials and devices with structural dimensions of approximately one-millionth of an inch-and molecular self-assembly. The Committee encourages the Institute to continue to advance these technologies, especially in partnership with those who have demonstrated an extensive record of work with these technologies.

Action Taken or to be Taken

Nanofabrication and molecular self-assembly hold promise for improving the assessment, evaluation. and prevention of environmentally related illness. A field is emerging within molecular biology that focuses on assemblages of components in structures having nanometer-scale dimensions. Some of these structures are created by moving individual atoms, but others are self-assembled and may contain more than a million molecules. The techniques of nanofabrication and self-assembly are at a point where they may be ready to be used in studies relevant to environmental health. NIEHS is exploring opportunities within this area of research and plans to hold a workshop to identify the most promising research opportunities.

Item

Minority populations -- There has been an increased recognition in the scientific and public health community that minority and disadvantaged populations are disproportionately subjected to a variety of health hazards, including air pollution. Its relationship to asthma and other pulmonary disorders is beginning to be well documented. To help examine these problems, the Committee encourages the NIEHS to consider convening a national scientific summit on air quality issues faced by the nation's urban communities, working closely with the public health and scientific community.

Action Taken or to be Taken

The Federal Summit on Environmental Justice Research is a multi-agency effort that will address air quality issues faced by the nation's urban communities. The Summit will incorporate leadership from science research, federal agencies, environmental groups, at-risk communities, and organizations affiliated with human health effects research. Participants will engage in an open dialogue and scientific review to identify indoor and outdoor air pollution inequities in urban communities, including those related to pesticide and lead particles; prioritize issues to effectively and efficiently begin to address the needs of these communities; and establish a coordinated research agenda by which federal agency managers, the scientific community and interested stakeholders can address existing environmental inequities. NIEHS will use the recommendations from the Summit to further define priorities for research, education, and outreach on air quality issues faced by the Nation's urban communities and to devise models for implementation.

Item

National Toxicology Program -- The National Toxicology Program (NTP) was established to provide information to health, regulatory and research agencies, and the general public about potentially toxic chemicals, as well as to strengthen the science base of toxicology. In recent years, the NTP has made great strides toward incorporating more information on dose-response relationships and mechanisms that are critical for improved risk assessment. Risk assessment is the cornerstone of environmental decision making and should be firmly based on sound science. The Committee encourages the NIEHS to continue to pursue research into improved risk assessment methodologies.

Action Taken or to be Taken

The NIEHS is deeply committed to mechanism-based toxicology in several ways including priority setting, human exposure assessment, dose-response evaluation, species comparisons and identification of sensitive subpopulations. In addition to our studies on mechanisms of action, we have expanded our efforts on the development of predictive models for more rapidly identifying which agents are hazardous and which are safe. We have also worked with regulatory agencies to develop strategies for incorporating the best science into the regulatory decision-making process. We have done this by helping to revise risk assessment

40-478 97 - 26

guidelines and by working with regulatory agencies on high visibility risk assessments such as dioxin and 1-3 butadiene. Thus, NIEHS and NTP are working hard to reduce uncertainty in risk assessments and to strengthen the links between fundamental knowledge, toxicology and risk assessment. We have helped achieve consensus in these areas by sponsoring several workshops which brought together stakeholders from industry, Federal government, academia, public interest groups, unions and state government.

Item

Environmental justice — . . . .The relationship between environmental justice and cancer is beginning to be documented. To help examine these problems, and to further research advances in this area the NIEHS and NCI are encouraged to work in a collaborative effort on this important public health problem, in an effort to address environmental justice issues faced by the Nation's disadvantaged inner city and rural communities. The Committee requests that the NIEHS and NCI be prepared to report on the implementation of this collaborative initiative at the fiscal year 1998 budget hearings.

Action Taken or to be Taken

The National Academy of Sciences/Institute of Medicine convened a committee of 14 individuals to conduct an 18-month study entitled, Environmental Justice: Research, Education, and Health Policy Needs. The purpose of the study is to evaluate and make recommendations to strengthen the medical research, education and health sciences policy aspects of environmental justice. This is a collaborative initiative of NIEHS and NCI to document the linkage between environmental justice and health in low-income and minority communities.

Item

Synthetic chemicals — Recent concerns have been raised over the effect of synthetic chemicals on human health and reproduction. Some research has indicated that man made chemicals mimic human hormones and interfere with the process of human development. While most of this research has focused on animals, there is emerging evidence suggesting a link to humans. The Committee recognizes that this research is still in its preliminary stages and encourages the NIEHS to further explore this field.

Action Taken or to be Taken

The NIEHS has had a long history of research on endocrine disrupting chemicals. For example, we are responsible for a significant portion of the scientific data base on environmental estrogens and dioxins and related compounds as they relate to human health.

Our current efforts involve research on basic mechanisms of hormone action, toxicological studies in rodents and a series of epidemiological studies. Information from this broad range of studies is being integrated into toxicological evaluations that state what we know and what we don't know about the human health effects of endocrine disrupters. Our research strategies are designed to address knowledge gaps that create uncertainty in risk assessments such as "exposure assessment" and "dose response evaluation." In addition, we are working with other agencies to identify research needs and to develop approaches for using mechanistic information in risk assessments for endocrine disrupting agents.

Item

Toxic tides – Toxic red tides produce serious detrimental effects in humans, including several different types of seafood poisoning, profound respiratory irritation, and general prolonged neurological malaise. The Committee encourages the NIEHS to support research to characterize the human disease states, the molecular mechanisms responsible for intoxication, and the therapies and diagnostics needed to cure and ultimately prevent such illnesses. The Committee encourages NIEHS to cooperate with the National Oceanic and Atmospheric Administration in developing a coordinated effort to address the red tide problem.

Action Taken or to be Taken

Throughout the world, marine toxins cause a variety of acute and chronic diseases in humans, ranging from neurologic diseases to gastrointestinal maladies and chronic dementia. Marine toxins cause disease predominantly through ingestion of contaminated fish, although certain diseases are initiated via skin contact or inhalation. The general source of these toxins, with the exception of tetrodotoxin in pufferfish and blue-green algae cyanophytes, are dinoflagellates and diatoms. Dinoflagellates are most notorious as the cause of "red tides." These tides are often associated with high toxin concentrations, which may produce large fish and bird kills as well as human illness. With increasing prevalence worldwide, as well as increasing scientific knowledge and technology, new research in this field is focusing on understanding the pharmacological and pathologic mechanisms in humans in order to develop biomarkers for improved clinical diagnosis, prevention, and epidemiology, and improved treatment capabilities. NIEHS has supported much of the mechanistic research in this arena in the past and continues to support new developmental investigations. Through its Marine and Freshwater Biomedical Sciences Center at the University of Miami, NIEHS is exploring a partnership with the National Oceanic and Atmospheric Administration to support a coordinated effort to address this problem.

1997 Senate Appropriations Committee Report Language

Item

Volcanic emissions -- The Committee continues to be concerned about the public health aspects of volcanic emissions (VOG) in Hawaii and urges the Institute to continue to collaborate with NINR in a multidisciplinary approach to this problem. The Committee appreciates the initial efforts of NIEHS to work with the University of Hawaii.

Action Taken or to be Taken

NIEHS recognizes the importance of obtaining information related to potential adverse health effects of VOG and of assessing other environmental health concerns of particular significance to the citizens of Hawaii and to Native Hawaiians. The Institute sponsored a workshop in 1996 to explore this topic and staff are working with investigators in Hawaii and on the mainland to explore the possibility of using our program of Community-Based Prevention/Intervention Research for studying the problem. This initiative is co-sponsored by NINR. In addition, in conjunction with CDC, NIEHS is supporting preliminary exposure assessment and epidemiology studies to be conducted by researchers at the Hawaii Department of Health and the Environmental Health Sciences Center at the University of Southern California. Such work may establish whether or not VOG adversely impacts human health, thus providing the basis for further research activities.

Item

Environmental disparities -- There has been an increased recognition in the scientific and public health community that minority and disadvantaged populations are disproportionately subjected to a variety of health hazards, including air pollution. Its relationship to asthma and other pulmonary disorders is beginning to be well documented. To help examine these problems, NIEHS is encouraged to convene a national scientific summit on air quality issues faced by the Nation's urban communities, and working closely with the public health and scientific community.

Action Taken or to be Taken

The Federal Summit on Environmental Justice Research is a multi-agency effort that will address air quality issues faced by the nation's urban communities. The Summit will incorporate leadership from science research, federal agencies, environmental groups, at-risk communities, and organizations affiliated with human health effects research. Participants will engage in an open dialogue and scientific review to identify indoor and outdoor air pollution inequities in urban communities, including those related to pesticide and lead particles; prioritize issues to effectively and efficiently begin to address the needs of these communities; and establish a coordinated research agenda by which federal agency managers, the scientific community and interested stakeholders can address existing environmental inequities. NIEHS will use the recommendations from the Summit to further

define priorities for research, education, and outreach on air quality issues faced by the Nation's urban communities and to devise models for implementation.

Item

Marine toxin standards -- In fiscal year 1994, Congress recognized the need to establish standards for marine food safety; and in fiscal year 1995 the Committee recommended that NIEHS support research to evaluate natural marine toxins and their effect upon human health. The Committee encourages NIEHS to expand this important research by establishing disease-related environmental health science centers. Such centers should integrate aspects of basic science focusing upon molecular structures of marine toxins and applied science focusing upon safety assessment of food sources and clinical diagnosis. This information should be disseminated to domestic and international public health officials as well as consumers.

Action Taken or to be Taken

With January 1996 implementation of the Hazard Analysis Critical Control Point program for seafood, the FDA has begun to seek and evaluate testing methods for prevention of exposure to marine toxins. Because marine toxin diseases often occur in clusters, follow-up can lead to the discovery of mechanisms and potential prevention of new cases. Work being supported by NIEHS through its Marine & Freshwater Biomedical Sciences Center at the University of Miami, emphasizes development and implementation of surveillance methods and bioassays of contaminated materials to minimize human contact with contaminated fish and shellfish. Continued research in this emerging area will lead to a more complete description of the molecular mechanisms by which marine toxins act as well as information necessary for developing diagnostic and therapeutic methods.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
				> $290,193,000		> $301,542,000
National Institute of Environmental Health Sciences	Section 463	42§285	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	11,805,000	b/	12,041,000
...						
Total, Budget Authority				301,998,000		313,583,000

a/ Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208).
b/ Reauthorizing legislation will be submitted

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation /1
1989	218,471,000 /2	216,985,000 /3	223,168,000	223,454,000
1990	226,471,000 /4	232,479,000	234,048,000	232,476,000 /5
1990 Sequester				(3,242,000)
1991	235,792,000	244,832,000 /6	242,765,000	241,028,000 /7
1992	254,484,000	254,912,000	250,873,000	251,575,000 /8
1993	261,513,000	252,564,000	255,115,000	251,187,000 /9
1994	261,306,000	264,249,000	264,249,000	264,249,000
1995 /10	267,955,000	266,400,000	267,955,000	266,988,000 /11
1995 Rescission				(422,000)
1996	278,832,000 /10	288,898,000 /12	275,861,000 /10	288,898,000 /12
1996 Rescission				(520,000)
1997	289,114,000 /10	308,258,000	294,745,000 /10	308,487,000 /12&13
1998	313,583,000 /10			

/1 Reflects enacted supplementals, rescissions, and reappropriations
/2 The 1989 request excludes funding for AIDS research and education ($4,234,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
/3 Excludes $9,183,000 in NRSA training programs not considered.
/4 The 1990 request excludes funds for the National HIV program ($4,377,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
/5 Excludes enacted administrative reduction of $788,000.
/6 Excludes $10,586,000 in NRSA training programs not considered.
/7 Excludes enacted administrative reduction of $8,064,000.
/8 Excludes enacted administrative reductions of $4,871,000 and $456,000. Includes $3,000,000 real transfer from the National Cancer Institute.
/9 Excludes enacted administrative reduction of $3,928,000.
/10 Excludes funds for HIV research activities consolidated in the Office of AIDS Research.
/11 Excludes enacted administrative reductions of $578,000.
/12 Includes funds for HIV research activities.
/13 Excludes enacted administrative reductions of $332,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	67	69	69
Division of Intramural Research	389	393	393
Division of Extramural Research and Training	48	48	48
Office of Management	136	130	130
Total, ICD	640	640	640

	Average GS/GM Grade
1993	10.30
1994	10.44
1995	10.69
1996	10.85
1997	10.85
1998	10.85

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences
Program Administration

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	0	1	1
ES-5	1	1	1
ES-4	6	5	5
ES-3	0	0	0
ES-2	0	0	0
Subtotal	7	7	7
Total - ES Salary	$802,216	$832,797	$858,613
GS/GM-15	37	37	35
GS/GM-14	61	61	61
GS/GM-13	64	64	64
GS-12	66	66	66
GS-11	97	97	97
GS-10	2	2	2
GS-9	58	58	58
GS-8	16	16	16
GS-7	65	65	63
GS-6	21	21	21
GS-5	15	15	15
GS-4	40	40	40
GS-3	16	16	16
GS-2	3	3	3
GS-1	0	0	0
Subtotal	561	561	557
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	8	8	8
Senior Grade	6	5	5
Full Grade	1	1	1
Senior Assistant Grade	0	0	0
Subtotal	15	14	14
Ungraded	94	95	99
Total permanent positions	532	532	532
Total positions, end of year	677	677	677
Total full-time equivalent (FTE) employment,end of year	640	640	640
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$114,602	$118,971	$122,659
Average GS/GM grade	10.85	10.85	10.85
Average GS/GM salary	$49,803	$52,044	$54,386

THURSDAY, FEBRUARY 27, 1997

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

WITNESSES

JAMES B. SNOW, JR., M.D., DIRECTOR
DONALD H. LUECKE, M.D. DEPUTY DIRECTOR
W. DAVID KERR, EXECUTIVE OFFICER
PATIENCE T. SPARKS, BUDGET OFFICER
MARSHALL MOORE, INTERPRETER
HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH
BILL BELDON, DIVISION DIRECTOR, OFFICE OF DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. Now we'd like to welcome Dr. Snow, Director of the National Institute on Deafness and Other Communication Disorders.

Dr. Snow, we're anxious to hear from you. And my first question will be to ask you whether you want to follow up on anything that Dr. Varmus had to say about autism. Why don't you proceed to introduce the people at the table and then your statement, and then if you'd like to address the autism question further, please feel free.

INTRODUCTION OF WITNESSES

Dr. SNOW. Thank you very much, Mr. Chairman.

It's my pleasure to introduce Dr. Donald H. Luecke, the Deputy Director of the NIDCD; Mr. David Kerr, the Executive Officer of the NIDCD; Ms. Pat Sparks, the Budget Officer of the NIDCD. Mr. Marshall Moore is the sign language interpreter. You, of course, know Dr. Varmus and Mr. Beldon.

OPENING STATEMENT

Mr. Chairman, members of the committee, I am grateful to have this opportunity to appear before you to report on the research progress of the National Institute on Deafness and Other Communication Disorders. That research benefits 46 million Americans who are challenged by diseases and disorders affecting hearing, balance, smell, taste, voice, speech and language.

The NIDCD is seizing opportunities to accelerate discovery that will lead to elucidation of the biology of brain disorders such as aphasia, finding new approaches to the pathogenesis of diseases including laryngeal carcinoma and spasmodic dysphonia; new treatment strategies against immune-mediated inner ear hearing loss; and applying genetic medicine to hearing impairment and the velocardio facial syndrome, while developing new therapy for disorders

of balance and the symptom of tinnitus that are critically important in improving the quality of life for those faced with communication disorders.

Progress that we're experiencing within the portfolios of the NIDCD is due to careful planning and emerging opportunity. In the past several years, with the support of the NIDCD, a multitude of genes for syndromic and nonsyndromic forms of hearing impairment, including autosomal dominant and recessive, X-linked and mitochondrial modes of transmission have been located in specific regions of the human genome. And at least 12 different genes on 10 different chromosomes have been located for various forms of autosomal dominant nonsyndromic hearing impairment and at least 11 different genes on as many chromosomes have been identified for autosomal recessive nonsyndromic hearing impairment.

Recent NIDCD-supported research will further our understanding of normative patterns of brain development in all children and provide a more detailed understanding of the acquisition of sign language in deaf children.

The Institute has established two clinical trial cooperative groups to plan, implement, conduct, analyze and disseminate results of priority research in the efficacy of treatment of diseases and disorders affecting human communication. The Institute is improving technology for individuals with communication disorders. A unique collaborative effort is fostering partnerships among scientists, industry and Federal laboratories to carry out research needed for commercialization of promising hearing aid technology.

There is progress in developing a new vaccine against otitis media in infants and small children. Plans are underway for a Stage I clinical trial in the NIH Clinical Center of a conjugate vaccine against the nontypeable hemophilus influenza.

The chemical senses, smell and taste, greatly influence nutrition. Scientists are studying the role of the gustatory thalamus in food aversions and food-seeking behavior that will help in the effort to understand life-threatening eating disorders.

NIDCD investigators are applying the newest tools and strategies to long-misunderstood and often misdiagnosed diseases and disorders of human communication.

Mr. Chairman, the fiscal year 1998 budget request for NIDCD is $192,447,000. I will be pleased to try to answer any questions you might have.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute on Deafness and Other Communication Disorders

Mr. Chairman and Members of the Committee, I am grateful to have this opportunity to appear before you to report on the research progress of the National Institute on Deafness and Other Communication Disorders (NIDCD) that benefits 46 million Americans who are challenged by diseases and disorders affecting hearing, balance, smell, taste, voice, speech or language.

The progress we are experiencing within the portfolios of the NIDCD is due to careful planning and accelerating discovery. Our scientists are studying the disorders of human communication in revolutionary ways. Seven years ago, when I first appeared before the Committee, I made a commitment that I would encourage the development and expansion of the use of molecular biology to uncover important information on how human communication systems work. With extramural expert advice to increase the extramural portfolio of the NIDCD in molecular biology, molecular genetics, imaging and integrative neuroscience, with a rigorously updated NIDCD National Strategic Research Plan, and with the addition of an outstanding molecular biologist as the Director of Intramural Research, we are seeing the results in new understandings of the mechanisms involved in human communication.

Until the establishment of NIDCD in 1988, only two genes responsible for hereditary hearing impairment had been located. In the past several years, with the support of NIDCD and through NIDCD-supported international consortia designed for the rapid exchange of information, a multitude of genes for syndromic and nonsyndromic forms of hearing impairment, including autosomal dominant and recessive, X-linked and mitochondrial modes of transmission have been located in specific regions of the human genome. Presently, at least 12 different genes on 10 different chromosomes have been located for various forms of autosomal dominant nonsyndromic hearing impairment and at least 11 different genes on as many different chromosomes have been identified for autosomal recessive nonsyndromic hearing impairment. The NIDCD has created an opportunity to accelerate discovery of the specific genes involved in hearing impairment using inbred mouse strains, sample sequencing and a cDNA library enriched for cochlear-specific cDNAs. This information will ultimately aid in the earliest identification of hearing impairment in infants. As these discoveries continue to be made, the NIDCD has started a new effort to identify the underlying mechanisms of hereditary hearing impairment based on functional analyses of the discovered genes.

During the early years of the NIDCD, investigators demonstrated that there is a "window of opportunity" for acquiring sign language just as there is for children acquiring spoken language and that they are parallel. Recent NIDCD-supported research studied manual and vocal babbling in deaf and hearing children. This research will further our understanding of normative patterns of motor development in all children and provide a more detailed understanding of the acquisition of sign languages in deaf children.

NIDCD has also taken a leadership role in the improvement of clinical research efforts in human communication. The Institute has established two clinical trial cooperative groups with an estimated 15 to 20 clinical facilities in each group. These facilities have clinical research experience and capability. The clinical trial cooperative groups represent a five-year commitment for the initiation and conduct of clinical trials. They will plan, implement, conduct, analyze, and disseminate results of priority research in the efficacy of treatment of diseases and disorders affecting human communication. This approach promises effective and efficient use of resources and expedited delivery of research findings to the public.

The NIDCD is committed to improving technology for individuals with communication disorders. Hearing aids continue to be the principal form of remediation for most individuals with hearing loss. Although 28 million Americans have hearing impairment, only about 20% of them have hearing aids. NIDCD with the Department of Veterans Affairs (VA) supports an innovative collaboration to promote hearing aid research and development. The first hearing aid clinical trial began in the spring of 1996. It will determine which commonly used hearing aid circuits benefit which subgroups of hearing-impaired individuals and under what circumstances.

Another important collaboration aimed at improving hearing aids, is a joint effort of the NIDCD, the National Aeronautics and Space Administration (NASA) and the VA. Beginning with a search of Federal laboratories for new technologies that might be applicable to improving hearing aids, this collaboration is designed to foster the formation and support of partnerships among scientists, industry and Federal laboratories to carry out research needed for the commercialization of technologies that could benefit those who use or could use hearing aids.

Computer and electronics industries are developing new and improved diagnostic and rehabilitative tools for individuals with hearing impairment. For example, scientists participating in the NIDCD Small Business Innovation Research (SBIR) program are developing a cost-effective and user-friendly listening system designed to interface with existing airplane sound systems. This will allow individuals with hearing aids to receive pilot and flight attendant announcements that include safety instructions, as well as to communicate with neighboring passengers. A collaboration with a major airline is currently in place. In yet another effort, better tools for infant hearing screening and diagnostic testing continue to be developed as many hospitals implement universal infant hearing screening programs.

There is continuing progress in the testing of conjugate pneumococcal vaccines against otitis media in infants and small children. Last year I reported to the Committee that we had a new preventive strategy against the nontypeable Haemophilus influenzae (NTHi). NIDCD intramural scientists have successfully prepared a detoxified lipooligosaccharide (dLOS)-based conjugate antigen from NTHi. This conjugate antigen induces a bactericidal humoral immune response in two animal species and reduces the incidence of otitis media in the only reliable animal model of otitis media, making it a promising vaccine candidate. Plans are underway to initiate a Stage I clinical trial of this vaccine in the NIH Clinical Center. I am delighted to announce that in cooperation with the NICHD, an announcement for commercial development of the vaccine has just been published. As the NTHi genome has recently been sequenced, this new knowledge will facilitate understanding of the pathogenesis of NTHi otitis media and ultimately accelerate the development of other vaccines against NTHi otitis

media. Additionally, the Otitis Media Vaccine Unit in the NIDCD is beginning work on a candidate vaccine against *M. catarrhalis otitis media.*

Chronic otitis media (OM) in children causes hearing loss, is responsible for major health care costs, and is a risk factor for delaying the acquisition of language. In the general population, many risk factors for OM have been identified, but their applicability in populations such as Native American children, with a higher incidence of otitis media, is not known. Studying OM risk factors in a population with a high incidence of this disease could elucidate the role of certain risk factors in both majority and minority populations. A NIDCD-funded investigator is currently working with mothers on the White Earth Reservation to examine risk factors for OM in Native American children. The protocol includes hearing screening and tympanometry for the Native American children. Results to date suggest a high rate of chronic OM in this group (approaching 50%), with half of the affected children exhibiting an associated hearing loss.

NIDCD scientists are comparing mechanisms underlying apoptosis or cell death with mechanisms of plasticity to promote regeneration of sensory capabilities lost to disease. Cochlear hair cells that are lost are not naturally replaced, resulting in permanent hearing loss. Current research efforts have focused on the role of growth factors and other mitogens in promoting hair cell regeneration. This approach provides a new avenue for investigating mechanisms of hair cell regeneration and repair in mammalian systems and promises to accelerate the discovery of therapeutic agents for the prevention and treatment of sensorineural hearing loss and vestibular (balance) abnormalities.

Disorders of balance and vestibular function constitute a major health problem. Individuals who suffer from recurrent debilitating vertigo, dizziness, or imbalance are often unable to hold jobs and unable sometimes to get up in the morning and perform simple acts of daily living such as showering, eating, or driving. It is estimated that 12.5 million Americans over the age of 65 have dizziness or balance problems that significantly interfere with their lives, and many of these individuals have difficulty caring for themselves independently. To assess the functional skills of individuals with chronic balance problems of vestibular origin, a NIDCD-supported investigator has developed and validated a scale of independence in activities of daily living. The scale developed in this study provides clinicians who manage individuals with balance disorders with a useful tool to evaluate the outcomes of newly developed treatment.

The chemical senses (smell and taste) permit interaction with the environment in highly complex ways. Smell and taste greatly influence nutrition. Eating disorders comprise a rapidly growing group of medical problems. Many individuals are afflicted with eating disorders such as anorexia that can result in malnutrition, wasting, or even death. Scientists have found some surprising results regarding the effect of gustatory (or taste) thalamic lesions on behavior that challenge earlier concepts of how taste information is processed by the gustatory thalamus and what its role is in guiding eating behavior. These results suggest that the gustatory thalamus is not simply a relay station for transmitting primitive, consummatory aspects of gustatory information from the brainstem to higher cortical centers, but that it plays a more pivotal role in the learning and execution of more complex tasks. Work in progress includes the investigation of the role of the gustatory thalamus in the information-processing of conditioned food aversions and food-seeking behavior.

For the working adult who becomes suddenly deafened by illness or injury, there had in earlier times been no way to maintain his or her former life, but with the development and improvement of cochlear implants, the neural prostheses that work by providing direct electrical stimulation to the auditory nerve, many of these individuals can maintain their jobs, talk on the phone and interact more easily with families and friends.

NIDCD is especially proud of three efforts designed to support minority scientists underrepresented in the area of human communication research. All are in collaboration with the Office of Research in Minority Health (ORMH) and include the NIDCD/ORMH Minority Dissertation Research Grants in Human Communication and the NIDCD/ORMH Mentored Research Scientist Development Award for Minority School Faculty. The NIDCD/ORMH Partnership Program is a pilot collaboration between NIDCD and four academic institutions with large minority enrollments. The program, in its third year, develops curriculum materials and workshops and provides research training for students and faculty and research administration experience for faculty and administrators. Building on an idea of a human infrastructure, several hundred individuals have participated in the program at the universities or the NIDCD.

The scientists supported by the NIDCD are applying the newest tools and strategies to long misunderstood and often misdiagnosed diseases and disorders of human communication. The NIDCD is seizing opportunities to accelerate discovery that will lead to: elucidation of the biology of brain disorders such as aphasia; finding new approaches to pathogenesis in diseases including laryngeal carcinoma and spasmodic dysphonia; new treatment strategies against autoimmune inner ear disease; applying genetic medicine to hearing impairment and velo-cardio-facial syndrome, while developing new therapy for disorders of balance and the symptom of tinnitus that are critically important in improving the quality of life for those challenged with communication disorders.

Mr. Chairman, the FY 1998 budget request for NIDCD is $192,447,000. I will be pleased to answer any questions you might have.

AUTISM RESEARCH

Mr. PORTER. Thank you, Dr. Snow.

Would you like to add to what Dr. Varmus said about autistic children?

Dr. SNOW. I'd just like to add an experience that I had yesterday. The first meeting of the Autism Research Coordinating Committee was held. All of the directors of the institutes involved were present. Some of the staff of the Institute are meeting with the Cure Autism Now group, actually right at this time this afternoon in Bethesda.

I think that the coordination is really enormously important and an agreement was made yesterday afternoon to try to work towards a common phenotyping clinical description of children in autism, so that all the various groups, the molecular geneticists supported by the National Institute of Mental Health, as well as those that will be supported by the NICHD and the NIDCD, will use a common basis for categorizing the patients. And that will greatly improve and hasten the work.

Mr. PORTER. Just one small question. Is it correct that the inability to properly hear sounds of human speech may contribute to the disorder of autism?

Dr. SNOW. Well, I don't think there has been any satisfactory demonstration of that as far as I know. Certainly autism is a disorder of human communication. It's a language disorder. It is of particular interest to us because it is at times associated with near-normal or even above normal intelligence, a situation where the language disorder occurs in the presence of normal cognition. And to approach the molecular genetics of that leads us directly to an understanding of the genetics of language. And that, of course, is an area that we have had great trouble breaking into. We have not had the success in that area that we have, let's say, in the hearing area, where we have literally a multitude of genes that have been discovered.

So we're very interested in trying to get a handle on the molecular genetics of language. And we think this may be a very fine opportunity to do that.

HAIR CELL REGENERATION

Mr. PORTER. Dr. Snow, last October, researchers in Philadelphia found a method to generate the growth of hair cells in chickens. This finding was the first to suggest a possible method to regenerate hair cells which are often the cause of deafness when they die. Is the scientific community optimistic that this finding may also work for mammals?

Dr. SNOW. Yes, we are optimistic that it may also work for mammals. I believe that you're referring to the work of the principal investigator that's supported by the NIDCD, Dr. Oberholtzer. And his finding in the chick was that compounds that activated cyclic AMP, and that in turn activate the protein kinase A system, led to the development of new hair cells when there had been no injury present. All of the other research on the regeneration of hair cells had been in a situation where first the hair cells had been destroyed.

So this is of enormous importance. This publication, which actually appeared in *Nature* in August, was brought to my attention immediately by Dr. James Battey, the Scientific Director of the Institute. And we agreed that this was an enormously important finding and indeed, in turn, acquainted Dr. Varmus with it. And indeed, that has become one of our areas of emphasis for 1998.

And in the development of the budget, $500,000 was committed to pursuing research along that line.

STOCHASTIC RESONANCE

Mr. PORTER. *Nature Medicine* Magazine reported last August a finding that translates a principle of physics into a possible aid for the deaf. Stochastic resonance is a process in which the addition of the right amount of noise results in an improvement in response. Applied to the cochlear implant device, it is thought that hearing is improved when noise is added to the stimulus. Do you expect random noise to be added to commercial cochlear implants to improve hearing for the deaf?

Dr. SNOW. Yes, I think that may well be, that in time the principles of stochastic resonance may be added to the input to cochlear implants. Stochastic resonance is a phenomenon of non-linear statistical physics, which as you say, introduces noise or interference, and in this case, it is truly noise, into a system. And this increases the informational content of responses when you're dealing with a non-linear system, and the auditory system, as well as some other sensory systems, is a non-linear system.

Actually, we benefit from stochastic resonance all the time in natural hearing. If we were presented with strictly pure tone rather than the ambient noise that exists all around us, both in a relatively quiet room like this, as well as in nature, it would be more difficult for us to understand and to appreciate certain phonemes, particularly those that are represented by the vowels. So not only is that helpful in normal hearing, but it would also be helpful in cochlear implantation.

For several years, we've recognized that the opposite of a stochastic resonance stimulation is a deterministic stimulation. And that, when there is electrical stimulation of the remaining nerve fibers, they tend to all respond at the same time. You might think of it as a military organization marching all together, all in step. They are all synchronized.

Although that tends to happen naturally in the normal auditory system, there's a certain amount of phase locking that brings that about which is beneficial. But when the system is being driven by electrical stimulation, that deterministic or phase locking becomes too severe. And as you rise in the auditory system from one waystation to another, that becomes more severe, and actually interferes with understanding.

Dr. Terry Hambrecht, who is in charge of our cochlear implant program, where we issue requests for proposals for directed research through contracts, has been aware of this for several years, and has investigators trying to achieve stochastic resonance, rather than a deterministic form of stimulation. So we've been incorporating this kind of principle into our cochlear implant research and development work for the last several years.

Mr. PORTER. Thank you, Dr. Snow.
Ms. DeLauro.

CONSENSUS CONFERENCE FINDINGS

Ms. DELAURO. My understanding is that the NIDCD has engaged in a number of activities and initiatives regarding kids, particularly the consensus conference to evaluate research on hearing impairment in children. Were there some findings that you might be able to discuss with us and how they are being put to use in doctors' offices in this country?

Dr. SNOW. Yes. We've had two consensus development conferences that involved hearing impairment in children. The first was in 1993. And it dealt with the early identification of hearing impairment in infants. And a very important recommendation came out of that consensus development conference. For the first time, anywhere in the world, there was the recommendation that there should be universal screening for hearing impairment of all newborn infants.

Now, that recommendation was made in 1993. And it has greatly influenced the field since then.

Ms. DELAURO. Are we doing that? Are we screening them?

Dr. SNOW. We're making progress in it, but we have a long way to go. Maternal and Child Health has recently awarded a grant to the University of Colorado to implement as a demonstration project, to implement infant screening in 19 states. And we are currently in conversation with the CDC and Maternal and Child Health to extend that screening to a larger number of states through Maternal and Child Health.

Hearing identification of infants is in the Secretary's initiatives for this year, under child care. And we're hopeful that we'll move forward in a major way this year.

Ms. DELAURO. Are there any states that are currently doing it?

Dr. SNOW. Yes. States that have the very best and most complete systems are Colorado and the Hawaiian Islands. Next I would probably put Utah.

The way in which this is developing, though, is to do it hospital by hospital. There are two good techniques for identifying hearing impairment in the newborn. The measurement of oto-acoustic emissions and the use of automated brain stem responses. Both are very effective, very efficacious in identifying hearing impairment. Once the infant is suspected of having hearing impairment on the basis of one or the other of these tests, then they are brought to a diagnostic evaluation, usually about six weeks later, to determine whether there is actually hearing loss that can be confirmed or not.

Both of these techniques have a very high success rate, though, high specificity. And so both are good for that purpose.

Ms. DELAURO. Has there been any evaluation in Colorado or the Hawaiian Islands or Utah? Are we able to affect any outcomes, finding something early enough to prevent it happening in the future? Do we have any results?

Dr. SNOW. Oh, yes. The average age of identification of hearing impairment in the United States is now at about two years. The latest information from CDC is that in their survey in the Atlanta

area, it's down to two years. That's down from two and a half to two years over the last seven years.

And then when we identify an infant that has a hearing impairment, we begin special education of that infant right away. And indeed, we'll put a hearing aid on the infant as early as six months of age. Then the family, of course, needs to begin to decide what form of education they wish to pursue, what form of rehabilitation in the way of special education, whether they follow the manual-visual approach through American Sign Language, or whether they follow an oral-auditory approach, which would make maximum use of any residual hearing, either with a hearing aid or with a cochlear implant.

Ms. DELAURO. Would hospitals hesitate to incorporate something like this? You say we need to go hospital by hospital. But what would be the hospitals' resistance? I am not saying that there is any, but what would be the hospitals' resistance?

Dr. SNOW. They have to work out a form of reimbursement for it. If this is a service that has not been delivered in that community before, both the insurance companies or the health maintenance organizations don't know what to do with the bill when they get it the first time. So there has to be negotiation over how the reimbursement is to take place for these services.

So that's the principal block.

Ms. DELAURO. Is this an expensive procedure?

Dr. SNOW. No. As screening procedures go, it is not. It costs about $35 per child. About 1 in 1,000 infants are born with hearing impairment. And in order to test all 1,000 of those, it would cost about $35,000.

What this says is that in order to identify a deaf child early, it costs about $35,000. That's $35,000 per deaf child, and $35 for each child screened.

The other consensus development conference had to do with cochlear implantation, both in adults and children. The outcome of that as far as adults were concerned is that there was a recommendation that individuals who did not get more than 30 percent of sentences correct on sentence material with the best hearing aid arrangement probably would benefit from a cochlear implant. This is because it was found that individuals who had received a cochlear implant did much better than those individuals who got 30 percent or less of their words or the sentences correct.

This was an enormous change in the field. There are 1 million people in the United States who fit this new classification. And so this increased the number of people that are now candidates for cochlear implants among adults increased by 1 million people.

As you probably know, cochlear implantation was not done in the United States until two years of age. There have been some experimental trials at an earlier age in Europe. And one of the recommendations of the consensus panel was that more research should be done about earlier implantation of children with cochlear implants. And of course, more study needs to be done on what leads to a successful outcome and what does not.

Ms. DELAURO. Thank you very much.

Dr. SNOW. Yes.

Ms. DELAURO. Thank you, Mr. Chairman.

SENSORY REGENERATION

Mr. PORTER. Thank you, Ms. DeLauro.

Dr. Snow, your budget justification mentions research demonstrating that odor responsive neurons in the brain are capable of regenerating and reconnecting in adults, and that this regeneration occurs throughout life. Does this finding have promise for restoring the sense of smell lost through injury or age, and more broadly, does this suggest research leads in other fields like spinal cord injury and neurodegenerative disease?

Dr. SNOW. Yes, the interneurons in the olfactory system are continuously replaced, even if there is no injury. If the system is injured, then that activity greatly increases. If the first order neurons are injured, those that have connections within the nose and extend to the olfactory bulb, if they are injured, they are reconstituted, not regenerated from themselves, but from other cells in the area. They make central connections and the function is restored.

And this ability throughout the olfactory system for neural regeneration or neurogenesis to occur suggests that this might be very helpful in bridging across a defect area, either in the brain or in the spinal cord. And we are supporting research through the grant mechanism that is studying the use of these interneurons in the repair of created neural lesion. And that could, if it proved to be successful, turn out to be of value in spinal cord injury.

EATING BEHAVIOR AND NUTRITION

Mr. PORTER. Dr. Snow, variations in eating behavior and nutrition among individuals have been linked to genetic variation in tasting ability. Is it far-fetched to think that genetic manipulation of tasting abilities would be a strategy for weight loss for the chronically obese? Or is consumption not likely to be altered by taste sensations?

Dr. SNOW. Well, there are many factors that enter into obesity. And the influence of smell and taste is only one. Characteristically, individuals who are tasters of PROP (propylthiouracil), particularly women who are tasters of it, tend to be thinner individuals. Some people are tasters of this compound, some people aren't; some have a mild reaction to the taste, others have a severe reaction to the bitter taste. Those that have the more severe reaction, among women, also experience more sweetness and more bitterness from the additives to food that provide those tastes. And as a group, they tend to be thinner, slimmer individuals.

It is an important consideration, but of course not the only one. And there is the genetics that primarily determines obesity, for which major discoveries have recently been made.

But assuming that the person does not have that sort of genetic predisposition to obesity, and is more governed by simply what the food intake is, this probably plays an important role in their body habitus.

Mr. PORTER. And maybe genetic manipulation could therefore be of help in those individuals?

Dr. SNOW. Well, what's been found is a good thing. You wouldn't want to change, I think, slim women. I don't know where the manipulation comes in.

If we had a finding, which we don't, not one that comes to mind, where it led to the obverse situation of obesity, then yes. But no, this is a healthy phenomenon.

Mr. PORTER. This is far-fetched, I can tell.

Dr. SNOW. We'll just let it be.

SENSE OF SMELL

Mr. PORTER. Women are thought to have a keener sense of smell than men. Is it known why that is the case, and is it true with any other senses? Is it true with that sense?

Dr. SNOW. Yes, it is very true with the sense of smell, and it goes throughout the lifetime. Young girls have a keener sense of smell than young boys of the same age. And that goes throughout the life span. There is of course a dropping off of the acuity of the sense of smell starting at about age 60, and that goes on for the rest of one's life. And all through the years, women maintain their sense of smell better than men for each comparable age.

In other sensory systems, I don't know. Of course, the same is true in hearing, in terms of the hearing level. Women hear better than men in advanced age. But young women don't hear better than young men and girls don't hear better than boys of a comparable age. And I don't think there is any difference in vision or the other sense that come to mind.

Mr. PORTER. Do we know why?

Dr. SNOW. No, I don't know why that is.

BALANCE DISORDERS IN THE ELDERLY

Mr. PORTER. Disorders of balance and vestibular function are common among the elderly. Do we have any idea what percentage of falls resulting in hip fractures, which often seem to be the first step toward assisted living, are attributable to balance disorders? Are any treatments or compensating rehabilitation techniques available for balance disorders?

Dr. SNOW. Yes. It is believed that 50 percent of the falls that result in hip fractures are due to a vestibular disturbance. The elderly tend to develop vestibular disturbances that lead to all sorts of uncertainties about their position in space and these can be improved. This inability or disability can be improved by physical therapy. There are techniques that the NIDCD has supported that lead to an improvement in an individual's ability to manage under relatively adverse circumstances, of shifting weight, getting in and out of a bathtub and other things in the way of daily living. And these individuals can be trained to cope with these situations and the actual exercise improves their ability to deal with them.

LOSS OF VOICE

Mr. PORTER. Your budget mentions that little research has been done in the field of voice loss. Is this condition thought to be a muscle disorder that may be amenable to therapy, or is it the result of cell death or some other degenerative condition? How prevalent is voice loss in the population?

Dr. SNOW. Mr. Chairman, I'm not sure what you're asking. Voice loss from what cause?

Mr. PORTER. All causes.

Dr. SNOW. Well, let me just say that 6 percent of our budget supports research on voice and voice disorders. There are a number of causes of voice loss. And we have a fairly extensive portfolio of research in that area.

Mr. PORTER. Does any of it relate to muscle disorder that's amenable to therapy, or does it relate to cell death?

Dr. SNOW. Yes, there is a lot that relates to muscle disorder, if you include both neuromuscular, both the neural supply as well as the muscle itself. For example, spasmodic dysphonia, a condition that I've discussed with the committee before, is an abnormal muscular activity, perhaps mediated through the central nervous system, but the end organ being the larynx. This is the condition, you know, that we have developed the treatment by injection of botulinum toxin into the muscles of the voice box. And that research continues, and actually we have engaged in that kind of research in the intramural program since 1989.

Current, new research efforts are aimed at developing objective clinical procedures for the diagnosis of these disorders, generally spoken of as dystonias, which spasmodic dysphonia is one part of. And these are patients that have generally been misdiagnosed or incorrectly diagnosed. And now there is a greater recognition of the problem, and a better recognition of what to do about it.

When it was recognized in the past, the recommendation was to cut one of the nerves to one of the vocal cords. And indeed, we practiced that for many years. And it was some help, but it tended to be a temporary one. Often the condition would return. And not only would the patient still have the spasmodic dysphonia, but would also have a vocal cord paralysis.

The botulinum toxin injection, on the other hand, does wear off after several months, but gives several months of relief, and then the injection can be repeated.

Mr. PORTER. Are there any side effects from that injection?

Dr. SNOW. Well, sometimes, if it's overdone, it can lead to an incompetence of the larynx. There can be aspiration of food or fluid. This is usually a temporary matter. And there can be weakness of the voice if it is overdone. In each patient, there has to be a calibration or a titration as to how much should be used. We start with a small dose and then gradually work up until a satisfactory response is reached. Sometimes there is an overshoot of that and it results in one of these complications. Fortunately, they're temporary. They wear off, too.

Mr. PORTER. Since I am suffering some voice loss today, I am very interested in this subject.

Did you tell us how prevalent voice loss is in the population in general, do you know?

Dr. SNOW. It's difficult to answer that question. We don't have good epidemiologic data on voice disorders. Voice disorders, of course, are very common. All of us may experience an episode of laryngitis in the course of a year, and have several days of hoarseness. We see many individuals who use their voice in their work, as of course we all do, but particularly in public speaking, who have chronic problems with their voice. And at the periods of time

when the voice has to be used more than others, that hoarseness recurs.

That's really a very common problem. But I really can't give you any data on the matter.

GOVERNMENT PERFORMANCE AND RESULTS ACT

Mr. PORTER. Of all the people, I know two people who have voice loss, one is being treated with the injections, the other one is the result of voice loss from an injury, and apparently can't be treated. But those are the only two I'm aware of.

Much of the research that NIH supports does not lend itself particularly well to measurement under the Government Performance and Results Act. It does seem, however, that GPRA standards could be appropriate for your research in the development of hearing aid technology. Have you considered performance goals and time frames for your contracts and grants in this area?

Dr. SNOW. No, we have not done that as yet. But we can certainly do that, as we develop the plan.

CLINICAL TRIALS

Mr. PORTER. Last fall, you announced the creation of a clinical trials branch within your Institute. How many trials do you expect to have in operation at one time, and what are the major research topics you would like the clinical trials branch to focus on?

Dr. SNOW. We are in the process of awarding two clinical trial cooperative groups. These are two of the major professional organizations in the field, and within each of those cooperative groups, there are 15 to 20 clinical centers.

In the case of one of these, the first protocol is on the treatment of immune-mediated inner ear hearing loss, either with corticosteroids, methotrexate or cytoxin. This problem of immune-mediated inner ear hearing loss is really a very serious problem. It often begins in mid-life, 35 to 45 years of age. And often goes on to bilateral deafness in an individual who had otherwise had healthy hearing.

This is quite a dilemma for the clinicians to know what form of treatment is to be used. And of course there is treatment that will prevent the progression of the hearing loss to deafness. So we consider this a very major and important study to be undertaken.

The other study that has undergone peer review and is ready to begin is the one on the aspiration of fluids in the elderly. And this clinical trial will compare two forms of therapy that are thought to be effective, one due to head positioning and the other due to changing the viscosity of the food and fluids that are ingested. This is particularly a problem in the elderly who are demented, either with Alzheimer's disease or some other form of dementia.

We look forward to a series of clinical trials in each of these cooperative groups, probably not starting one each year, although that would be very desirable. Because each have four more proposals, important studies such as the use of diuretics in Meniere's disease, again a prevalent disease, and it's quite unclear as to what the efficacy of this form of therapy is.

I'm very keen to see the carrying out of the next protocol in the other group, which will deal with the use of magnesium sulfate in

the prevention of noise induced hearing loss. As you know, there are 10 million people in the United States that have noise induced hearing loss. And there are another 20 million that are exposed to hazardous noise in the work place. And so this is a problem of enormous magnitude.

About three years ago, an Israeli study was done of Israeli army recruits who were given magnesium sulfate during the period of time that they were in basic training. And those that received the magnesium solution did not develop as much noise induced hearing loss as those who did not receive it. We are very anxious to replicate that study to see whether it can be corroborated or not. That, of course, involves impulse noise and we need to determine whether magnesium solutions can prevent noise induced hearing loss of the impulse type. And then the next step would be to move on into the industrial kind of noise where it is more continuous due to machinery.

VACCINE FOR OTITIS MEDIA

Mr. PORTER. Dr. Snow, we've heard for a number of years about a vaccine for otitis media. Are there multiple types of bacterial pathogens responsible for otitis media, each of which requires its own vaccine?

Dr. SNOW. Yes, there are. The three principal organisms are the pneumococcus, the non-typeable Haemophilus influenzae, and the Moraxella catarrhalis. More progress has been made in the pneumococcal vaccines. In order for these vaccines to be useful in otitis media, they have to produce the immune response during the first few months of life, just like with the hemophilus influenza type B vaccine, which is given to prevent meningitis, and is given during the first month of life, and then there are booster doses at three and subsequent months.

We need the same sort of vaccines for otitis media. And in the case of the pneumococcus, the same strategy that was used in the Haemophilus influenzae type B vaccine, that is to conjugate the polysaccharide coating of the organism with a protein led to immunogenicity early in life, in the first month of life. We need to do the same thing.

Well, the pneumococcal vaccines are now in a stage 2 trial. And so that's going very well. We now have the non-typeable Haemophilus influenzae vaccine which is ready for the stage 1 trial: if it is found to be safe in adults, then we will move on to a stage 2 trial that will very likely be conducted by a pharmaceutical company that manufactures vaccine. Our work will probably stop at that time, and we will turn it over to the appropriate vaccine manufacturer.

We are just starting the same process with the M. catarrhalis and carrying out a similar strategy of conjugating the polysaccharide that is the endotoxin of the organism with a protein and then seeing if it produces immunogenicity.

Mr. PORTER. Assuming you are successful in that, will there ever be a vaccine that handles all three different types?

Dr. SNOW. Yes. Probably the three vaccines will be combined in a single injection, and so just as youngsters receive their immuni-

zation against Haemophilus influenzae type B meningitis, they will also receive their immunization against otitis media at that time.

SPECIFIC LANGUAGE IMPAIRMENT

Mr. PORTER. I was not familiar with the condition called specific language impairment, SLI, in which children have unexpected and unexplained difficulties learning and using spoken language. Is this thought to be a single condition or a family of disorders?

Dr. SNOW. I believe it is best looked at as a family of disorders. One of the early epidemiologic studies that we did through a contract was to determine the prevalence of specific language impairment in children. And we, as the whole scientific community, were shocked to learn that 8.36 percent of the population has this disorder. And these youngsters have difficulty, academic difficulty, difficulty reading, they often speak late, and develop speech relatively late in childhood. And this turns out to be a lifelong problem for these individuals.

This encompasses all of those who are spoken of as having dyslexia, and yes, there are receptive forms of this, there is the motoric form of it, the expressive form of it. But there are commonalities among these children that make it reasonable to lump them together for certain purposes. And now that the incidence or prevalence of this is known, we are now pursuing the molecular genetics of this problem.

Mr. PORTER. And this could be severe enough to require them to be placed in special education classes?

Dr. SNOW. Yes. There is variation from mild learning disability to very severe learning disability.

Mr. PORTER. Dr. Snow, you've answered all of our questions very forthrightly and candidly. We thank you for the wonderful job you're doing at NIDCD and thank you for coming before us to testify today.

Dr. SNOW. Thank you very much, sir.

Mr. PORTER. Thank you, Dr. Varmus.

We stand in recess until next Tuesday at 10:00 a.m.

[The following questions were submitted to be answered for the record.]

RESEARCH FUNDING

Mr. Porter: Identify FY 96-98 spending on the following: hearing aid development, otitis media vaccine, Meniere's disease, stuttering, noise-induced hearing loss, tinnitus, spasmodic dysphonia, and dystonia?

Dr. Snow: In hearing aid development, the NIDCD obligated $4,381,000 in FY 1996; we estimate we will obligate $4,818,000 in FY 1997; and $4,944,000 in FY 1998.

In otitis media vaccine research, in FY 1996 the NIDCD obligated $5,760,000; we estimate we will obligate $6,113,000 in FY 1997; and $6,318,000 in FY 1998.

In Meniere's disease, the NIDCD obligated $882,000 in FY 1996; we estimate we will obligate $918,000 in FY 1997; and $939,000 in FY 1998.

In stuttering research, the NIDCD obligated $1,486,000 in FY 1996; we estimate we will obligate $1,572,000 in FY 1997; and $1,610,000 in FY 1998.

In noise-induced hearing loss, the NIDCD obligated $4,766,000 in FY 1996; we estimate we will obligate $5,077,000 in FY 1997; and $5,260,000 in FY 1998.

In tinnitus research, the NIDCD obligated $93,037,000 in FY 1996; we estimate we will obligate $99,856,000; and $102,935,000 in FY 1998. All research in the Institute's hearing program may yield solutions to the problem of tinnitus, and the NIDCD estimates that 100 percent of research supported in the hearing program relate to tinnitus.

In spasmodic dysphonia research, the NIDCD obligated $622,000 in FY 1996; we estimate we will obligate $657,000 in FY 1997; and $667,000 in FY 1998. The only form of dystonia for which the NIDCD supports research is spasmodic dysphonia.

PUBLIC INFORMATION ACTIVITIES

Mr. Porter: How much does your 1998 budget include for public information activities?

Dr. Snow: The FY 1998 budget includes approximately $800,000 for public information activities, which include materials development for the public and for professionals, the NIDCD Clearinghouse, and evolution of the NIDCD Home Page.

COLLABORATIVE EFFORTS IN HEARING AID TECHNOLOGY

Ms. Northup: What is the time line of the collaborative effort with NIDCD, NASA, and the VA?

Dr. Snow: The NIDCD, NASA and the Department of Veterans Affairs agreed in 1995 to initiate a federal technology transfer program for hearing aids by developing partnerships among scientists, industry and Federal laboratories for commercialization of promising technologies for the benefit of individuals with hearing impairment. A search of all Federal laboratories for acoustic and electronic technologies that might improve hearing aids was completed in September 1996 utilizing a NASA contract with Research Triangle Institute (RTI). Individuals with appropriate expertise reviewed the identified technologies at the National Institute of Standards and Technology and the most promising was selected for presentation by their developers at the NIDCD/NASA/VA Hearing Aid Improvement Conference: Facilitating Partnerships for Technology Transfer will be held on May 1 and 2, 1997 on the NIH campus in Bethesda, Maryland. Scientists, representatives of hearing aid manufacturers, and individuals from the Federal laboratories are invited to attend the conference. The purpose of the conference is to initiate the development of partnerships among scientists, hearing aid manufacturers and Federal laboratories to carry out research that will lead to the commercialization of the promising technologies. A joint NIDCD/NASA program announcement is planned to solicit applications to support multidisciplinary collaborative research needed to transfer promising technologies into practical implementation of improvements in hearing aid performance. The program announcement is planned to be published in June of 1997, with an application receipt date in the fall of 1997, with probable award(s) in FY 1998.

Ms. Northup: Please be more specific on what type of technologies you believe would be applicable to improving hearing aids.

Dr. Snow: Technologies related to signal processing algorithms, noise reduction circuits, microphone development, speech recognition processing, and battery and power source design would be applicable to improving hearing aids.

Ms. Northup: Are you working with industry as well in this effort?

Dr. Snow: Yes. Hearing aid manufacturers have been encouraged to attend the May 1-2 conference. The published program announcement will also reinforce the collaboration with industry by specifying that participation of hearing aid manufacturers is essential to stimulate early assessment of commercial viability and to facilitate technology implementation.

OTITIS MEDIA

Ms. Northup: You mentioned in your testimony that OM is responsible for major health care costs. What are the health care costs to private industry and the Medicaid program?

Dr. Snow: Seventy-five percent of children born each year will experience at least one episode of otitis media by their third birthday. Almost half these children will have three or more ear infections during their first three years. It is estimated that Americans spend more than $5 billion a year in medical costs and lost wages because of otitis media. The source of this expenditure to the American public is an article by G. A. Gates, published in Otolaryngology-Head and Neck Surgery, 114(4), April 1996, entitled "Cost-effectiveness Considerations in Otitis Media Treatment." The NIDCD does not have information on the cost of otitis media to Medicaid.

Ms. Northup: Why is otitis media incidence higher in Native American children?

Dr. Snow: The NIDCD has supported an ongoing prospective study of risk factors for Otitis Media in the Native American population of northern Minnesota. This study includes the development and implementation of prevention strategies to reduce the burden of middle ear disease in this population. The lack of a prospective patient cohort for interventional studies previously prevented investigators from discerning causal risk factors from those that only have a statistical association.

Contributors to the possible increased incidence of otitis media in Native Americans might include: environmental factors that enhance the incidence of otitis media in other populations, factors that may be culturally specific to the Native American population, and possibly genetic factors. Native Americans have a much higher rate of smoking than other American population groups, and tend to live in rural areas in which wood burning stoves is a common method of home heating. Like tobacco smoke, wood burning stoves increase the level of particulates in indoor air, which is an otitis media risk factor. Other environmental factors that could contribute to an increased incidence of otitis media include poor pre- and post-natal nutrition (including a lower rate of breast feeding).

There is some evidence that middle ear function is different in Native Americans, compared with other population groups. Whether these differences are purely genetic, or involve environmental factors (such as prenatal nutrition), requires further investigation.

Ms. Northup: What is the status of the protocol you mentioned in your testimony?

Dr. Snow: Scientists in the Intramural Research Program have planned a Phase 1 clinical trial to assess the safety and efficacy of the lipo-oligosaccharide vaccine candidate for otitis media caused by nontypeable Haemophilus influenzae. We are awaiting institutional review board approval before beginning this important clinical trial.

HEARING IMPAIRMENT AND INCIDENCE

Ms. Northup: Please list the types of deafness which exist and the incidence rates associated with them.

Dr. Snow: More than 28 million Americans are deaf or hearing impaired, making this the third most common chronic condition affecting people of all ages. Levels of hearing impairment vary from a mild but important loss of sensitivity to a total loss of hearing. The largest group of Americans suffering from hearing loss is the elderly. About one-third of the people over the age of 65 (about 11 million people) have serious hearing loss. This number is expected to increase substantially in the coming decades due to longer life expectancy and the consequent aging of the population.

Noise-induced hearing loss affects more than 10 million Americans. The prevalence of noise-induced hearing loss is about 5% of persons aged 20-64, although it can occur at all ages. Noise-induced hearing loss may involve exposure to sounds (for example, use of firearms) that are sufficiently loud to damage sensitive inner ear structures. This could produce hearing loss that is not reversible by any presently available medical or surgical treatment. It can also result from long-term exposure to less intense but still hazardous sounds, commonly encountered in the workplace. Hearing impairment associated with noise exposure is also often associated with a potentially troublesome symptom, tinnitus (ringing in the ears). In a recent U.S. study, tinnitus occurring during a 12-month period was reported in 8% of the population. Tinnitus causes major disruptions in about 15% of people over their lifespan.

Also, one of every thousand infants is born deaf and many more will be diagnosed with less severe impairments later in childhood. More than 50% of these childhood impairments are believed to be genetic in origin. However, the most common cause of hearing loss in children is otitis media, or middle ear infection. Otitis

media is predominantly a disease of infants and young children. Eighty percent of American children have an episode of otitis media by the time they are three years old. The annual cost of treating children with this disease is estimated to be several billion dollars.

Hearing impairments may also be caused by exposures to drugs (for example, aminoglycoside antibiotics) or to toxins, by accidents (for example, head trauma), by maternal infections during pregnancy (for example, cytomegalovirus--CMV), or by other environmental exposures leading to acquired hearing loss. Furthermore, many acquired hearing losses may result from a genetic predisposition or susceptibility to the development of hearing loss due to these factors.

There has been insufficient appreciation of the importance that good hearing plays in the quality of life as well as the severe economic impact of living with deafness or hearing impairment. Regardless of when a hearing loss occurs, the earlier it is identified, the sooner its effects can be mitigated through suitable intervention techniques.

OTITIS MEDIA VACCINE

Mr. Stokes: To what extent is the Institute making progress with regard to the discovery of a vaccine for otitis media?

Dr. Snow: The most common bacterial pathogens in otitis media are the Streptococcus pneumoniae (pneumococcus), nontypeable Haemophilus influenzae (NTHi) and Moraxella catarrhalis. All three have polysaccharide capsules. Polysaccharide vaccines alone have not been successful in preventing otitis media since they lack immunogenicity when administered to infants and young children. However, vaccines using polysaccharides conjugated with protein such as the Haemophilus influenzae type B vaccine against meningitis have been effective in stimulating immunity in infants and young children. Stage I clinical trials of conjugated vaccines against the pneumococcus in infants and children have been completed, and Stage II clinical trials are underway. NIDCD scientists have successfully prepared a detoxified lipooligosaccharide (dLOS)-based conjugate antigen from NTHi that induces a bactericidal humoral immune response in two animal models and reduces the incidence of otitis media in the only reliable animal model of the disease, making it a promising vaccine candidate. Plans are underway to initiate a Stage I clinical trial of this vaccine candidate. In addition, intramural scientists are beginning work on a candidate vaccine against M. catarrhalis otitis media.

PRESBYCUSIS

Mr. Stokes: In general, what is the extent of hearing impairment in the United States? As the baby boomers enter their elderly years, how extensive a problem is hearing projected to be and how is the Institute preparing to address this problem?

Dr. Snow: Approximately 28 million individuals in the United States have a hearing impairment, and it is estimated that approximately 75 percent of these persons are over the age of 55. The magnitude of presbycusis now and in the foreseeable future will place novel demands on the delivery of services for the hearing impaired. The NIDCD currently supports several research projects related to hearing loss in the elderly. These projects investigate age-related changes in the peripheral and central auditory system from the molecular to the perceptual level for purposes of improving diagnostic, rehabilitative, and preventive measures for presbycusis. The findings from these projects have potential significance for advancing basic scientific knowledge about the aging auditory system and for dramatically improving clinical services and devices for the elderly population. It is only through such research efforts that we will be able to adequately address this issue in the future.

HEARING AID RESEARCH

Mr. Stokes: What is the current status of hearing aid research and development, what new and advanced technologies are on the horizon? To what extent will the FY 1998 budget request allow the Institute to exploit these opportunities?

Dr. Snow: The NIDCD is currently supporting more than 40 grants related to hearing aid research and development. The focus of these grants ranges from ways to reduce noise interference in hearing aids to neural network modeling studies designed to elucidate the basis of impaired speech understanding in noise. In addition, the NIDCD and the Department of Veterans Affairs (VA) are continuing an innovative collaboration designed to support the development of better hearing aids. The first clinical trial began in the spring of 1996 through an interagency agreement with the VA. This trial will determine which commonly used hearing aid circuits benefit which subgroups of hearing-impaired individuals most and under what circumstances.

The first hearing aid research and development conference, entitled Advancing Communication: An Interdisciplinary Forum on Hearing Aid Research and Development, was held in September 1995, at the National Institutes of Health. The conference was very well attended and has become a meeting of national and international importance to those in fields related to speech understanding with the use of hearing aids. The second is scheduled for September 22-24, 1997.

The NIDCD has also entered into collaboration with the National Aeronautics and Space Administration (NASA) and the VA to search Federal laboratories for new technologies that may be applicable to improving hearing aids. This collaboration also seeks to foster the formation and support of partnerships among scientists, industry and Federal laboratories for the commercialization of existing promising technology that could, when applied to hearing aids, benefit the hearing-impaired public.

The cochlear implant is now firmly established as an effective option in the habilitation and rehabilitation of individuals with profound hearing impairment, with the multichannel cochlear implant becoming widely accepted as the auditory prosthesis for both adults and children. Scientists are currently investigating how temporal cues in different spectral bands combine to allow speech recognition as they compare different waveform and speech processing strategies.

Advances in the computer and electronics industries have resulted in the development of new and improved diagnostic and rehabilitative tools for individuals with hearing impairment. For example, scientists participating in the NIDCD Small Business Innovation Research (SBIR) program are developing a cost-effective and user-friendly listening system designed to interface with existing airplane sound systems. This will allow individuals with hearing aids to receive pilot and flight

attendant announcements, as well as to communicate with neighboring passengers. A collaboration with a major airline is currently in place. In another example, better tools for infant hearing screening and diagnostic testing continue to be developed as many hospitals and other health service providers implement universal infant hearing screening programs. In order to improve driver and passenger safety on the nation's roadways, research has begun on the development of a device that will alert a hearing-impaired driver to an approaching emergency vehicle siren using a visual signal. Each of these projects shows promise for commercialization of important new products designed to benefit millions of persons who are deaf or hard of hearing. The NIDCD estimates that $4,944,000 will be spent for hearing aid research in FY 1998.

Mr. Stokes: As you are aware, Department of Defense (DOD) technologies are being examined for benefits to furthering advances in breast and prostate cancers, and other diseases and disorders. Are there technologies in DOD and other agencies that would help to accelerate the development of new and improved hearing aid devices, and that would help to facilitate research on deafness and other communication disorders in general?

Dr. Snow: The NIDCD, NASA and the Department of Veterans Affairs agreed in 1995 to initiate a federal technology transfer program for hearing aids by developing partnerships among scientists, industry and Federal laboratories for commercialization of promising technologies for the benefit of individuals with hearing impairment. A search of all Federal laboratories for acoustic and electronic technologies that might improve hearing aids was completed in September, 1996. Department of Defense laboratories were included in this search and several DOD technologies were identified for potential application to hearing aids. This will facilitate research on deafness and other communications disorders in general.

CLONING TECHNOLOGY

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists' cloning of adult sheep. These articles expressed excitement with regard to opportunities for advances in medical treatments, and concern with regard to misuse of the technology and the possibility of human cloning. This is another area where we must now be certain to assess and address the ethical, legal and social issues of research on the front end. As a leading researcher and as an Institute Director, what is your professional opinion of this technology and what are your most serious concerns?

Dr. Snow: For many years scientists, physicians, educators and others have agreed that multicellular organisms possess complex arrangements of cells which though identical in genetic code one from the other, nonetheless are organized in ways which allow them as tissues or organs to function in special ways. Thus, for example, muscle cells are characteristically elongated at rest but capable of significant shortening

or contraction. The commonly held view has been that the more specialized or differentiated cells, while more efficient at a particular function, have lost the potential to change to other kinds of cells. Those that were most highly differentiated, for example, neurons of the central nervous system were not only incapable of dedifferentiating to a simpler form, but had even lost the ability to repair or regenerate following disease or injury. Although every cell possessed the entire genetic code for that organism, only those genes involved with particular functions were "switched on." The recent report from the Roslin Institute in Scotland showed in dramatic fashion that the genetic material (nucleus) from a differentiated udder cell in sheep, whose active genes were those related to milk production, was capable under certain strict conditions of reconstituting an entire multicellular organism.

If these remarkable scientific findings are reproducible, there is promise that the new technology will facilitate the use of animals to produce drugs, or other biological products, to combat an array of human health problems. A milk formula enriched for key nutrients for premature infants or milk supplying a missing enzyme or other protein to individuals with an inherited disorder are two examples. Cloning technology may someday allow the production of animal organs for human transplantation that are genetically engineered to avoid rejection by the human immune system.

Of less immediate benefit, but perhaps even more important for future progress, will be a better understanding of the interactions between the nuclear DNA of the "donor" and important elements from the cytoplasm of the "recipient", and how these interactions regulate the potential for gene expression. Knowledge of these fundamental interactions will undoubtedly be important not only for developmental biology, but for aging, cancer and virtually all chronic diseases or disorders.

As with other powerful tools, cloning offers the potential for abuse. While unknown at present, the cloning of human beings may be possible. In contrast to cloning transgenic animals for the purpose of providing therapeutic benefit or prevention of human disorders, the cloning of human beings would be to perpetuate the existence of a particular individual. There is a great need for citizens to understand the very different underlying motives behind these activities and for there to be agreement that cloning of human beings is not appropriate.

Maintaining genetic diversity is desirable, not only in humans, but also in animal populations. To that extent, the cloning of animals for particular animal husbandry and biomedical or other purposes should be limited to discrete numbers of animals in certain well defined environments. Although unlikely to occur, an indiscrete use of cloning to "improve the breed" in large, or entire populations, could result in great susceptibility to deleterious agents occurring in nature.

Mr. Stokes: With regard to the diseases and disorders studied by your Institute, what are the most significant benefits that the cloning technology would yield for your major areas of research?

Dr. Snow: The cloning technology has resulted in a fundamental change in the way scientists view the processes called differentiation, where a developing cell with the potential to perform many functions and express many genes (a pluripotential cell) specializes into a mature cell that performs a limited repertoire of functions and expresses a limited number of genes (a differentiated cell). Traditionally, scientists felt that, once differentiated, specialized cells could never return to a state where they were again able to perform a broader repertoire of functions and express a larger number of genes. The cloning technology teaches us that it is possible for the genes no longer expressed in a specialized, differentiated cell to return to their previous pluripotential status.

This new understanding raises hope that when we understand the molecular mechanisms that allowed a differentiated genome to return to a pluripotential genome, we may be able to use this technology to treat diseases and disorders that involve neuronal degeneration. Neurons are differentiated cells that, while becoming specialized in their functions, lose their capability to divide, or regenerate. Once neuronal function is lost, it can never be recovered. If we were able to systematically reverse neuronal differentiation, perhaps we could create pluripotential cells with the capability of both regeneration and differentiation into mature neurons which could be used to restore lost neuronal function that underlies many diseases of the nervous system. In the auditory system, this technology might allow scientists and physicians to restore the neuronal hair cells in the inner ear that are often lost in diseases and disorders of the auditory and vestibular system. This capability would open up whole new vistas of treatment modalities for these diseases, in particular acquired hearing impairment and balance disorders.

MULTICULTURAL LANGUAGE ASSESSMENT

Mr. Stokes: As language is one of the areas of emphasis in the Institute's research portfolio, to what extent is the Institute conducting research that relates to multicultural language assessment?

Dr. Snow: For more than 30 years, there has been a long-standing problem for clinicians--determining whether or not there is a language difference or a language disorder in young children. The NIDCD has issued a Request for Proposals (RFP) entitled "Development of a Language Assessment Instrument or Protocol for Children Speaking Non-Standard English." Under this solicitation, two separate contracts are envisioned to collect cross-sectional data on language abilities in: 1) normally developing 4 to 6 year old bilingual Hispanic children whose primary language is not English, or is a nonstandard form of English; and 2) normally developing 4 to 6 year

speakers of Black English. In the United States, data will be collected for each group within an urban, a suburban, and a rural environment. Age-appropriate language milestones/behaviors including aspects of phonology, syntax, semantics and pragmatics will be determined. Subsequently, these normative data will be used to develop items for a language assessment instrument or procedure which could be used to differentiate between language impairment and normal language development in each language group. A pilot study validating these language assessment instruments/procedures with children in the targeted language groups will be conducted. The focus of NIDCD's interest is upon creating an instrument that will differentiate between language differences and language impairments for the clinician.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are currently underway and what are the expected benefits to be achieved from this investment?

Dr. Snow: In Fiscal Year 1995, the NIDCD issued a Request for Applications (RFA) to organizations and institutions that had the capability and resources to organize multicenter cooperative clinical trials of the efficacy of treatment for diseases and disorders of human communication. Two applications were approved for award at the October 1996, NIDCD Advisory Council meeting. Start dates for these two awards are anticipated in 1997. These consortia, referred to as Cooperative Groups, will plan, implement, conduct, analyze and disseminate results of clinical studies on the treatment or management of diseases and disorders of hearing, balance, smell, taste, voice, speech or language, or any combination thereof. The goal of these studies is to evaluate: (1) innovative therapeutic approaches; (2) established but controversial therapeutic approaches; or (3) modifications in existing therapeutic approaches to diseases and disorders affecting the processes involved in human communication.

Mr. Stokes: What major clinical trials that are ready to be implemented will the FY 1998 budget request allow the Institute to pursue?

Dr. Snow: The NIDCD, under its Clinical Trial Cooperative Groups, initiated two major clinical trials in FY 1997: Immunosuppression of Autoimmune Inner Ear Disease and Treatment for Liquid Aspiration in the Elderly. It is anticipated that "start up" of these trials will run into FY 1998, and other major clinical trials will not be added until FY 1999.

INVESTIGATOR-INITIATED RESEARCH APPLICATIONS

Mr. Stokes: According to the budget justification, the NIH considers investigator-initiated research project grants its highest priority. How many "new" research project grants will your institute support in FY 1997, and how does this compare to the number supported in FY 1996 and proposed for 1998? Please include in the record a chart displaying your institute's grant success rate for each of the last five fiscal years, and the FY 1998 budget request projected rate.

Dr. Snow: In FY 1997 the National Institute on Deafness and Other Communication Disorders (NIDCD) will support 98 new research project grants (RPGs), compared to 92 new RPGs in FY 1996. It is projected that the NIDCD will support 101 new RPGs in FY 1998.

NIDCD
Research Project Grant
Success Rates
FY 1993 - FY 1998

FY 1993 Actual	FY 1994 Realigned	FY 1995 Actual	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
29%	32%	34%	33%	35%	37%

PARTNERSHIP PROGRAM

Mr. Stokes: What is the status of the Institute's Partnership Program? Why does the Institute consider this initiative to be an important investment?

Dr. Snow: In 1994, the NIDCD launched a pilot program, The NIDCD Partnership Program, with the support of the NIH Office of Research on Minority Health (ORMH). The purpose of the program is to encourage students, faculty, and administrators at institutions previously underrepresented in research in human communication to partner with scientists and scientific administrators at the NIDCD. These institutions are the Morehouse School of Medicine/Atlanta University Complex, the University of Puerto Rico, the University of Alaska System, and Gallaudet University. Collaborations with these institutions include laboratory, program, grants management, planning and communication experiences, as well as curriculum development and workshops.

The NIDCD Partnership Program is in its third year, and student research results have already been presented at four different research festivals. Undergraduate and graduate students, medical students, faculty, and administrators have participated in the program. NIDCD staff have served as mentors, and university faculty have served as

program liaisons as well as mentors at the participants' home institutions. The first NIDCD Partnership Program Conference was held in September 1996, marking the first time that everyone associated with the program had a chance to meet together to share information, exchange ideas and experiences, provide feedback to program staff, identify the successful elements of the program, and to offer suggestions for the future. NIDCD has supported development of curriculum resources and supported a special meeting preliminary to the Society for Neuroscience for teams from all of the institutions. The NIDCD expects to enhance its involvement in the Partnership Program by seeking means of strengthening the human communication research infrastructures of historically underrepresented colleges and universities.

In May 1997, an outside panel of experts will be convened to assess the program and make recommendations for the future of the program.

The Institute considers this initiative to be an important investment because it is aimed at fostering the research training and career development of underrepresented minority individuals in the scientific disciplines related to human communication. This initiative will also strengthen the relationship between and among the partners while providing a "human infrastructure."

Mr. Stokes: How much is included in the Institute's FY 1997 appropriation for this initiative, and how does it compare to the funding level contained in the Institute's FY 1998 budget request?

Dr. Snow: The NIDCD will provide approximately $100,000 for the Partnership Program. The NIDCD also provides the conceptual framework, administrative staff to manage the Program, and the professional mentorship for faculty staff who participate, and the facilities in which the participants obtain their training experience.

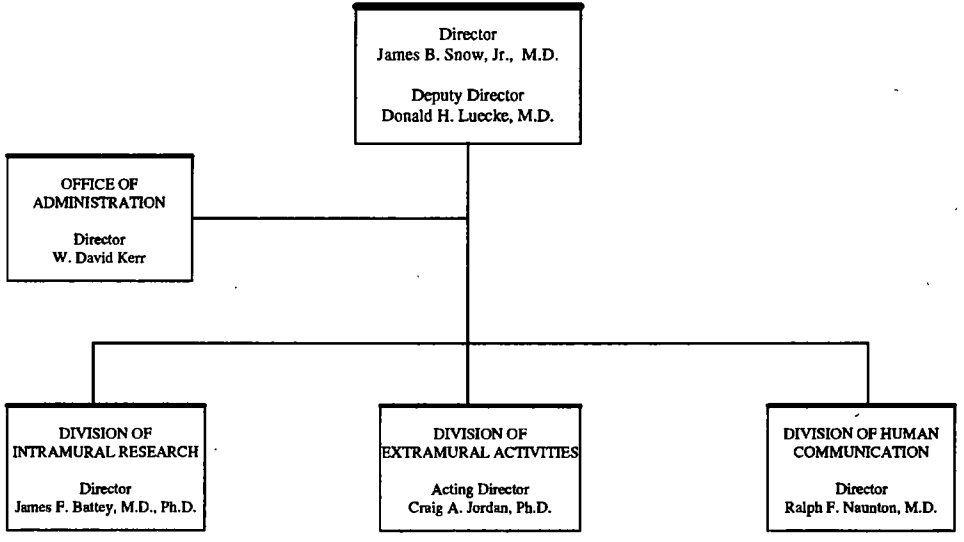
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

FY 1998 Budget	Page No.
Organization chart	2
Appropriation language	3
Amounts available for obligation	4
Narrative justification	5
Budget mechanism tables	20
Budget authority by activity	21
Summary of changes	22
Budget authority by object	24
Administrative costs	25
Significant items in House and Senate Appropriations Committee reports	26
Authorizing legislation	27
Appropriation history	28
Detail of full-time equivalent employment(FTE)	29
Detail of positions	30

NATIONAL INSTITUTES OF HEALTH
National Institute on Deafness and Other Communication Disorders



NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to deafness and other communication disorders, [$188,422,000] *$192,447,000.*

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriation Act, 1996, P.L. 104-208)

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$176,502,000	$188,422,000	$192,447,000
Rescission in accordance with P.L. 104-134	(119,000)	---	---
Reduction in accordance with P.L. 104-208	---	(77,000)	---
Subtotal, Adjusted Appropriation	176,383,000	188,345,000	192,447,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority	(471,000)	0	0
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	(1,650,000)	(1,820,000)	0
Subtotal, adjusted budget authority	174,262,000	186,525,000	192,447,000
Unobligated balance, lapsing	(38,000)	0	0
Total obligations	174,224,000	186,525,000	192,447,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1996 - $3,177,000; FY 1997 - $4 ,300,000; FY 1998 - $4 ,300,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research: FY 1998 - $1,774,000.

Note: Excludes $93,283 in FY 1996 and $97,947 in FY 1997 for royalties.

Justification
National Institute on Deafness and Other Communication Disorders

Authorizing Legislation - Sections 301, 464 and 487 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
126	$174,262,000	126	$186,525,000	126	$192,447,000	---	$5,922,000

Introduction

This document provides justification for the FY 1998 Non-AIDS activities of the National Institute on Deafness and Other Communication Disorders. Justification of NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute on Deafness and Other Communication Disorders (NIDCD) is responsible for conducting and supporting research in human communication. Included in the program areas are research and research training on normal and disordered mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. The NIDCD is actively involved in health promotion and disease prevention.

The NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute also supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

The Molecular Genetics of Hereditary Hearing Impairment: A Story of Accelerating Discovery

For centuries, deafness and hearing impairment were observed to occur within some families. However, until NIDCD was established in 1989, only two genes responsible for hereditary hearing impairment were known. In this past decade, a multitude of genes for syndromic and nonsyndromic forms of hearing impairment, including autosomal dominant and recessive, X-linked and mitochondrial modes of transmission, have been located in specific regions of the human genome. In addition, several clinically relevant genes essential for normal auditory development and/or function have been cloned. There has been much controversy regarding what interventions (if any) should be part of the educational experience of deaf people, and when such efforts should begin. Years ago, deaf people were often isolated in institutions or not educated at all. It is hoped that having this type of genetic information will ultimately aid in the early identification of hearing impairment in infants, thereby helping parents to plan for the educational and habilitation needs of their children at the earliest possible opportunity and ensuring the acquisition of language, spoken or signed, on a normal schedule. This should

improve the effectiveness of the habilitation and, consequently, the quality of life for these children over a lifetime.

Among the syndromic forms of hereditary hearing impairment for which the genes have been mapped are Waardenburg syndrome, Usher syndrome, Alpert syndrome, Apert syndrome, branchio-oto-renal syndrome, Crouzon syndrome, familial amino glycoside ototoxicity, maternally inherited diabetes and hearing loss, neurofibromatosis type I and type II, osteogenesis imperfecta, perilymphatic gusher (DFN3) Stickler syndrome, Treacher Collins syndrome and X-linked deafness with stapes fixation.

Presently, at least 12 different genes on 10 different chromosomes have been located for various forms of autosomal dominant nonsyndromic hearing impairment and at least 11 different genes on as many different chromosomes have been identified for autosomal recessive nonsyndromic hearing impairment.

Recently, mutations in mitochondrial chromosomes have been found to be associated with a variety of hearing disorders. NIDCD-supported scientists identified a mitochondrial mutation in combination with a nuclear mutation that cause nonsyndromic deafness in a large Arab-Israeli pedigree. More recently, these same scientists have identified a family in New Zealand with maternally transmitted nonsyndromic sensorineural hearing impairment. The mitochondrial mutation in this family was identical to the one that had previously been identified in a Scottish pedigree. This research suggests that nonsyndromic deafness can be caused by mutations in genes responsible for generalized cell processes, such as oxidative phosphorylation, as well as in genes responsible for hearing-specific molecules.

Several important new strategies for predicting how the inheritance of a genetic mutation acts to disrupt auditory function have been developed. One strategy depends on the fact that some mutant genes produce protein products that are ineffective or have deleterious effects on auditory function. On the other hand, a gene may alter the synthesis of another protein essential to auditory development or function. Using animal models that exhibit the clinical features of human hearing impairment, scientists can now identify the exact nature of the defect by analyzing genetic information in the model system. Investigators use mice in which a specific gene has been experimentally inactivated to examine how the gene and gene product produce auditory deficits. By using these "knockout mice," investigators found that the deletion of one gene, BRN-3.1, leads to animals with a complete lack of hair cells, profound deafness and vestibular disability. Also insertion of genetic material into mouse embryonic cells has led to the disruption of a gene that has a selective effect on hearing. The product of this gene is found in the outer hair cells of the cochlea and is lost due to this disruption. This gene could therefore be important in the growth and differentiation of hair cells. Genes can also be inserted in the mouse to induce more or less of a protein important in inner ear development and audition. Targeted mutations of genes coding for neurotrophins, factors for nerve cell growth and differentiation, also provide much needed data on the signals that control normal growth and development of the inner ear. The temporary reduction in the level of gene products is also possible using sequences related to the gene of interest. These synthetic sequences bind to the gene to block temporarily

the production of the gene of interest. These models provide exciting opportunities to apply advances in the field of molecular genetics to solving human hearing health problems.

Manual and Vocal Babbling in Deaf and Hearing Children

Babbling was long viewed as a phenomenon of speech that did not depend on the availability of linguistic input. It was believed that all children would begin vocal babbling between the ages of 6 to 8 months. Since it has been suggested that a manual analog of babbling can be identified in the gesturing of deaf children reared in signing environments, investigators are seeking to confirm that babbling is not unique to speech but is rather a stage in language acquisition in all modalities. Three subject groups are being examined: 1) deaf children of deaf parents, 2) deaf children of hearing parents, and 3) hearing children of hearing parents. The children from each of these groups are being followed longitudinally from the ages of 5 to 15 months; hour-long videotaped samples of each child interacting with a parent are being collected at biweekly intervals. This research, by examining gestural development in hearing children born into non-signing families, furthers our understanding of normative patterns of motor development in all children. Research into the gestures of deaf children reared in signing environments will enable more comprehensive comparisons between the acquisition of sign and speech than was previously possible. Most systematic developmental research on American Sign Language has focused on the acquisition of syntax and morphology beyond age two. A more detailed understanding of the acquisition of sign languages in deaf children will contribute toward the development of clinical test batteries that will enable the proper identification of language delays or disorders in signing children.

New Potential for Cochlear Hair Cell Regeneration

Cochlear hair cells that are lost or nonfunctional are not replaced, resulting in permanent hearing loss. Current research efforts have focused on the role of growth factors and other mitogens in promoting hair cell regeneration following experimentally induced damage. A new direction for understanding hair cell regeneration has been provided by an NIDCD-supported scientist investigating hair cells in the chick basilar papilla. New hair cells could be generated in the undamaged basilar papilla by adding agents which stimulate intracellular cyclic adenosine monophosphate (cAMP) signaling pathways. Of significance is that hair cell proliferation occurred in the absence of a predisposing traumatic stimulus and proliferation could be blocked by selective antagonists of cAMP. This approach provides new avenues for investigating mechanisms of hair cell regeneration and repair in mammalian systems. This research promises to accelerate the discovery of therapeutic agents for the treatment and prevention of sensorineural hearing loss and vestibular (balance) abnormalities in human populations.

Native American Children and Their Risk for Otitis Media

Chronic otitis media (OM) in children creates hearing loss, carries significant health care costs, and is a risk factor for delayed language. While there are many risk factors for OM in the general population, the applicability of these studies to Native Americans is not known. In addition, studying OM risk factors in a population with a high incidence of this disease could provide evidence for the relative importance of certain risk factors in both majority and minority populations. An NIDCD-funded investigator is currently examining risk factors for OM in Native American mothers and their children on the White Earth Reservation in Minnesota. The White Earth Reservation study protocol includes hearing screening and tympanometry of Native American children. Results to date suggest a high rate of chronic OM in this group (approaching 50%), with half of the affected children exhibiting an associated hearing loss.

Epidemiology of Hearing Loss in Hispanic Populations

The epidemiology of hearing impairment in underrepresented populations has not been adequately described in the literature. The effect on the quality of life for these underrepresented groups may be substantially different from that of the general population. Examining the epidemiology of hearing loss in Hispanic children, investigators have found that the prevalence of hearing loss in Cuban-American and Puerto Rican children is significantly higher than in African-American and non-Hispanic white children. Of note, the percentage of hearing-impaired Hispanic children and adults in this study living in economically disadvantaged households was significantly greater than for Hispanics without hearing impairment. Hearing-impaired children were more likely to be performing below their expected grade level academically. This finding suggests that hearing loss and socioeconomic status in Hispanic individuals may be associated, and that these hearing-impaired individuals may be at greater risk for a variety of adverse health outcomes associated with residing in economically disadvantaged homes.

Technology Advances for Individuals With Hearing Impairment

Hearing aids continue to be the principal form of remediation for most people with permanent hearing loss. Although 28 million Americans have hearing impairment, only about 20% of that number have hearing aids. More than 40 grants related to hearing aid research and development are currently supported by the NIDCD. The research focus of these grants ranges from finding better ways to reduce noise interference in hearing aids to neural network modeling studies designed to elucidate the fundamental basis for impaired speech understanding in noise. In addition, the NIDCD and the Department of Veterans Affairs (VA) are continuing an innovative collaboration designed to support the development of better hearing aids. The first clinical trial began in the spring of 1996 through an interagency agreement with the VA. This trial will determine which commonly used hearing aid circuits benefit which subgroups of hearing-impaired individuals most and under what circumstances. The second hearing aid research and development conference is scheduled for September 22-24, 1997, at the William H. Natcher Conference Center, National Institutes of Health, Bethesda, Maryland. The first such conference, entitled Advancing Communication: An Interdisciplinary Forum on Hearing Aid Research and Development, was held in September 1995. The initial conference was very well attended and it

is already apparent in the final stages of preparation for the second conference that these initiatives are of national and international importance to persons in fields of research and development related to speech understanding with hearing aid use.

The NIDCD has also entered into collaboration with the National Aeronautics and Space Administration (NASA) and the VA to search Federal laboratories for new technologies that may also be applicable to improving hearing aids. This collaboration also seeks to foster the formation and support of partnerships among scientists, industry and Federal laboratories for the commercialization of existing promising technology that could, when applied to hearing aids, benefit the hearing-impaired public.

The cochlear implant is now firmly established as an effective option in the habilitation and rehabilitation of individuals with profound hearing impairment. The multichannel cochlear implant is becoming widely accepted as the auditory prosthesis of choice for both adults and children. Scientists are currently investigating how temporal cues in different spectral bands combine to allow speech recognition as they compare different waveform and speech processing strategies. Research continues to indicate that children implanted by five years of age may make greater and more rapid speech perception gains than children implanted after this time. Additionally, results continue to demonstrate that children who get minimal benefit from hearing aids might benefit more from a cochlear implant. These results are important in determining who would benefit from a cochlear implant, device selection choices, and the timing of cochlear implantation.

Advances in the computer and electronics industries have resulted in the development of new and improved diagnostic and rehabilitative tools for individuals with hearing impairment. For example, scientists participating in the NIDCD Small Business Innovation Research (SBIR) program are developing a cost-effective and user-friendly listening system designed to interface with existing airplane sound systems. This will allow individuals with hearing aids to receive pilot and flight attendant announcements, as well as to communicate with neighboring passengers. A collaboration with a major airline is currently in place. In another example, better tools for infant hearing screening and diagnostic testing continue to be developed as many hospitals and other health service providers implement universal infant hearing screening programs. In order to improve driver and passenger safety on the nation's roadways, research has begun on the development of a device that will alert a hearing-impaired driver to an approaching emergency vehicle siren using a visual signal. Each of these projects shows promise for commercialization of important new products designed to benefit millions of persons who are deaf or hard of hearing.

New Findings Show Differences in Children With Learning Problems

The inability to hear the differences among the sounds of speech known as phonemes has long been a hallmark of certain speech, language, and learning problems. A biological basis for this problem has now been found in a study of the speech discrimination abilities, standardized learning and academic achievement scores, and neurophysiology in a large group of children with and without learning problems. The brain waves of the learning-impaired children who had

trouble distinguishing sounds, such as "da" and "ga", were different from those of the children who were not learning impaired. The results indicate that the brain fails to process these sounds adequately in the early stages of sound processing, even before the child is consciously aware of the sounds. This is the first neurophysiologic demonstration of a difference between these two groups of children. This finding is particularly important in light of the recent discovery that forms of therapy designed to teach children with language impairments to distinguish between certain sounds delivered very rapidly, can improve their language skills. The hope is that neurophysiologic testing will provide early identification of children at risk for learning problems. Then, appropriate therapies, begun early, may prevent or alleviate the long-term disabilities caused by these learning disorders.

Limitations of Daily Living for Patients With Chronic Vestibular Disorders

Disorders of balance and vestibular function constitute a major health problem, adversely affecting an individual's sense of independence, vocational opportunities and quality of life. The elderly are particularly vulnerable to the effects of disequilibrium. It is estimated that 12.5 million Americans over the age of 65 have dizziness or balance problems that significantly interfere with their lives, and many of these individuals have difficulty caring for themselves independently. To assess the functional skills of individuals with chronic balance problems of vestibular origin, an NIDCD-supported investigator has developed and validated a scale of independence in activities of daily living. Early results from this study suggest that individuals with chronic vestibular disorders in the adult age range are significantly impaired when compared to groups of normal individuals on tasks that require stabilizing the body during weight-shifting, bending or rapid head motion. These tasks include: transferring in and out of a bathtub or shower, getting in and out of bed, lower extremity dressing (e.g., putting on pants, socks and shoes), climbing stairs and reaching for objects in low or high cabinets. Weight-shifting changes in body posture that involve head motion are particularly destabilizing for these individuals, and often provoke a sensation of vertigo. These findings give a better understanding of the disability of chronic vestibular impairment and suggest when rehabilitation services should intervene. The scale developed in this study provides clinicians who manage individuals with balance disorders with a useful tool to evaluate the outcomes of experimental treatments.

Taste: Links to Nutrition and Health

Variation in eating behavior and nutrition among individuals is related to genetic variation in taste ability. Studies with a bitter substance called PROP (6-n-propylthiouracil) are providing an important key to understanding taste-nutrition links. People are born as "nontasters," "medium tasters," or "supertasters" of PROP. Nontasters have the fewest number of taste buds, and supertasters have the most. Women are more likely than men to be supertasters. Research has shown that women of childbearing age who taste PROP and find it to be the most bitter also dislike sweets the most. In a sample of elderly women, a greater ability to taste PROP also associated with nutritional indexes (such as lower body mass) that indicate a low risk for cardiovascular disease. Additionally, it has been found that supertasters experience the most intense tastes from a variety of sweet and bitter substances present in foods. Further studies are attempting to determine whether there are variations in taste ability and number of taste buds that can be related to variation in sex hormones.

Eating disorders comprise the most rapidly growing group of medical problems affecting Americans. Many individuals are afflicted by an eating disorder such as conditioned food aversions or anorexia that can result in malnutrition, wasting, or even death. Scientists have found some surprising results regarding the effect of gustatory thalamic lesions on behavior that challenge earlier notions of how taste information is processed by the gustatory thalamus and what its role is in guiding eating behavior. These results suggest that the gustatory thalamus is not simply a relay station for transmitting primitive, consummatory aspects of gustatory information from the brainstem to higher cortical centers, but rather plays a more pivotal role in the learning and execution of more complex tasks, including sophisticated, preparatory aspects of taste-guided behavior. Work in progress includes the investigation of the role of gustatory thalamus in the information-processing of conditioned food aversions and food-seeking behavior.

Neurotransmission and Regeneration in the Olfactory System

The NMDA (N-methyl-D-aspartate) receptor is one of the most intensely studied molecules in the brain because of its key role in plasticity and neuronal development. Together with the excitatory amino acid transmitter called glutamate, NMDA is implicated in the long-term increase in the strength of synaptic transmission over days. This fascinating phenomenon, called "long-term potentiation" has become one of the most productive areas in neuroscience and provides the best available model for the cellular basis of learning, memory, and neural plasticity. A novel form of long-term potentiation has recently been discovered in the central part of the olfactory system. This potentiation, evidently NMDA-dependent, is induced by repeated high-frequency stimulation of association fibers in the olfactory bulb or olfactory cortex, and is manifested as selective long-term potentiation of the late components in potentials evoked in the olfactory bulb and olfactory cortex. Another important but unexpected discovery is that there is long-term potentiation at the synapse of the olfactory receptor neuron. This is the first demonstration of long-term potentiation at any first order synapse in any sensory system. Additional studies of this form of long-term potentiation will contribute to the understanding and eventual treatment of olfactory disorders, and will increase the understanding of the mechanisms underlying learning and memory.

The adult mammalian brain is limited in its recovery following stroke, trauma or neurodegenerative disease due in part to its inability to replace lost neurons. In contrast, the odor-responsive neurons located in the nose, the olfactory receptor neurons, are capable of regenerating and reconnecting to the brain's olfactory bulb. Signals from the olfactory receptor neurons are received by olfactory bulb interneurons. Some studies indicate that these interneurons, unlike almost all other neurons within the brain, are generated throughout life. Preliminary research results suggest that the destruction of olfactory receptor neurons and their subsequent regeneration and reconnection to the olfactory bulb leads to an increase in the population of newly generated olfactory bulb interneurons. These important findings may be explained by either an increase in the production of olfactory bulb interneurons or an increase in the number that can integrate into the circuits of the olfactory bulb and survive. Experiments are in progress to determine the mechanism by which the newly generated interneurons couple with the brain's reorganizing neural network, following peripheral regeneration of olfactory receptor neurons. The implication of these findings is that following neuronal loss, compensatory neurogenesis is possible in the adult mammalian brain. The olfactory system, studied both *in*

vivo and *in vitro*, should serve as a model for determining which signals encourage the production and survival of neurons in the adult mammalian brain. Previously published findings suggest that these processes may also hold true in the adult human brain. An understanding of factors that regulate adult brain neurogenesis and neuronal survival may lead to treatments promoting replacement of lost or damaged neurons in the brain and other parts of the central nervous system.

Making Progress in the Treatment of Stuttering

Scientists are seeking to overcome one of the major roadblocks to research and treatment of stuttering: the absence of a reliable method for measuring stuttering in the speech of chronic stutterers. Previous research has shown repeatedly that trained and untrained judges have exceedingly poor levels of intra- and interjudge agreement in identifying occurrences of stuttering. Such agreement is a prerequisite to the development of systems for automatically recognizing stuttering during speech. A solution to this problem is emerging through the investigation of a time-interval measurement system. This system has been found to improve both the level of agreement in the measurements obtained by different raters and the accuracy of raters for perceptual judgments of stuttering. Current studies have: (1) developed a library of audiovisually recorded exemplar intervals of adults' and children's stuttered speech from time-interval judgments made by recognized authorities on stuttering; (2) shown that training based on these exemplars will produce satisfactory judgment skills for clinicians, (3) determined that there are fundamental and clinically significant differences between speaker- and observer-identified intervals of stuttered speech; and (4) used time-interval measures to investigate procedures for modifying stuttering. Current investigations are designed to develop a standardized time-interval measurement training system for use by clinicians working with adults and children who stutter.

Speech Development and Production in Special Populations

Research has demonstrated that infants, even in the first months of life, coordinate their actions across modalities (vocalization, gesture, facial affect) in systematic bids for attention and attempts to communicate. To determine whether communication disorders are marked by special difficulties in such coordination, scientists are evaluating communication development in normally developing infants and in infants with hearing impairment, Down syndrome and autism. While the pattern of coordination has been found in both normally developing and disabled infants, differences are notable. For example, autistic children show different patterns of vocalization and gesture than do normally developing, Down syndrome or deaf infants. Deaf infants show particular problems in production of speech-like sounds, and Down syndrome infants show a general slowing-down of the pattern of vocalization. This research has indicated that assessment of disorders of communication can be fruitfully moved down in age to infancy. In addition, the results indicate that standardized instruments of assessment need to consider not only delays in developmental patterns for disabled children and infants, but also differing patterns of coordination of action across modalities in children with specific disabilities.

Because late onset of canonical babbling (the ability to produce well-formed syllable sequences, such as "baba" or "didi") is such a strong indicator of emerging disability, it is important to evaluate vocal development of all infants at 11 to 12 months of age. Research has demonstrated

that infants who are late in onset of canonical babbling are at extreme risk for various disorders. Many infants that show late onset are found to have neurogenic or motoric disorders and most show late onset of speech. Investigators conducted over two thousand telephone interviews with parents of infants at 4 to 12 months of age. Parents across socioeconomic levels proved amazingly accurate in their reports about infant babbling, with a concordance between laboratory judgments of canonical babbling and parent reports higher than 90%. Using the telephone interview in this manner can therefore be both extremely informative and cost effective.

The Laryngeal Mechanism in Health and Disease

Voice disorders can have a devastating effect on an individual's health, employment and quality of life. Loss of voice is a significant economic problem for individuals who rely on the use of their voices in their daily work and for employers who have workers with disabilities. Loss of normal voice function also has a major impact on quality of life for people of all ages. Yet there has been, in the past, little basic research on understanding the causes of voice loss. Scientists are examining laryngeal structure and function from differing perspectives to provide a basic understanding of the laryngeal mechanism in health and disease.

Investigators have recently identified regurgitation of stomach fluids during sleep as a common cause of voice disorders. In treatment outcome studies, therapy for chronic recurring hoarseness, sore throat, chronic cough and other manifestations of chronic laryngitis has been demonstrated to be effective when the cause is gastroesophageal reflux. Scientists are also investigating how tremor of the head and the structure of the throat disturb phonation. As a result, it has been demonstrated that some voice disorders previously lumped together under a common diagnosis, such as spasmodic dysphonia, may in fact be caused by different neurogenic disorders. Gaining a better understanding of such disorders is important to devising effective treatment strategies. For individuals with Parkinson's disease, for example, understanding the laryngeal abnormality that results in voice loss has led to treatment that significantly improves voice strength. An ongoing study designed to improve understanding of how the normal velopharyngeal mechanism works is important in improving the performance of the dysfunctional mechanism. As this mechanism is most typically impaired in individuals with cleft palate and other structural disorders, investigations will be of great value in guiding the surgical reconstruction of palatal muscles in such a way as to optimize and improve soft palate function.

Epidemiology of Specific Language Impairment in Children

Children with Specific Language Impairment (SLI) have unexpected and unexplained difficulties learning and using spoken language in the presence of normal hearing and age-appropriate development in all other areas. Although these difficulties are most apparent during the preschool and early school years, evidence now exists that these problems are usually present well into adulthood and are probably present throughout the person's life. Impairments in reading and writing are often associated with difficulties in spoken language that first become evident during early childhood. As a result, individuals with this condition are at high risk for academic difficulties. Despite the life-long academic, social and occupational consequences of SLI on those affected, there has been, until recently, little information on the prevalence of this

condition or the factors that place persons at risk for SLI. The few studies that do exist suffer from small sample sizes, poor study designs and inadequate diagnostic procedures; furthermore, none of these studies have been performed in the United States.

The NIDCD, through a contract with the University of Iowa, conducted an epidemiologic study of SLI in five-year-old children based upon a sample of more than 7,256 children in the states of Iowa and Illinois. The prevalence rate of SLI in the total population is estimated to be 8.36%. Three subtypes of SLI were examined. The subtypes were defined according to the presence or absence of a deficit in one or both modalities of language usage. Of those children with SLI, 28% presented receptive only impairments, 33% presented with expressive only impairments, 35% presented with generalized impairments, and 4% showed no deficit based on modality composite scores. Of those children with SLI, 34% also presented phonological impairments; 24% of the children with normal language status were found to have a phonological impairment. Prevalence estimates for SLI among five-year old boys was 8.6% and for girls was 7.1% resulting in a 1.21:1 male to female ratio. These results differ from earlier anecdotal information suggesting male to female gender ratios of around 2:1 for children with SLI. These current findings, however, are consistent with recent epidemiologic findings for dyslexia.

Short-Term Memory and Syntactic Deficits in Aphasia

Most brain-damaged individuals with aphasia have severely reduced short-term memory spans--they are able to recall lists of only one or two words as opposed to the five or six that a normal person can recall. Scientists are examining whether this reduced short-term memory capacity causes some of the difficulties with language comprehension and speech production these individuals face, as well as whether such short-term memory deficits impair the ability to learn new verbal information. Investigators have found that aphasic individuals have different types of short-term memory deficits, which in turn have specific consequences for comprehension and learning. Individuals whose short-term memory deficits involve difficulties in retaining the sounds of several words simultaneously have particular difficulty in learning (or relearning) the pronunciation of words. Individuals whose short-term memory deficits involve difficulties in remembering several word meanings simultaneously have particular difficulty learning new word meanings. However, both types of individuals have no difficulty understanding and remembering stories that consist of words they already know.

The results imply that there are different areas of the brain involved in short-term memory for word sounds and meanings, and that both of these differ from the area involved in understanding and integrating the meanings of known words. They also imply that there is a linkage between the ability to retain a particular type of information over the short-term and the ability to form a permanent memory representation for that information. Future studies will examine whether specific training procedures can be used to overcome the limitations on learning caused by short-term memory deficits.

Brain Asymmetry and Language Development

The human brain is functionally and anatomically asymmetrical. Asymmetry of the planum temporale (Wernicke's area) and pars triangularis (Broca's area) are believed to be the

neurobiologic substrate of this functional lateralization. During childhood, functional lateralization becomes irreversible. In a longitudinal study of 100 children, scientists are exploring the development of brain structures, their asymmetry, and their relationship to language development during a critical period in the development of both brain and language. Children aged 5 ½ years to 7 ½ years, with normal IQs, are administered a language history questionnaire as well as a neurolinguistic battery that includes tests of phonemic awareness, reading and oral language and an MRI scan. The children will be tested and scanned again two years later. The results of this study will shed light on the neuronal substrate of normal language development in childhood and provide a normal database from which comparisons to the brain structures in language- and learning-impaired children can be made. The data will also enable the accurate mapping of language areas for correlation with EEG and other functional studies in children.

Supporting Minority Researchers through Collaborations

In FY 1996, the NIDCD, in collaboration with the NIH Office of Research on Minority Health (ORMH), issued two Request for Applications (RFAs) aimed at fostering the research training and career development of underrepresented minority individuals in the scientific disciplines related to human communication: 1) NIDCD/ORMH Minority Dissertation Research Grants in Human Communication, and 2) the NIDCD/ORMH Mentored Research Scientist Development Award for Minority School Faculty. The Minority Dissertation Research Grants program provides small grants for up to two years to support dissertation research in human communication for doctoral candidates from minority groups underrepresented in biomedical and behavioral research. The Mentored Research Scientist Development Award is an intensive program of research career development, providing salary and research development support to minority and nonminority faculty members at academic institutions that are engaged in the education of students from underrepresented minority groups. The purpose of this initiative is to foster programs for research and research training in human communication at minority academic institutions. Recipients of this award commit at least fifty percent of their professional efforts over three, four, or five years to the career development program they have developed, working under the mentorship of a scientist experienced in the research area of the application. Five Minority Dissertation Research Grants and four Mentored Research Scientist Development Awards have been made in FY 1996 by the NIDCD with funds from the ORMH.

Bridging Opportunity and Progress: NIDCD Special Areas of Investigation

Current efforts of NIDCD to elucidate the biology of brain disorders and to reveal the underlying mechanisms of nonsyndromic hereditary hearing impairment have created an opportunity in the upcoming year for NIDCD to accelerate defining the specific genes involved in hearing impairment through specialized mouse strains, sample sequencing and using cDNA library enriched for cochlear-specific cDNAs. NIDCD is also extending its commitment to applied research through the use of clinical trial cooperative groups poised to plan, implement, conduct, analyze and disseminate results of priority clinical trial research in disease affecting human communication. This effort will yield new avenues for development of therapeutics. Improved understanding of the inheritance patterns of diseases and disorders of hearing, voice, speech and language is being identified in syndromic and nonsyndromic forms of hearing impairment and in

stuttering. Better understanding of the roles of apoptosis and the mechanisms of plasticity and regeneration are to be explored through new approaches to pathogenesis to promote regeneration of sensory capabilities lost to disease.

Vaccine for Nontypeable Haemophilus Influenzae

Otitis media is the major reason cited for taking infants and young children to emergency rooms or to a physician's office. The three most common bacterial pathogens in otitis media are the *Streptococcus pneumoniae* (pneumococcus), *nontypeable Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis*. All three have polysaccharide capsules. Polysaccharide vaccines alone have not been successful in preventing otitis media in young children since they lack immunogenicity when administered to infants and small children. In contrast, vaccines using polysaccharides conjugated with protein such as the *Haemeophilus influenzae type B* vaccine against meningitis have been effective in stimulating immunity in infants and small children. Stage I clinical trials of conjugated vaccines against the pneumococcus in infants and children have been completed, and Stage II clinical trials are underway. An unsolved problem in the development of a vaccine against NTHi had been identification of the proper target in the NTHi structure against which to direct the immune response. An approach to selecting the candidate antigen from NTHi has been followed by scientists in the NIDCD Division of Intramural Research. They have successfully prepared a detoxified lipooligosaccharide (dLOS)-based conjugate antigen from NTHi. This conjugate antigen induces a bactericidal humoral immune response in two animal models making it a promising vaccine candidate for humans. Plans are underway to initiate a Stage I clinical trial of this vaccine candidate. As the NTHi genome has recently been sequenced, this new knowledge will facilitate understanding of the pathogenesis of NTHi otitis media and ultimately accelerate the development of other vaccines against NTHi otitis media. Additionally, the Otitis Media Vaccine Unit at the NIDCD is beginning work on a candidate vaccine against *M. catarrhalis otitis media.*

Bombesin Receptors

Work is continuing on the analysis of the structure, function, and regulation of three pharmacologically distinct mammalian bombesin neuropeptide receptors, a subfamily of G-protein coupled receptors implicated in regulation of gastrointestinal hormone release and neuromodulation. One study is examining the hypothesis that certain gastrin releasing peptide-receptor (GRP-R) alleles may be important in the pathogenesis of autism. Several GRP-R allelic variants isolated from individuals with autism have been defined thus far, and the properties of these receptors in *in vitro* assays that measure ligand affinity, coupling, internalization, phosphorylation and desensitization are being studied.

Assembly and Targeting of Glutamate Receptors in Neurons

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. Four subtypes of ionotropic glutamate receptors, each with multiple subunits, and eight metabotropic glutamate receptors have been identified. Most neurons express multiple subtypes

of receptors and multiple subunits of each ionotropic receptor. This past year, three studies addressed the complex question concerning the assembly and targeting of glutamate receptors in neurons. Together, these studies show that neurons can control both the assembly of the receptor complex and the targeting of receptors to different synaptic populations.

Genes Associated with Neoplasms Affecting Human Communication

Benign and malignant tumors of the throat are the most common disorder affecting both human communication and survival. Squamous cell carcinoma, affects over 30,000 Americans, and results in about 12,000 deaths in the U.S. annually, according to 1994 estimates. Many of the patients who are successfully treated for these tumors suffer permanent impairments in voice, speech, smell, taste and/or swallowing.

During the past year, three known and four previously unidentified genes have been determined to be associated with the spread of cancer of the throat. Further studies of these genes are underway to determine the part they may play in the cause and spread of these cancers, and whether they may provide a target for therapy in patients with these neoplasms. Additionally, a phase I clinical trial for patients with throat cancer which combines radiation therapy with paclitaxel (taxol) to sensitize tumor cells to radiation therapy has been initiated in coordination with the National Cancer Institute. The first six patients to receive the therapy have tolerated the combination, and all have experienced a reduction in the size of the tumors. It is anticipated that information on long-term effects of the new combination will be available within two years to determine if larger scale clinical trials are warranted.

Vocal Fold Paralysis

In recent years it has been found that persons with persistent vocal fold paralysis following nerve injury or idiopathic paralysis, presumably of viral origin, usually have reinnervation of their laryngeal muscles in spite of persistent movement abnormalities. A study was completed this year in which the pattern of muscle activity in the thyroarytenoid muscle was examined in individuals with vocal fold paralysis either of idiopathic origin or following nerve injury. All patients had persistent vocal fold immobility even though thyroarytenoid muscle reinnervation had occurred. In all except one individual, thyroarytenoid muscle activation was normal in amplitude and pattern of activation for respiration and phonation. The results suggest that the thyroarytenoid muscle was not affected by synkinesis (aberrant muscle activation); other muscles and joint fixation should be evaluated to determine the basis for the persistent vocal fold immobility despite reinnervation. These findings have the potential for improving understanding of persistent vocal fold immobility and developing procedures for early intervention in the future.

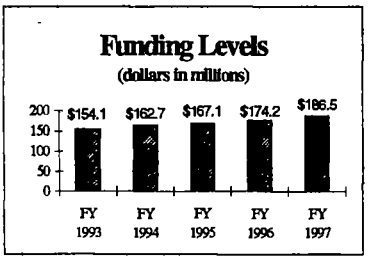
The Partnership Program

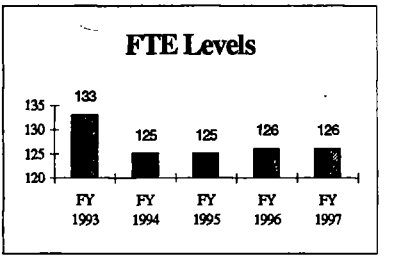
In 1994, the NIDCD launched a pilot program, The Partnership Program, with the support of the Office of Research on Minority Health. The purpose of the program is to encourage students, faculty, and administrators at institutions previously underrepresented in research in human

communication to partner with scientists and scientific administrators at the NIDCD. The collaborations include laboratory, program, and grants management experiences, as well as curriculum development and workshops. The program is in its third year, and student research results have already been presented at two NIDCD Research Festivals and at the University of Puerto Rico Medical School and the University of Alaska. Several hundred faculty, administrators, and students have participated in related training and grants workshops. The NIDCD expects to enhance its involvement in the Partnership Program by seeking means of strengthening the human communication research infrastructures of historically underrepresented colleges and universities. In the spring of 1997, an expert extramural panel will review the progress of the program and give advice to the Institute on future directions for the program.

Budget Policy

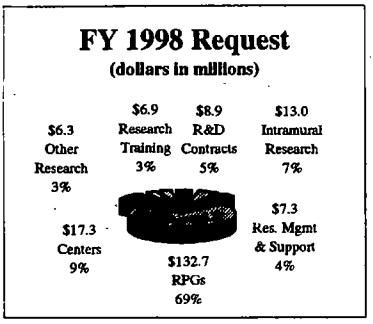
The FY 1998 budget request for the NIDCD totals $192,447,000, or 3.1% increase over the FY 1997 estimate. The FY 1998 request will support 126 full time equivalent positions (FTEs), the same number as the FY 1997 request. Total funding and FTE levels for the past 5 years are highlighted. Of the increase requested in FY 1998, $4,300,000 is targeted toward special areas of emphasis to highlight NIH initiatives. The NIH areas of emphasis include: biology of the brain -- $1,500,000, new approaches to pathogenesis -- $500,000, therapeutics/drug development -- $1,000,000, and genetics in medicine -- $1,300,000.





The NIDCD supports its extramural research program through research project grants, center grants, other research grants, training grants and fellowships, and research and development contracts. In addition, the Institute conducts an intramural research program. The scientific and administrative management of the Institute is funded through the research management and support budget mechanism.

The NIDCD FY 1998 budget request for research project grants is $132,685,000. This is an increase of $4,984,000, or 3.9 percent over the FY 1997 level. NIH policy links RPG average cost increases to total budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for research project grants (RPGs). In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs will increase by up to



two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP). The FY 1998 request will support 628 total RPGs including 178 competing awards. This is an increase of 24 total and 5 competing awards over the FY 1997 estimate.

Included in this increase is $1,500,000 directed toward the NIH emphasis area on biology of the brain to support research on nonsyndromic hereditary hearing impairment; $500,000 for the NIH emphasis area on new approaches to pathogenesis to continue support in hair cell regeneration; $1,000,000 in support of the Clinical Trials Cooperative Groups (NIH emphasis area--therapeutics/drug development); and $500,000 directed toward the NIH emphasis area on genetics of medicine to support molecular genetics of hearing, voice, speech and language.

In research centers, a total of $17,302,000 is requested for FY 1998. This represents the same number of centers and an increase of $339,000 or 2.0 percent over the FY 1997 estimate.

Funding for activities in the other research mechanism which includes research career awards, cooperative clinical research, minority biomedical research support and other research grants would be supported for a total of $6,249,000. This also reflects a 2.0 percent increase over the FY 1997 estimate.

In research training, the Institute will support 230 full-time equivalent trainees in FY 1998 for $6,930,000. The number of trainees remains the same, with an increase of $136,000 (2 percent) over the FY 1997 estimate.

The request for R&D contracts is $8,942,000, an increase of $68,000 or 2 percent over the FY 1997 level.

In intramural research, the FY 1998 funding level is $13,047,000, an increase of $193,000 or 1.5 percent over the FY 1997 estimates. Of the total provided, $800,000 is included for the NIH emphasis area on genetics of medicine to support research in the molecular genetics of hearing.

For research management and support, the FY 1998 funding level is $7,292,000. This is the same dollar level as included in the FY 1997 estimate.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	395	$86,180,000	409	$89,517,000	434	$92,907,000
Administrative supplementals	(19)	415,000	(18)	300,000	(19)	300,000
Competing:						
Renewal	69	17,517,000	74	19,284,000	76	20,132,000
New	92	12,903,000	98	14,192,000	101	14,816,000
Supplemental	0	0	1	105,000	1	105,000
Subtotal, competing	161	30,420,000	173	33,581,000	178	35,053,000
SBIR/STTR	14	3,351,000	16	4,303,000	16	4,425,000
Subtotal, RPGs	570	120,366,000	598	127,701,000	628	132,685,000
Research Centers						
Specialized/comprehensive	16	15,985,000	16	16,963,000	16	17,302,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research centers in minority institutions	0	0	0	0	0	0
Subtotal, Centers	16	15,985,000	16	16,963,000	16	17,302,000
Other Research						
Research careers	32	2,694,000	38	3,382,000	39	3,531,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	1	1,177,000	1	908,000	1	935,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	163,000	0	576,000	0	576,000
Other	10	553,000	16	1,181,000	16	1,207,000
Subtotal, Other Research	43	4,587,000	55	6,047,000	56	6,249,000
Total, Research Grants	629	140,938,000	669	150,711,000	700	156,236,000
Training	FTTPs		FTTPs		FTTPs	
Individual	51	1,323,000	54	1,538,000	54	1,569,000
Institutional	174	4,912,000	176	5,256,000	176	5,361,000
Total, Training	225	6,235,000	230	6,794,000	230	6,930,000
Research & development contracts	26	7,573,000	27	8,874,000	21	8,942,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	46	12,177,000	46	12,854,000	46	13,047,000
Research management and support	80	7,339,000	80	7,292,000	80	7,292,000
Cancer prevention & control	0	0	0	0	0	0
Construction	0	0	0	0	0	0
Total, NIDCD	126	174,262,000	126	186,525,000	126	192,447,000
(Clinical Trials)		(9,556,000)		(13,654,000)		(15,188,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Deafness and Other Communication Disorders		154,708		166,379		172,108		
Subtotal, Extramural Research		154,708		166,379		172,108		5,729
Intramural Research	46	12,177	46	12,854	46	13,047	0	193
Research Management and Support	80	7,339	80	7,292	80	7,292	0	0
Total Obligations	126	174,224	126	186,525	126	192,447	0	5,922
Unobligated Balance Lapsing		38		0		0		0
Total, Budget Authority	126	174,262	126	186,525	126	192,447	0	5,922

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Summary of Changes

1997 Estimated budget authority				$186,525,000
1998 Estimated budget authority				192,447,000
Net change				5,922,000
	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$5,246,000		67,000
b. Annualization of January 1997 pay increase		5,246,000		44,000
c. January 1998 pay increase		5,246,000		112,000
d. Legislative proposal, 1.51% increase in CSRS rate		5,246,000		25,000
e. Service and supply fund		515,000		25,000
f. Increased cost of laboratory supplies, materials, and other expenses		5,455,000		130,000
Subtotal				403,000
2. Research Management and Support:				
a. Within grade increase		4,817,000		83,000
b. Annualization of January 1997 pay increase		4,817,000		40,000
c. January 1998 pay increase		4,817,000		104,000
d. Legislative proposal, 1.51% increase in CSRS rate		4,817,000		28,000
e. Service and supply fund		261,000		3,000
f. Increased cost of laboratory supplies, materials, and other expenses		247,000		10,000
Subtotal				268,000
Subtotal, Built-in				671,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders
Summary of Changes--continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	409	89,817,000	25	3,390,000
b. Competing	173	33,581,000	5	1,472,000
c. SBIR/STTR	16	4,303,000	8	122,000
Total	598	127,701,000	38	4,984,000
2. Centers		16,963,000		339,000
3. Other research	55	6,047,000	2	202,000
4. Research training		6,794,000		136,000
5. Research and development contracts	27	8,874,000	2	68,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes		12,254,000		(410,000)
b. Special emphasis areas		600,000		200,000
Subtotal, intramural		12,854,000		(210,000)
7. Research management and support		7,292,000		(268,000)
Subtotal, program		186,525,000		5,251,000
Total changes				5,922,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Authority by Object

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:				
Full-time employment		126	126	0
Full-time equivalent of overtime and holiday hours		0	0	0
Average ES salary		$121,378	$123,928	$2,550
Average GS/GM grade		10	10	0
Average GS/GM salary		$51,533	$52,615	$1,082
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)				
Average salary of ungraded positions		$43,378	$44,290	$912
		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$5,506,000	$5,725,000	$219,000
11.3	Other than Full-Time Permanent	1,393,000	1,448,000	55,000
11.5	Other Personnel Compensation	202,000	227,000	25,000
11.8	Special Personnel Services Payments	1,342,000	1,557,000	215,000
11.9	**Total Personnel Compensation**	**8,443,000**	**8,957,000**	**514,000**
12.0	Personnel Benefits	1,614,000	1,956,000	342,000
13.0	Benefits for Former Personnel	6,000	6,000	0
	Subtotal, Pay Costs	**10,063,000**	**10,919,000**	**856,000**
21.0	Travel & Transportation of Persons	207,000	177,000	(30,000)
22.0	Transportation of Things	51,000	47,000	(4,000)
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	445,000	420,000	(25,000)
23.3	Communications, Utilities & Miscellaneous Charges	624,000	606,000	(18,000)
24.0	Printing & Reproduction	44,000	33,000	(11,000)
25.1	Consulting Services	84,000	79,000	(5,000)
25.2	Other Services	758,000	699,000	(59,000)
25.3	Purchase of Goods & Services from Government Accounts	6,885,000	6,694,000	(191,000)
25.4	Operation & Maintenance of Facilities	709,000	665,000	(44,000)
25.5	Research & Development Contracts	6,589,000	6,611,000	22,000
25.6	Medical Care	100,000	94,000	(6,000)
25.7	Operation & Maintenance of Equipment	270,000	235,000	(35,000)
25.8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**15,395,000**	**15,077,000**	**(318,000)**
26.0	Supplies & Materials	1,127,000	1,057,000	(70,000)
31.0	Equipment	1,024,000	915,000	(109,000)
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	157,505,000	163,166,000	5,661,000
42.0	Insurance Claims & Indemnities	40,000	30,000	(10,000)
43.0	Interest & Dividends	0	0	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**176,462,000**	**181,528,000**	**5,066,000**
				0
	Total Budget Authority by Object	**186,525,000**	**192,447,000**	**5,922,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders
Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$5,506,000	$5,725,000	$219,000
Other Than Full-Time Permanent (11.3)	1,393,000	1,448,000	55,000
Other Personnel Compensation (11.5)	202,000	227,000	25,000
Special Personnel Services Payments (11.8)	1,342,000	1,557,000	215,000
Total Personnel Compensation (11.9)	**8,443,000**	**8,957,000**	**514,000**
Civilian Personnel Benefits (12.0)	1,614,000	1,956,000	342,000
Benefits to Former Personnel (13.0)	6,000	6,000	0
Subtotal, Pay Costs	**10,063,000**	**10,919,000**	**856,000**
Travel (21.0)	207,000	177,000	(30,000)
Transportation of Things (22.0)	51,000	47,000	(4,000)
Rental Payments to Others (23.2)	445,000	420,000	(25,000)
Communications, Utilities and Miscellaneous Charges (23.3)	624,000	606,000	(18,000)
Printing and Reproduction (24.0)	44,000	33,000	(11,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	84,000	79,000	(5,000)
Other Services (25.2)	758,000	699,000	(59,000)
Purchases from Govt. Accounts (25.3)	4,200,000	4,057,000	(143,000)
Operation & Maintenance of Facililties (25.4)	709,000	665,000	(44,000)
Operation & Maintenance of Equipment (25.7)	270,000	235,000	(35,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**6,021,000**	**5,735,000**	**(286,000)**
Supplies and Materials (26.0)	1,127,000	1,057,000	(70,000)
Subtotal, Non-Pay Costs	8,519,000	8,075,000	(444,000)
Total, Administrative Costs	**18,582,000**	**18,994,000**	**412,000**

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

1997 House Appropriations Committee Report Language

Item

Dysphonia -- ....Spasmodic dysphonia is a voice disorder that affects women predominantly and usually renders a person difficult to understand because of uncontrolled voice and pitch breaks. The Committee is pleased with NIDCD intramural and extramural study into spasmodic dysphonia and encourages continued aggressive efforts in this promising scientific area.

Action Taken or to be Taken

Laryngeal dystonias, also known as spasmodic dysphonia has been studied in the NIDCD intramural research program since the Institute was formed in 1989. Current research efforts are aimed at developing objective clinical procedures for the diagnosis of these disorders, because patients often go undiagnosed for many years preventing them from receiving appropriate and beneficial treatment. In the area of treatment, patients with abductor spasmodic dysphonia who do not respond well to laryngeal botulinum toxin injections are now the focus of the development of new treatment approaches by NIDCD scientists. These scientists have also begun investigating the potential role of genetic risk factors for the development of these disorders in families with several members affected by these disorders.

The NIDCD currently supports a number of extramural research projects within the Voice and Speech Program that are related to the scientific area of dystonia. The NIDCD will continue to fund meritorious applications that examine dysphonia.

40-478 97 - 28

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Institute on Deafness and Other Communication Disorders	Title IV, Part C Subpart 13 Sections 464-464F	42§285M	Indefinite	$179,731,000	Indefininte	$185,517,000
National Research Service Awards	Section 487(d)	42§288(d)	a/ b/	6,794,000	b/	6,930,000
Total, Budget Authority				186,525,000		192,447,000

a/ Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208).

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1989 2/	---	---	87,600,000	86,530,000
1990	99,902,000	99,952,000	121,116,000	118,839,000 3/
1990 Sequester				(1,256,000)
1991	122,847,000	125,623,000 4/	148,247,000	134,935,000 5/
1991 Sequester				(2,000)
1992	146,321,000	144,495,000	151,106,000	149,102,000 6/
1993	157,301,000	153,466,000	157,301,000	154,814,000 7/
1994	153,088,000	162,823,000	162,823,000	162,823,000
1995 8/	167,129,000	166,155,000	167,129,000	166,761,000 9/
1995 Rescission				(101,000)
1996	172,399,000 8/	174,852,000	170,540,000 8/	174,852,000
1996 Rescission				(119,000)
1997	179,090,000 8/	189,243,000	182,693,000 8/	188,345,000 10/
1998	192,447,000 8/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The House allowance excluded funds for the unauthorized training programs (National Service Awards). The Senate allowance includes the budget for NRSA's. It included up to $93,100,000 for establishment of the proposed new National Institute on Deafness and Other Communication Disorders (NIDCD). The appropriation included the budget of the NRSA program and provided up to $96,100,000 for the establishment of the proposed new institute, NIDCD.

3/ Excludes enacted administrative reductions of $161,000.

4/ Excludes $3,123,000 in NRSA training programs requested but not considered.

5/ Excludes the enacted administrative reduction of $3,562,000.

6/ Excludes the enacted administrative reduction of $1,041,000.

7/ Excludes the enacted administrative reduction of $1,528,000.

8/ Excludes funds for HIV/AIDS Research Activities consolidated in the NIH Office of AIDS Research.

9/ Excludes enacted administrative reductions of $125,000.

10/ Excludes enacted administrative reductions of $77,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	5	7	7
Office of Administration	38	36	36
Division of Intramural Research	46	46	46
Division of Extramural Activities	20	20	20
Division of Human Communication	17	17	17
Total, NIDCD	126	126	126
	Average GS/GM Grade		
1993	10.0		
1994	10.0		
1995	10.0		
1996	10.0		
1997	10.0		
1998	10.0		

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	0	0	0
ES-5	1	1	1
ES-4	1	1	1
ES-3	0	0	0
ES-2	0	0	0
Subtotal	2	2	2
Total - ES Salary	$236,894	$242,757	$247,855
GS/GM-15	9	9	9
GS/GM-14	15	15	15
GS/GM-13	11	11	11
GS-12	23	23	23
GS-11	5	5	5
GS-10	2	2	2
GS-9	8	9	9
GS-8	7	7	7
GS-7	21	21	21
GS-6	1	1	1
GS-5	1	1	1
GS-4	2	2	2
GS-3	1	1	1
GS-2	0	0	0
GS-1	0	0	0
Subtotal	106	107	107
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	1	2	2
Senior Grade	0	0	0
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Subtotal	1	2	2
Ungraded	29	29	29
Total permanent positions	104	111	111
Total positions, end of year	138	140	140
Total full-time equivalent (FTE) employment,end of year	126	126	126
Average ES level	4	4	4
Average ES salary	$118,447	$121,378	$123,928
Average GS/GM grade	10.0	10.0	10.0
Average GS/GM salary	$50,288	$51,533	$52,615

TUESDAY, MARCH 4, 1997.

NATIONAL HEART, LUNG AND BLOOD INSTITUTE

WITNESSES

DR. CLAUDE LENFANT, DIRECTOR, NATIONAL HEART, LUNG AND BLOOD INSTITUTE

DR. CARL ROTH, ASSOCIATE DIRECTOR FOR SCIENTIFIC PROGRAM OPERATIONS

JAMES WEHLING, FINANCIAL MANAGEMENT OFFICER

SHEILA MERRITT, EXECUTIVE OFFICER

DR. HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTRODUCTION OF WITNESSES

Mr. PORTER. The subcommittee will come to order.

This morning we will hear from the National Heart, Lung, and Blood Institute. We're very pleased to welcome the Director, Dr. Claude Lenfant. And if you would introduce the people who are with you, Dr. Lenfant, and proceed with your statement, please.

Dr. LENFANT. Thank you, Mr. Chairman.

On my far left is Sheila Merritt, who is the Executive Officer of the Institute; Mr. Wehling, with the Budget Office of the Institute. On my right is Dr. Roth, the Associate Director for Scientific Programs of the Institute; and of course, Dr. Varmus.

OPENING STATEMENT

And I'm very, very pleased to be here today, Mr. Chairman, to present the 1998 budget of the Institute. It's especially meaningful to us because 1998 will be the year that the Institute will celebrate its 50 anniversary.

As we look back on what has been accomplished during the last 50 years, we see considerable progress. For example, when the Institute was created in 1948 under the name of the National Heart Institute, the country was experiencing an epidemic of heart disease, of which heart attack, coronary heart disease was the most common. If we adjust for the aging of the American population, the death rates that existed at that time have been reduced by more than half during that period of time.

A very recent study has shown that the decline in the death rate can be accounted for 25 percent from primary prevention, that is preventing people from developing heart disease, and 75 percent from improved treatment. The net result of all that is that coronary heart disease which was 50 years ago a very acute condition, from which most people would die very quickly, has become a rather chronic condition which today affects between 12 and 14 million

Americans. The good news of all that is that we clearly have added years to the life of the American people.

As we look at the years which are ahead of us, we see many researchers with new ideas, new directions which, if successful, will continue to improve the life of patients, and new treatments will certainly be developed.

IMAGING TECHNOLOGY

One of the questions that is most important is: Can we prevent further this coronary heart disease? And last week, Dr. Varmus mentioned to you the advance of new technology, new imaging technology, and in the next few minutes I would like to tell you how these technologies are going to help us to, in effect, help to prevent more of these diseases.

On your right side, what you see here is the conventional angiogram, which is an invasive procedure that requires cutting up the skin, opening up a blood vessel, introducing a catheter up to the heart, injecting dye and exposing the patient to x-ray. On your left side, you see a magnetic resonance imaging angiogram, which is non-invasive. Basically, it takes the patient into a magnet and that's what you get.

[See figure].

Conventional Angiogram
(Invasive)
Magnetic Resonance
Imaging Angiogram
(Non-Invasive)

Let me spend a minute to show you what we see here. Those two circles are the aortic valve, which keeps the blood from returning into the heart after it has been ejected by the heart into the aorta. On both sides, you see coronary arteries, this one here which originates from the aorta, and this one, which is the one that is most often obstructed in the case of coronary heart disease.

The point I would like to make is that this very small vessel that you see here has a diameter which is approximately half a millimeter, and so that you visualize what half a millimeter is, I would like you to see the piece of pencil lead that I have attached to the picture in front of you. That is what half a millimeter is. And that is what you can see with this technique.

The beauty of course is that if, through this process, using this technology, we can see abnormalities inside the arteries, then we can act upon them and basically do something before the development of overt disease.

The advantage of such technology is that it can be repeated without any danger as many times as one would want. One thing that I should tell you is that conventional angiogram is a procedure that costs approximately between $6,000 and $8,000. This one here is in the order of less than $1,000, and that's what it costs today. I would expect the devices would be further developed and the technique itself would be further developed, it would cost much less than that.

So basically, I think that we have amazing opportunities to help in the prevention of this disease by basically detecting abnormalities in the arteries before the development of symptoms and clinical problems. And the opportunity therefore to do something about them.

LUNG AND BLOOD DISEASES

So far I have talked exclusively about heart disease. But in the late 1960s or early 1970s, the Institute changed from the Heart Institute to the Heart, Lung and Blood Institute. I would be remiss not to underscore that the research programs of the Institute in lung diseases, such as for example asthma, or the pulmonary complications of cystic fibrosis and research on blood diseases, have been just as successful.

For example, 20 years ago, most patients with cystic fibrosis died from the pulmonary complications that developed. They would die in their teens or early 20s. Today, the same patients live to their 40s and 50s. They have jobs, they have families and although they have to take care of themselves on a daily basis, they can really enjoy life.

With regard to asthma, let me remind you that three of the gold winners that we had at the Olympics last year were asthmatic patients. Twenty years ago, it is not certain that their condition would have been properly diagnosed. In addition, if it had been diagnosed, the treatments that are available today were not available then.

Regarding blood diseases, I would like to mention that 25 years ago, the Congress enacted the Sickle Cell Disease Control Act. Then, many patients with sickle cell disease died in their second

or so decade of life, after a life of suffering. Today, these patients live later with much less suffering.

So to conclude my remarks, I would like to say that as we reach 50 years of age, and after 50 years of investment by the American people, you can point to remarkable public health benefits with regard to heart, lung, and blood diseases. And I should say, in the future, maybe the next 50 years, I believe the potential of the research that we're undertaking will bring about results which I believe will eclipse the accomplishments of the past.

I will be pleased to answer questions, Mr. Chairman.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Heart, Lung, and Blood Institute

I am pleased to address this Committee once again on behalf of the National Heart, Lung, and Blood Institute (NHLBI).

We are now on the threshold of the Institute's golden anniversary, an opportunity to reflect with pride—and a certain sense of awe—on the remarkable achievements of medical research that have occurred since the National Heart Institute was founded in 1948. Undoubtedly, more than a few people in this room had grandparents who suffered heart attacks 50 years ago. The grim reality was that many of them died on the spot; and for the few who made it to the hospital alive, we had little to offer but bed rest, painkillers, and the gloomy prognosis of life as a "cardiac cripple" and death before one's time. Worse, we had very little idea of how such devastating events could be prevented.

Progress made during the intervening years has been truly outstanding. Consider the array of approaches that we now call upon to combat heart disease: diagnostic tests to assess heart and blood vessel anatomy and function; CPR, defibrillation, coronary care units, and emergency care to address life-threatening events; "clotbuster" drugs and such other treatments as aspirin and beta-blockers to protect the heart in the hours after an attack; and high-technology approaches, such as pacemakers, coronary bypass surgery, "balloon" angioplasty, and heart transplantation to extend life and enhance its quality. Moreover, we have gained valuable insight into the characteristics and habits that predispose people to develop cardiovascular disease—hypertension, high blood cholesterol, smoking, obesity, diabetes, lack of exercise—and have raised public awareness of the importance of modifying these risks.

The public health benefits that have accrued from our investment in research have been of such magnitude that we can justifiably point to the Institute's first half century as the "golden age" of cardiovascular, lung, and blood investigation. Nonetheless, we have much reason to believe that the next half century—indeed, the next 5, 10, or 20 years—may eclipse the accomplishments of the past. Let me share with you our vision of the future.

Fixing the failing heart. Heart failure is one of the most vexing illnesses of the 1990s because its relentless downhill course is overtaking ever greater numbers of Americans. A central problem of heart failure is that adult heart muscle cells, once lost to disease, are irreplaceable. Thus, treatments to date have focused on optimizing the function of the cells that remain or replacing the heart in its entirety, through transplantation of a human donor heart or provision of an artificial heart. Research advances now offer clues to innovative approaches for rejuvenating the failing heart. For example, it may be possible to "turn on" the capacity that existed in fetal life for

heart muscle cells to reproduce themselves, thereby replacing old or damaged cells. Investigators are also exploring the possibility that healthy cells from donor muscle can be grafted into a failing heart to enhance its pumping ability. Innovative preliminary work in rats indicates that grafted cells taken from skeletal muscle may be able to "heal" areas of heart muscle that have been damaged by heart attack. A third area of investigation involves examination of the genetic factors that regulate apoptosis, the "programmed death" that normally occurs in cells. This work offers much promise not only for treating, but also for preventing, heart failure.

Opportunities for asthma prevention. Asthma is an increasingly prevalent condition that diminishes the quality of life for millions of children and adults in the United States. While it has long been known that asthma tends to "run in families" and to be triggered by allergens, infections, pollutants and other exposures found in day-to-day life, real progress is now being made in unraveling the genetic and environmental factors that influence this disease. Scientists have uncovered evidence of genes that affect allergy and bronchial hyperresponsiveness, two key aspects of asthma, and the quest to pinpoint specific genes and determine their function is now under way. This information should lead to better understanding of the primary defects in asthma, and to development of effective preventive strategies focused on individuals who are vulnerable but have not yet acquired the disease. Equally exciting work is capitalizing on recent observations that respiratory infections may actually protect some children from developing asthma, while exacerbating asthma in others. Using modern techniques of cell and molecular biology, scientists now have the opportunity to understand how infectious agents interact with both the lungs and the immune system to induce the airway inflammation and hyperresponsiveness that characterize asthma.

New hope for hereditary blood disorders. Exciting developments are taking place in research and treatment of hemophilia, the scourge of generations of families worldwide. It was only in 1987 that NHLBI-supported basic research led to identification of the genes for clotting factors VIII and IX, whose lack causes hemophilia A and B, respectively. Rapid subsequent advances led to development of recombinant factor VIII, created with minimal use of blood-derived products for a much lower risk of infection; quite recently, recombinant factor IX, the first hemophilia treatment that is totally free of blood products, was shown to be effective in clinical trials not only for bleeding episodes, but also for use in surgery. Further genetic engineering techniques are being used to create new "combination" clotting factors that have high activity and can be given in low doses, thereby reducing today's high treatment costs. As work proceeds on improved treatments, scientists are closing in on a cure. Although much remains to be done before gene therapy can be offered to patients, a number of studies have shown that hemophilic mice and dogs given the appropriate factor VIII or IX gene can produce normal, healthy clotting factors. The fact that only a small increase in production of active clotting factor is needed to correct severe hemophilia indicates that gene therapy, when it comes, has the potential to halt the frequent, painful, and dangerous bleeding episodes that result in so many factor infusions and hospitalizations.

Targeted preventive strategies. Disease prevention has always been our ultimate goal, and our efforts in the area of hypertension detection and control, for example, have paid off handsomely in preventing stroke deaths. Nonetheless, we have to treat a large number of hypertensives to prevent a smaller number of deaths, because we are as yet unable to identify the subset of patients who are most susceptible to stroke. Similarly, we advocate lifestyle modifications to prevent hypertension, such as limitation of sodium intake, on a population-wide basis because we lack the knowledge to target this advice to the people most likely to benefit from it. Our vision of the future includes a vastly increased ability to understand and detect individual susceptibility to disease and provide targeted interventions on the basis of that information. First, our accelerated search for the genetic causes of such complex diseases as hypertension promises to reveal the reasons for individual variations in susceptibility and lead to tailored prevention and treatment strategies. Second, our increasing ability to detect subclinical disease may enable us to halt pathological processes before conventional signs and symptoms appear. These new approaches offer enormous potential for cost-effective improvements in the health of the nation.

I recognize that much of the bright promise I have outlined for you here may seem speculative and futuristic, because I am relying on very basic studies using scientific approaches that were unheard of even a decade ago. The pathway between basic science investigations and real-life applications may not be straightforward, but it has met the test of time and it is growing ever shorter. For example, a scant 6 years ago I reported findings about a class of inflammatory mediators, leukotrienes, that are involved in asthma attacks, and suggested that this discovery might someday inspire development of new asthma drugs that block leukotriene activity. Flip through a major medical journal today, and you will find a full-page advertisement for such a drug under the headline "Leukotrienes—This asthma troublemaker is in for a surprise." Such is the pace of current heart, lung, and blood research.

During the past half century, life expectancy has soared due, in no small measure, to the fruits of biomedical research. Advances against cardiovascular, lung, and blood diseases have added years to the lives of many Americans. Our goal and our expectation are that the next decades of research will enable us to "add life to years," so that the long life we have earned is also a comfortable and fulfilling one.

Mr. Chairman, the FY 1998 budget request for NHLBI non-AIDS research is $1,404,770,000, an increase of $33,818,000 over the 1997 comparable appropriation. I would be pleased to answer any questions that the Committee may have.

IMAGING TECHNOLOGY

Mr. PORTER. Dr. Lenfant, thank you very much for your statement.

We very definitely congratulate you on 50 years of great progress. We want, obviously, that progress to continue. Is 2.4 percent for the next fiscal year going to allow that progress to continue?

Dr. LENFANT. Well, it will allow some to continue. Maybe not as much as one could do with more, but we will be able to undertake very significant, useful and important projects.

Mr. PORTER. You're a good soldier.

Let me say preliminarily that when we looked at the schedule of hearings for the Institutes, I decided that we had them much too compacted and wanted to provide a little extra time. This morning, since there are no recorded votes scheduled for the floor of the House, our members are not probably in town, with the exception of Mr. Bonilla and Mr. Miller. Mr. Miller we expect later on, but if he does not arrive in time, I have received from him some questions that he wants me to ask you. And I will ask those as well.

Let me also apologize for the condition of my voice, which is the result of having a very bad cold. And let me ask about MRI as opposed to a conventional angiogram. Can you use MRI to tell the degree of clogging of arteries just as well as you can use an angiogram?

Dr. LENFANT. Yes, indeed. The picture that I showed you here is from a normal person. But as you can see, if you look at the smaller vessels at the bottom of the yellow rectangle, or even much higher, you could detect irregularity on the line that separates, if you want, the vessels from what is next to it. And that would be an indication of the development of abnormalities in the arteries. That can be seen, and there are also some examples which I didn't bring where you can see very clearly the beginning of an obstructive process of these arteries.

Mr. PORTER. And would a physician go directly from an MRI angiogram that showed clogging to an operation, a heart bypass, let's say, or would they perform a conventional angiogram following up on it?

Dr. LENFANT. One thing I would like to say, Mr. Chairman, is that the conventional angiogram, the invasive procedure, is a diagnostic tool. The other one, the MRI, assumes that you have patients, somebody who is part of a family where there is a history of heart attack, where you know that this person has elevated blood cholesterol, but yet does not do anything, because an elevated blood cholesterol is a little bit too abstract.

A physician might say, well, let me see if there are some abnormalities which are developing in your arteries, and that is before the occurrence of symptoms. And that is the beauty of it, to find the abnormalities in these arteries. And to show a picture to the patient would be much more convincing than just the result of a blood cholesterol test. And we believe, and there is some evidence, actually, that people would respond to that. Because that's something that they see inside themselves.

One thing I should underscore is that these little arteries that you see there, the smallest ones, are basically three or four inches below your skin. So it's quite remarkable what we see there.

Mr. PORTER. So it could tell you that you don't have clogged arteries, and you would end your investigation of that as a problem. But if it told you that you did have clogged arteries, you might then go to see the extent of how they're clogged?

Dr. LENFANT. No, I don't think you would go. You would initiate a medical treatment for this patient, telling this patient to check their blood pressure, if that's the case, if this patient has an increased blood cholesterol, it would be a much more convincing argument for that patient to do something about that elevated cholesterol than just if you see a number on a piece of paper.

Mr. PORTER. I guess my real question is, is MRI imaging going to replace conventional angiograms completely?

Dr. LENFANT. It might. It might also become a diagnostic tool, that is correct. And in this case, it would be much cheaper. But again, the conventional angiogram today is used exclusively as a diagnostic tool. You have a patient who comes to you and says, I have chest pain, I have this, I have that, and the physical examination reveals that this person is a likely candidate for coronary heart disease, and you want to confirm it, to set up a treatment which is a very serious treatment, such as, for example, angioplasty or coronary bypass. And that's what you would do.

The other one, we see that as a tool of the future to basically try to detect abnormalities before the occurrence of clinical symptoms. And if that works, and we do believe that it will work, basically what you can say is that the development of an overt disease is no longer inevitable. You can do something before it becomes overt.

IN UTERO BONE MARROW TRANSPLANTATION

Mr. PORTER. Last December, the *New England Journal of Medicine* reported what sounded like an extraordinary finding, that a bone marrow transplant had been done in utero to successfully treat severe immunodeficiency disease. Does this research present the possibility of a new form of treatment for other diseases, like Cooley's anemia?

Dr. LENFANT. The answer is yes. Yes, it offers that opportunity. I think there is much more work that needs to be done before it is done. But the potential exists.

In fact, almost any, or many genetic diseases could be corrected that way.

Mr. PORTER. Does this in utero transplant bypass some of the difficulties that have been encountered in transplants after birth?

Dr. LENFANT. Yes, yes. In fact, the paper that you refer to, was a story of a woman who had two children. The first one died with that inherited immunodeficiency which is, I should say, very rare. And the first child received a bone marrow transplantation after birth. But that was not successful, and eventually the child died. And the new pregnancy was a child with the same disease, that was diagnosed in utero, and that's what led to the treatment, the in utero transplantation.

The reason is that during fetal life, the immune system is not developed or not as developed, and therefore you know, you do not

have the problem that you would have after birth dealing with immune reaction to bone marrow if you don't have a perfect match.

GENE THERAPY

Mr. PORTER. Last August, a Tufts University research team reported the successful treatment of gangrene through gene therapy. A gene that codes for vascular growth was coated onto an angioplasty balloon, which was inserted into an artery to stimulate the growth of new blood vessels and restore blood flow. Could this type of procedure some day be a less invasive alternative to heart bypass surgery?

Dr. LENFANT. Yes. In fact, in our laboratories on the campus of the National Institutes of Health, we do have a protocol which is studying this very question. That is, to insert this growth factor in the coronary arteries and see if we can elicit the sprouting of new blood vessels.

The case that you report is quite interesting. And not all of its aspects would be applicable to what you could do in the coronary arteries, owing in great part to the size of the arteries, and things of that sort. But eventually, you can conceive that it would become possible.

Mr. PORTER. Are there other examples of successful gene therapy?

Dr. LENFANT. To my knowledge, I think that is the only case which is successful. I think one of the reasons for it is the following, that this gene, the naked DNA, if you want, can go directly into the smooth muscle cells which surround the arteries. These particles of DNA, the naked DNA, go directly into the smooth muscle cells. And that has greatly facilitated the issue of the transplant insertion of that gene into the cells.

In other areas, the issue of vector is one which is often hampering the gene therapy.

CELL DEATH

Mr. PORTER. Your research on congestive heart failure is targeted to stopping cell death and generating cell growth. This seems similar in many ways to the strategies being pursued in other diseases, like neurological disorders, spinal cord injury and stroke. Is it likely that lessons learned with heart tissue would be transferrable to these other disorders or vice versa?

Dr. LENFANT. I think it's going to work both ways. Apoptosis, which is the cell death process, we learned about it relatively recently. The process and what triggers it is being investigated in many cell systems. I think that what we learn from the heart would be applicable to the other systems and conversely.

In the old days, we saw cell death being caused by necrosis, that is, the matter that was around the cells would be altered for some reason. And that would lead to the cell death. The deaths occurred from alteration, from the nucleus, for example, inside the cells. But it's an entirely different process. And there is a lot of work which is going on to try to understand the differences which lead to it.

ASTHMA

Mr. PORTER. Your statement mentioned the findings reported in *Science* magazine in January that asthma prevalence may be increasing because of the lack of exposure to respiratory infections. Children in Eastern Bloc countries are much more likely than children in the West to contract these infections, and paradoxically, seem to be protected against asthma. How can these findings be used to develop asthma treatments for children who have not grown up with the disadvantage of frequent respiratory infections?

Dr. LENFANT. This is a very interesting issue which has really become apparent during the last few years. Because a few publications have occurred in various journals, showing that indeed, an infection in the early age of individuals modifies or alters the immune system in such a way that later in life it would offer prevention against exposure to allergens. And the mechanism is really not fully understood. And actually our Institute, at this very moment, is preparing the initiation of a program to explore these mechanisms so that we can understand it.

You are making a reference to the East European countries. In fact, this argument can be taken to other parts of the world. There are many developing countries such as New Guinea, for example, where they have very high prevalence of acute respiratory infection in the early months of life. And in fact, it's responsible for the deaths of many of these children.

But there, although there is considerable exposure to pollutants, since they are living in huts and so forth, the prevalence of asthma is very low. And for years, epidemiologists, as well as asthma experts were wondering, how could that be, with the same level of exposure in the United States or developed countries, we would have a very high prevalence of asthma, but not there. And these publications, which have occurred, and these studies which have been reported during the last few months, shed an explanation which needs to be pursued quite actively.

SLEEP DISORDERS AND MELATONIN

Mr. PORTER. Dr. Lenfant, melatonin seems to be widely extolled in the popular press as a therapy for sleep disorders. Yet the National Sleep Foundation commissioned a paper which concluded that the use of melatonin cannot be justified for any sleep disorder at this time, since neither the therapeutic nor potential toxic effects of prolonged use have been documented. Do you agree with this assessment of the current scientific data? Do you think melatonin should be categorized as a drug rather than a food supplement and regulated by the FDA?

Dr. LENFANT. The question is difficult for me to answer at this time. All I can say is that there is no question that the use of melatonin, based on public consumption, raises hopes that it will do wonders without too much evidence. If used for pharmacological purposes, if that becomes the case, I would think so. We are beginning to believe that it suppresses the perception of light, meaning that when melatonin increases in our system, then we understand that it's time to sleep, and vice versa.

Now, if the melatonin is used pharmacologically and taken freely, I think that it may certainly have some adverse effects which in this case could be controlled by way of calling melatonin a medication.

Mr. PORTER. Is the Sleep Disorder Center within your Institute supporting any research on melatonin?

Dr. LENFANT. Not at this time. But we are in the process of supporting a very significant program on the molecular biology of circadian rhythms. And in effect, melatonin is very closely tied to a study on this, and I think it's become incorporated to this line of work.

Mr. PORTER. Thank you, Dr. Lenfant.

Mr. Bonilla.

STROKE RESEARCH

Mr. BONILLA. It is nice to see you again, Dr. Lenfant.

I'd like to start out by asking you something about a study that was just released in the last 30 days about dealing with strokes and the ability to pump blood in reverse to the brain through the veins. I suppose this technique is to quickly reverse the negative impact and paralyzation or the after effects. It seems to be a profound way of dealing with stroke. And I'm wondering if this is going to be more widely used or what is the status?

Dr. LENFANT. I don't know if it's going to be widely used. What I would like to say before commenting on your question on that issue is that this approach is something that has been taken from cardiology. Years ago, when a patient had a heart attack, in some centers, these heart attacks were treated by what we call retrograde perfusion, that is, a catheter was put into the venous side and blood or liquid with anticoagulant was forced against the normal current, if you want, into these vessels, in order to push back whatever the obstruction was.

In the heart, it has been found to be not, or it has been found to be a fairly complex procedure. In the brain, when you have stroke, I don't know if it will be developed in such a way that it could be used everywhere. In specialized centers, yes.

Having said that, the usefulness of this approach cannot be denied. Any way that a physician has to take to the clot, if you want, an anticoagulant or something which is going to destroy the clot, would be of tremendous benefit to these patients.

The advantage of doing it this way is that not only are you putting in a drug which is going to eliminate the clot, the blood clot, but also you can push it out which you could not do if you were doing the same thing on the artery side. Because the clot would have to go through very, very small vessels and it wouldn't be possible to push it out that way.

Mr. BONILLA. I heard that the recovery is remarkable in these cases where they actually pump the blood in reverse back into the brain. And if it's done within a short period of time, it's almost as though nothing had happened. In the past, these patients were oftentimes never able to use the left side of their body, or speak, or whatever the side effects would be.

Dr. LENFANT. The great issue with stroke, Mr. Bonilla, is that there is a diagnosis that needs to be done before you start the

treatment. There are two types of stroke, one which is an obstructive stroke, like what we are talking about, and another one which is due to a vessel being ruptured and the blood leaking out into the brain and causing the same kind of damage as if the blood does not go through.

And of course, in the latter case, knowing what we are talking about would considerably worsen the condition of the patient instead of improving it. And that brings me back to the MRI. One of the best ways that we have today to diagnose between an obstructive and an hemorrhagic stroke, is to do magnetic resonance imaging of the skull, of the brain.

GENETIC PREDISPOSITION

Mr. BONILLA. And don't forget, Dr. Varmus, I remember, no imaging institute. I remember that.

Moving to a different area now, Dr. Lenfant, it's just something we discussed before——

Dr. LENFANT. I was here, I remember the question. [Laughter.]

Mr. BONILLA. I understand that the NHLBI has found the approximate location of three stroke related genes. I know the Chairman touched on genetic research a moment ago. Would you tell the subcommittee about this progress and what it means for stroke detection, prevention and rehabilitation?

Dr. LENFANT. Well, I think, if I understand your question, there are two approaches which are under study now. The first one is to identify the genes which are determinant factors for high blood pressure, which is the number one cause of stroke. The second is that we do know today, and that has been found through genetic studies, we do know today that individuals susceptible to complications of high blood pressure, whereas other people can have high blood pressure for many years and not develop any of the complications.

And indeed, this genetic susceptibility to one of the complications such as stroke has been found in animals, not yet in human beings. And that is an avenue of research which is extraordinarily exciting, actually. Because it's true for stroke, it's true for congestive heart failure. It's true for kidney failure, which are all three being consequences of high blood pressure.

And I should say, the same thing is true for cancer. It's true for chronic lung disease. You have people who smoke all their life, for 50 years, 60 years, and never develop any disease. But somebody else does, very quickly. And that is in fact caused by this genetic susceptibility, which we are talking about here.

Mr. BONILLA. Someone just used the example last week about Deng Zao Peng, and how he had a cigarette in his hand all his life, and seemed to live a pretty full and prosperous life. I think he was 92 when he died. So we can see how your genes affect—how you're predisposed to a great degree.

If someone is predisposed, though, for example, to have a stroke, and you could determine that through genetic research, how much can good diet, exercise and doing all the right things change that? Is there a figure you could put on it, like if you're predisposed to have a stroke and your chances are, let's say, 40 percent, can you cut that back to 20 percent?

Dr. LENFANT. Well, before you came in, I was telling the Chairman that the death rate from coronary heart disease and heart attack has been reduced by more than 50 percent during the last 50 years, actually, since the Institute has been created. And that it has been reported out from various studies just recently that 25 percent, a quarter of this decline in death rate, is due to prevention of the development of coronary heart disease, and 75 percent is due to better treatment.

Now, that 25 percent, that's what we are talking about, you see, it's better lifestyles, it's not smoking, it's keeping the cholesterol low and appropriate diet and so forth.

LATINO OUTREACH PROGRAM

Mr. BONILLA. Let me ask now about your Latino community outreach program, Dr. Lenfant, because as you know, heart conditions are prevalent in every ethnic group, but because of the diabetic factor among Hispanics, it's an additional increase in risk that they suffer. Can you tell me about the program to reach out to the Latino community and how that's working?

Dr. LENFANT. Yes. We, first of all, our Institute and of course our sister Institute for Diabetes and Digestive Diseases, are supporting very substantial research on diabetes, which is indeed a risk factor of heart disease. Diabetes, for a reason which is not clearly or fully understood, is more prevalent in the Hispanic Americans than people from other ethnicity.

The way we address that, besides the research, is to have community outreach and to be able to communicate to the communities what needs to be done to minimize the risk of diabetes developing and coronary and heart disease. We have a model program here in Washington, actually, which we are pursuing with the Hispanic community that involves community leaders as well as church leaders and so far, it has been fairly effective.

One of the biggest problems that we have with this community outreach is really, there are two problems. The first one is, what message do you give, and second, who gives the message. And it is true for Hispanics, it is true for African-Americans.

The message must be culturally sensitive to the needs of that community. It must not be, you know, turn your life upside down. We have to adapt what we want to say and communicate to the way of life of the community in question.

And the second thing is that it is very important to have a member of the community to go and deliver the message. That's why we are working with the community leaders here in Washington and in Texas where we have several activities, to communicate these messages.

Mr. BONILLA. Just a comment on that subject, because I think in minority communities, churches are often the most influential entities within the community. If you could somehow channel those programs through those organizations, I think they somehow are more effective and listened to more carefully by people in those communities.

Thank you, Dr. Lenfant.

Mr. PORTER. Thank you, Mr. Bonilla.

Mr. Stokes, as a ranking member on another subcommittee, has requested that he be taken out of order so that he can return to his other assignment. And the Chair recognizes Mr. Stokes.

Mr. STOKES. Thank you very much, Mr. Chairman. Thank you, Ms. DeLauro. Appreciate it also from you.

Dr. Lenfant, it's always a pleasure to welcome you back before our subcommittee. Dr. Lenfant, as you know, this year marks the 25th anniversary of the National Sickle Cell Disease Control Act. What has been the most significant progress the Institute has made in sickle cell research and treatment over this quarter of a century?

Dr. LENFANT. Well, there is more than one, Mr. Stokes. As I hear your question, I am reminded that I have appeared before you some 15 times. And each year, you say, well, what have you done since last year. And when I give you an answer, you say, but you already told me that last year.

If you ask me over a span of 25 years, I think there are lots of very important things which can be said. The first one, as I mentioned in my opening comments, is that 25 years ago, patients with sickle cells disease, many patients with sickle cell disease, were dying in their teens. Today the same patients live to their fourth or fifth decade or even later. When they were dying in their teens, they were dying after years of suffering. For many of these patients, that suffering has been alleviated, so that in effect they can have an active life and participate in the community.

Now, the most significant achievements have been, number one, to realize that the treatment of patients with sickle cell disease must not be fragmented, must not be when somebody has a crisis, but it must be a continuous treatment. And that is the result of the Comprehensive Sickle Disease Centers that we have had.

The second thing that has been established during this period is the development of the prenatal diagnosis of the disease. Now, the prenatal diagnosis of the disease has led subsequently to the prophylactic treatment of many of these infants who, as you know, develop pulmonary infection and in fact, approximately 30 years, 25 years ago, the newborn infant with sickle cell disease could die from that pulmonary complication. That is no longer the case. Now we know how to treat this, and they survive. And we know that we can stop the treatment when they are five or six years of age.

In addition, because of that, the legislature I believe for 42 or 43 states has passed legislation requiring that prenatal diagnosis of sickle cell disease.

Another advance, which I reported to you some years ago, is that the hydroxyurea, which is basically the first effective treatment of pain crisis in these patients with sickle cell disease, and that has been controlled quite effectively. And then the last thing that I would like to mention, which is work which is now ongoing, is treating these patients with bone marrow transplantation, and of course the prospect that successful gene therapy will have in the years to come. So I think a lot has been accomplished on sickle cell disease.

Mr. STOKES. I appreciate very much the type of improvement and progress that has been made, as you have referenced here this morning. But ultimately, we must be talking, hopefully, about a cure. How far, Doctor, are we from being able to arrive at a cure?

Dr. LENFANT. Well, there is one cure for which we have great hope. But not all sickle cell patients will be eligible. And that is bone marrow transplantation. Bone marrow transplantation has been used relatively rarely in children with sickle cell disease. I believe that today, only 30 or maybe 40 children have received a bone marrow transplantation.

What is remarkable about it is that 92 percent of these children, basically 35 or so, are now cured of their sickle cell disease and have had no difficulties. And in the others, the treatment has not been successful. But when it is successful, it seems to result in long-term treatment.

The second treatment that is being investigated by our projects is that of gene therapy. And there is very significant work which is ongoing on two avenues. The first one is to, if you want, modify the abnormal mutations that exists in the gene. And the second is to find vectors which would permit the implant of normal genes in these patients.

CARDIOVASCULAR DISEASE IN MINORITIES

Mr. STOKES. Thank you. Doctor, let me ask you this. I happen, here in the Congress, to be a co-chairman of the Congressional Heart and Stroke Coalition, a coalition between members of the House and the Senate. And this coalition is very concerned about the impact of cardiovascular disease on families across the Nation.

I understand that cardiovascular diseases cause a death every 33 seconds in the United States. And so it's rather shattering to think that in the span of the time I pose a question to you and the time that you respond to that question, more than three people could conceivably die from cardiovascular disease.

According to the World Health Organization, heart disease is projected to replace pneumonia as the leading disease cause of premature death and disability worldwide by the year 2020. Let me zero in on an area already touched upon by Mr. Bonilla, who articulated some concerns in this same area. And I have some similar concerns. What is the extent, Doctor, of cardiovascular diseases among African-Americans, Hispanics and other minorities, and is the onset of the disease earlier than that of the general population?

Dr. LENFANT. In African-Americans, the prevalence of heart disease is a little bit higher than in Americans of European descent. Among Hispanics, however, although it is high, it is a little bit lower. And the risk factors are very different between the two populations. Among Hispanics, it is predominantly diabetes that is the most important risk factor. In African-Americans, the risk factor, the dominant risk factor is high blood pressure and also elevated cholesterol.

In the Institute and elsewhere, there is considerable work which is done to determine these risk factors, as I mentioned, when I talked about Hispanics. With African-Americans, the same kind of program is being developed. But there I have to say that we are

a little bit ahead of what we do with Hispanic Americans, because we have been working on that for a longer period of time.

One thing that we have, and which I will say we are very, very proud, we have developed a physician network. Basically it's working with the National Medical Association and with the Association of Black Cardiologists to enroll them in this effort of prevention and treatment in the community. And we hope that it will give us the opportunity to make very significant headway.

Mr. STOKES. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Stokes.

Ms. DeLauro.

COOLEY'S ANEMIA

Ms. DELAURO. Thank you, Mr. Chairman.

Dr. Lenfant, pleasure to see you here today. And I'm glad to see you after my hiatus. It's good to be here.

Let me ask several questions. First, last September, the Institute convened a special emphasis panel that looked at new therapies for Cooley's anemia. Let me just, from my point of view, Cooley's anemia disproportionately affects individuals of Mediterranean heritage, particularly Italian-Americans, so I was happy to see the Institute express an interest in the disease.

The panel recommended that the NHLBI establish a network of collaborative clinical centers to address interventions, clinical interventions to the illness. I know that the Institute has had success in establishing these centers in the areas of heart disease, asthma, and other diseases. The recommendation of the panel to address Cooley's anemia, how has that been implemented at the Institute?

Dr. LENFANT. Well, the recommendations of the group, to be very honest, were a little bit of a surprise to us. Let me explain why.

You mentioned clinical networks and centers, a network of centers for asthma or sickle cell disease, for example. It is difficult to do that. Because asthma, for example, there are 12 million people with asthma in this country. So any center somewhere in the country has a large group of such patients.

For Cooley's anemia, there are only 1,000 or 1,200 patients in the United States. And they are scattered all over the country. There is admittedly a prevalence, a high prevalence in New York. But they are really scattered all over the place. And for that reason, it makes it difficult, not to say impossible, to develop a network.

So what can we do instead? We are prepared to work with the institutions and the medical centers where they have a substantial population, so that within that population studies can be conducted. And we have done that in the past, very successfully, looking at the iron chelator, for example, which has been and is still one of the most significant treatments for the disease.

So we are still, this group met about two or three months ago, and we are still looking at what they have recommended. Whether it will be possible to implement it or not, I cannot tell at this time.

Ms. DELAURO. So what you're going to take a look at are population centers where this is more common?

Dr. LENFANT. Yes.

Ms. DELAURO. Is there any sense of a time frame? For instance, is there something that can be done, and I would rely on you for the information, in the northeast for example, the tri-state region of New York, New Jersey. You've got the statistics. Are there places where the networks can be established in these particular places, rather than your point about asthma, which is where there's 12 million people.

Dr. LENFANT. There is in the tri-state, which I assume is New York, Connecticut and New Jersey, a high prevalence of patients with Cooley's anemia. Our intention is to work with the people there who are doing this research and see what needs to be done.

One thing, though, that I should point out, is that at the present time, unfortunately, there is no new treatment which is being developed. And therefore, you would want to have a network of centers to test something, try out the new procedures or what have you, if the procedure or new treatment exists, but at the present time, these patients are still treated with blood transfusion, iron chelators and that's where we are at this time.

There are some, you may have heard that there is some discussion and some ideas which are emerging that perhaps hormonal treatment may be of some value in these patients. At the present time, we really don't have enough with that to go ahead with the implementation of a network, which is what was recommended in this report.

Ms. DELAURO. That doesn't give me a sense of real hope here for at least the immediate future, Dr. Lenfant, of pursuing this. And I don't mean that in a disparaging way. It just seems that it's a small population, and there's no new work or information about potential treatment. And I understand it's a small population, but these are——

Dr. LENFANT. Well, I don't want my comments to be perceived that because it's a small population, it is being ignored or neglected, not by a long shot. In fact, I would say that proportionately, we have a very significant program of research on this disease.

What I am really saying is that to create a center, a network of centers, we want to maximize use because it costs lots of money, where there is a network like this one. And unless we have something that we can feed to this network to do, there is really no point at this time for the network.

Ms. DELAURO. I understand. I would just comment that if there is a way to, as I said, not as expansive as what may have been recommended in terms of a network, but some way in which a network can be tailored to what the size of the population is, that some thought with regard to that area, to begin to scale, if you will, the recommendation to the need.

Dr. LENFANT. I can tell you, and you have a commitment on my part, any recommendation which can be implemented, we will do it. There is no question about that. Here I am basically, well, the question is how to do it, not whether we are going to do it.

Ms. DELAURO. I understand that as well, and how in terms of a timely fashion to be moving. I know you have lots of other priorities.

Dr. LENFANT. That one is very important, basically for two reasons. First of all is that, while it is a small population, it is one that we are very concerned about. Also, we know that what we can learn from the disease will be applicable to many other conditions. And vice versa.

SMOKING AMONG YOUTH

Ms. DELAURO. I understand that recently the Institute supported a lung health study that examined effects that stopping smoking has on lungs. As I've said on this committee before, I'm a strong advocate of people stopping smoking, particularly our young people. I have instituted a program in my district called the Kick Butts Connecticut campaign to get youngsters in middle school to have an impact on their younger peers in terms of not starting to smoke at all.

Did your study examine the effects of smoke on youth and their lungs, and if so, what kind of results did you obtain? If not, are you doing anything in regard to this area that targets youth and smoking?

Dr. LENFANT. Yes. The answer is yes to both questions. The population that was looked at for this particular study, which incidentally I should say, to my knowledge is the largest epidemiological study on the effects of smoking and smoking cessation in the United States, in men, women, African–Americans and Caucasians. It has been a huge study. And in fact, it's being continued now through research grants.

And the results which we found are really applicable to everybody, irrespective of age or job. That is, the benefits of smoking cessation and the goal of the study is for us not only to look at the benefits of the smoking cessation but also to have a program whereby the cessation would last. The big problem with smoking cessation is that people return to smoking very quickly.

In this particular study, which is now, I think it started close to eight or nine years ago, the number of, well, it's—the second phase started in 1993. So therefore, I would assume that the first phase probably started in 1989 or 1988, close to nine years ago. The number of individuals that stopped smoking is still very high, something like 85 percent. And that is not a modest success.

Now, because of that, actually, the Institute now is moving into a new activity, which is a lung health educational program, in order to disseminate to a larger group or community what we have learned from that study. And many investigators in the country are getting together to develop this program. And hopefully, working with the American Lung Association and all kinds of professional groups we will be able to disseminate the results from this lung health study.

Mr. PORTER. Thank you, Ms. DeLauro.

I would remind members that we will have time for a second round.

Mr. Wicker.

PREVENTING HEART DISEASE

Mr. WICKER. Thank you very much, Mr. Chairman.

And Dr. Lenfant, it's a pleasure to have you before the subcommittee.

You discussed in your prepared testimony fixing the failing heart. And we've had several rounds of questions already concerning heart disease. Let me just say that I appreciate the work that you're doing. This is an area of vital concern to the Nation, but particularly to me. Because I represent the State of Mississippi, which leads the Nation in the rate of death from heart disease.

And I want to ask you if you have any idea why that might be. In 1994, according to the CDC, and this is a fantastic figure to me, cardiovascular disease contributed to 46 percent of the deaths in my State, according to CDC. And 33 percent of the deaths under the age of 65. So I'm very, very much concerned about doing something about this.

And that leads to my question concerning prevention versus treatment. In that regard, I want to bring to your attention a study that you're probably already familiar with from the Harvard School of Public Health. It appeared in the *Journal of the American Medical Association* recently. I cite an article from the *Boston Globe* in February of this year which says that, for all the talk about exercise and low fat diets, a new analysis finds that the most recent progress against heart disease has come from better management of existing disease rather than from prevention.

And the figures given are that adopting healthier lifestyles accounted for only about 25 percent of our progress. Treatment, such as clot busting drugs for heart attacks and coronary bypass accounted for about 43 percent, and another 29 percent was saved by drugs to lower blood pressure or cholesterol.

The article goes on to say that the study suggests that efforts to prevent cardiovascular disease need to be redoubled. But points out that many authorities worry that our biggest gains in the area of prevention have already been won. So with all of that information, I wonder if you could comment on these two different approaches to heart disease.

Dr. LENFANT. Well, I'm very familiar with the study that you just mentioned. But I would like to disagree on the conclusion which is the statement that all that could be gained from prevention is now behind us. In fact, I think the prospects for more effective preventions are enormous. And that's what I was discussing at the beginning of this hearing. At the risk of being redundant, I may go through that again.

What we have today is an approach to recognize that in people who have no symptoms, no other disease, no nothing, that they may have some alterations in their cardiovascular system which are not visible when you look at them, and they don't complain about anything. But problems are there. And if you can identify people that, you've got a problem and here it is, I can show it to you, then we have here a tool to change the approach of people to their own behavior and their own well being.

Having said that, I would like to comment on what you have there, on this poster. On your right side, you have what we call the conventional angiogram, which is a diagnostic tool to really look at the heart arteries of people when they come to the physician complaining about chest pain and whatever. And so if the physician,

after the physical examinations and having spoken to the patient, says, aha, that must be somebody who is developing heart disease, an angiogram will be done.

Now, what you see on your right side, that is the conventional way to do it, which is an invasive way to do it. You have to cut the skin, open a vessel, push a catheter into the heart and all those things, which of course you cannot do very often. Now, what you have on the left side is a non-invasive angiogram. That is, basically all you do is to take a picture of the patient, like taking an x-ray if you want, you're putting, it's not behind a screen like an x-ray, but inside a magnet, that's what it is. And you can do that as many times as you want. There is no invasion, no skin cutting, no vessel opening, no putting dye into the patient. Therefore, it can be done as often as you want.

And the idea here is that if you have somebody who has, say, a high blood cholesterol or a high blood pressure and you want to know if these indices have already caused some alterations in the arteries, you can do what you have here, a non-invasive angiogram, and see whether inside the small vessels, the smallest vessels, which are here, you see, at the bottom, have some alterations and may be the precursors of overt disease. And you can determine that and prevent the development of physically overt conditions.

For that reason, I believe that this kind of technology is opening the door to further preventive interventions which in effect will be much more successful than looking at blood pressure or taking a blood cholesterol. Because most people, you tell them, well, you have elevated blood cholesterol or high blood pressure, they may be concerned, but they won't pay too much attention to it, because they don't feel it. However, if you take them inside their body, as we do here, and show them some alteration, they will pay attention to it. I mean, that's the way people are.

Therefore, I think that the option, the opportunities for further prevention, not in everybody, not all the people in this country, but in selected cases, are really quite remarkable.

Mr. WICKER. Well, getting back to that poster, what is the difference in the cost of both of these procedures?

Dr. LENFANT. That is the thing. The invasive one is $6,000 to $8,000, it depends where you have it done. But that's what we are talking about. The non-invasive one that you have on your left here is in the order, is less than $1,000 today. But with the developments which are taking place in the kinds of instruments that are needed to do that, I would expect that in the future, the devices will be much cheaper than what they are today, and therefore, the examination will also be much cheaper.

One thing that I would like to point out, again, the smallest vessels that you see here have a diameter which is half a millimeter, and half a millimeter, few people recognize what it is. On the poster which is in front of you, you can see a pencil lead which is stuck there with a piece of tape. And that lead is half a millimeter. So as you see, it is really seeing what is going on inside the individuals with a high level of sensitivity.

CARDIOVASCULAR DISEASE IN MISSISSIPPI

Mr. WICKER. Just a follow-up, you heard my statistics about my State.

Dr. LENFANT. Yes.

Mr. WICKER. Would you speculate? I realize it would probably lead to speculation, but what is it that would cause us to lead the Nation?

Dr. LENFANT. We know in part what's going on in your State. Your State is part of what we call the stroke belt. There are nine States which are in the southeast of the United States, beginning with Virginia, Maryland, and going south and a little bit to the west where you are, where we know that the prevalence of coronary heart disease and stroke is highest in the country.

And that's why, actually, we began a few years ago a program which is called the stroke belt, because there's a high prevalence of stroke there, in order to work with the local communities, civic leaders and religious leaders, to basically send a message to the communities of what needs to be done to reduce this risk.

And I should tell you that if you are concerned with the numbers that you see today, and I don't know from what year are the numbers that you quoted—1994. But I can tell you that 10 years before that, they were much higher than what they are now. I can tell you that we have been very successful in reducing the death rate from stroke and heart disease in these States.

Mr. PORTER. Thank you, Mr. Wicker.

Ms. NORTHUP.

BLACK LUNG RESEARCH

Ms. NORTHUP. Dr. Lenfant, let me direct this question to you. The Office of Workers Compensation Program has prepared new regulations that refer to black lung, and whether or not somebody qualifies for workers compensation. Apparently, it intended to make a lot more people qualify for black lung benefits or workers compensation benefits. This is at the Federal level.

I believe I'm right that these definitions were tried in the 1970s and so many States and the Federal Government were swamped, everybody that had ever been in a mine, practically, qualified for these benefits. They were starting to sink the systems, and the Federal Government reduced them, every single State except Kentucky reduced them.

Finally, Kentucky reduced its in December in an emergency special session. It's not just the benefits and the cost of the program. It's also the fact that we have a whole section of Kentucky of people that are on these benefits and can't go to work. They lose the benefits if they work, even though they're perfectly capable of working.

We thought that when we changed this, this was actually a new governor, a governor that was from the mining area and had the support of the mine community. I guess I'm wondering if you have any research that would support these mining regulations, or do they just have political support?

Dr. LENFANT. Most of the research on black lung is supported by the National Institute of Occupational Safety and Health, which is

under the CDC. And I have to admit that I cannot comment on the basis of that regulation. I'm aware of them, but I am not aware of the reasons why these regulations were reactivated, so to speak, after a period of interruption.

Ms. NORTHUP. Can you go back and look, or do you know off hand, why NIH hasn't done any additional research in the last, recent years?

Dr. LENFANT. No, and our Institute certainly does not do any research in this area. The other Institute which could possibly look at that would be the National Institute of Environmental Health Sciences. I would surmise that, it has got to be looked at, but I would surmise they probably do very little, because you have an Institute under the CDC whose responsibility is to do that.

Ms. NORTHUP. Okay. So you're sure that there's nothing that NIH has done?

Dr. LENFANT. I'm sure for our Institute.

Ms. NORTHUP. Okay. That's all, Mr. Chairman.

Mr. PORTER. Thank you, Ms. Northup.

Mr. Hoyer.

ALLOCATING FUNDS BY FORMULA

Mr. HOYER. Thank you, Mr. Chairman.

Dr. Lenfant, I apologize for missing the bulk of your presentation. I'm the ranking member, as so many people on this committee are, on another subcommittee. It's very tough to make them both, obviously. But I wanted to come by, mainly to say hello and to congratulate you on the continuing excellence of the work that you do, and your leadership.

Dr. Varmus, Dr. Lenfant has been, as you know, with us a long time. And I'm always intrigued by his presentations. I'm sorry I wasn't here earlier to learn about the diagnostic capabilities and the savings that are being effected.

Doctor, one of the reasons I wanted to be here is that you head up the agency where, if you look to Medicare, I suppose, it's pretty close to the top in terms of consequential costs incurred. Therefore, if we use sort of formula based funding, relative to incidence, not just of old people, although I increasingly believe that old people now is a relative term starting at about 80. I have an 83 year old mother-in-law who wouldn't say that she's old at all, Mr. Chairman.

But, in any event, your Institute would presumably be one of the beneficiaries of such a formula based funding. And because of your expertise both in terms of your particular discipline, but also in terms of your expertise in dealing with the internal discussions. I, of course, would not call it politics related to NIH, but the internal discussions at NIH relative to the allocation of resources. I would like your comment for the record now on the issue of the appropriateness of funding by incidence of or cost consequences of Medicare or some other yardstick of particular diseases as it relates to NIH.

Dr. LENFANT. Let me answer that in a generic way, by saying that I suppose all of us are coming into this committee and all of us would say, we think any amount of money you can give us, go ahead and do it. The issue as I understand it, is whether this com-

mittee thinks we should get more than this one and so forth, irrespective of what the incidence and prevalence of the disease might be. And as I hear there are several ways to——

Mr. HOYER. Doctor, as I understand the question, it is more pointed than that. You sort of stated the obverse. It's the reverse, I think, which is to say, it ought to be funded based upon the incidence as it writes the cost consequence to Medicare in the particular discussion. But I presume because Medicare deals with 65 and over, presumably you'd have a broader spectrum of dealing with children, and young adults, and middle aged, etc., so that you would take as a formula, a yardstick for funding, the incidence of the disease.

As opposed, for instance, to AIDS, where the incidence of disease as it relates to heart is relatively minor in the United States, notwithstanding its consequences internationally. And the epidemic nature of it, I would use those two as examples; there are others, diabetes being one, that's focused on as well.

Dr. LENFANT. I think that the incidence and prevalence of diseases are one factor, but they cannot be the only one. Because it also depends on whether you can do it, and I would say that at any one time, there may be opportunities which exist in one field, and you have to support these opportunities so that this field moves ahead. Because it can do it. In another area, your opportunities are different, or even the needs, the importance of the public health issues.

Relative to our Institute, as I'm sure you know, the most important component of our Institute is that concerned with cardiovascular disease. It's approximately 60 percent or so of the Institute. And then we have 20 for the lung and 20 for the blood. To look at that 60 percent and say, why shouldn't it be 80, or why shouldn't it be 60 but in twice as big of an envelope, I consider that deceptive. Because in effect, there is research which is supported throughout the NIH. Earlier we were talking about diabetes, well, now that the Director of the diabetes institute is not here, but I would submit that whatever that Institute is spending on diabetes is in effect working for the cardiovascular diseases. Because of the close relationship between this condition and our diseases.

And so the way I look at it, you see, is that to look just at the budget of our Institute and not see what is being done with regard to the entire establishment relative to cardiovascular diseases may lead to an erroneous interpretation. You may be interested to know that we consider that, of the whole budget of the Institute, our Institute, approximately $800 million is cardiovascular.

But the fact of the matter is that if you look at the Diabetes Institute, the Aging Institute, neurology and what have you, NIH is spending approximately $1.2 billion on cardiovascular. Basically, there is 50 percent of the monies that are allocated to this disease category that do not come from our Institute.

So if you look at that in relation to the incidence, look at my $800 million, you say, well, you know that is maybe not as much as it should be. But I think that we should look at the $1.2 billion. And that is significantly different.

So, that's a very difficult question, which during the last two or three years has come up regularly during these hearings. My an-

swer to that is that we, sure, everybody could use more money. But I don't think that that money must necessarily be allocated based on either of the incidence or the prevalence or the number of people who die from that condition. I think there are many other factors.

And again, returning to how the diseases work. You know, as you heard, the decline that we have in death rates are due to, a quarter of the decline is due to primary prevention. And so we could say, well, we've got to increase primary prevention. And we all agree with that. But you see, primary prevention is not an activity where we have as many opportunities as we may have in another area.

And so you know, to me it would be important to allocate money where more opportunities exist and more progress can be made.

BENEFITS FROM RESEARCH

Mr. HOYER. Thank you, Doctor. With respect to your particular Institute, Doctor, remind me, when did you start as the Director of the Institute?

Dr. LENFANT. I am in my 15th year.

Mr. HOYER. So you and I are on a parallel track; I think I started in this committee about 15 years ago.

As it relates to when you started, you may have had a chart, and didn't repeat the information. Maybe we have it, but one of the things that, frankly, I'm a little better able, I think, this week to deal with is, my wife's illness; I thought of all the billions of dollars we had spent on cancer since the war on cancer started in the 1970s under President Nixon, and how, notwithstanding those incredible sums of money, it was still impossible, except in the very late stages, to diagnose. She had an MRI. In fact, the interesting thing is, she had a stint put in, because she became jaundiced on December 17th, and on December 19th, which was her birthday, they put a permanent stint in. I believe it was the MRI, but it may have been the CAT scan operator came back in preparation for that incident, and told Dr. Yo, the surgeon, "I can't find the cancer". Her stomach was replete with cancer at that time, and she died, of course, some 45 days later from the cancer.

But one of the things you think about, and the Dental Institute always talks about, is that they get a relatively small sum of money and a big payoff in terms of the very sharp decrease in dental disease, particularly long-term, as you grow older. But also cavities and fluorides and obviously all those things. If you presented it, I'll just look at it.

But for instance, we've spent so much money but that $1 invested has had a $10, or $20, or $40 payoff because of the decreased incidence, decreased loss of work, decreased loss of family support, and all those sorts of things that result from either very serious or terminal outcomes?

Dr. LENFANT. Yes. I don't have this data here, but we could produce this kind of data. But you could also look at it the other way, you see. Earlier this morning I explained, and reported to the Chairman that in 1998, we are going to be 50 years old, the Institute. And it's an interesting time to reflect to see what we have done during that period of time, after all, lots of money has come from the American people.

So I feel strongly that after 50 years, it's time to give a report. Well, today we know that about half of the people, well, the death rate, if you want, of coronary heart disease, let's take that simple disease, which is not so simple, actually, but everybody knows what that is. But the death rate from that is half today what it was 50 years ago.

Now, admittedly, there are problems with that, in a way, because you have many more people today who are running around with coronary heart disease than there were 50 years ago, because they didn't die. But they have the disease. We are not as successful to prevent it from occurring as we are to fix it. So the net result of that is that you increase the number of people with the disease. But the fact of the matter is that these people are walking, they are producing, they are very income producing citizens for many years.

So you could say, sure enough, the fact that today we have many more people with that disease, it's costing the country. But I would like to submit to you that in effect, many of these people are paying their way, because they can work and before they didn't produce, they were not contributing to society. So these are very complex issues. And that's why I think that, you know, I don't want to put words in Dr. Varmus' mouth, but I think what he advocates is that the best way for us to make progress is to go where we have the opportunity, scientific opportunities.

And I think the second part of this is that today, because of the very nature of the science that we are doing, the opportunity which is good for this disease is also important for that disease and for the third one. And so there is a great deal of overlap among the disease categories.

And so you know, the net result of all that is to focus on the opportunity, what can be done, where we see a payoff is a good way to do it. Now, that does not mean that, coming back to cardiovascular disease, there are no opportunities. In fact, we are full of opportunities.

But I think that the opportunities that we have now are being met with the way the judgements are made. In fact, for 1998, with the discussions that took place at the NIH, an allocation was made, a special allocation was made to this Institute in order to meet an emerging opportunity where we think that we can do something and we can do well

Mr. HOYER. Thank you, Doctor. I think it would be a ballpark hypothesis, because as you point out, if you live longer, you sustain more medical costs with a disease. On the other hand, if you died, your productivity, your support of family, your payment of taxes, etc., would be lost to this society. But what I think we all believe is that there is a great plus, both in terms of dollars and in terms of society as a whole.

But that might be an interesting thing. As we debate this, the Chairman has been extraordinarily supportive, as you know, of funding for NIH. His predecessor used to always say, the budget for NIH is x billions of dollars. If it were $3 billion or $4 billion more, it would not be too much. His premise being that whatever resources we could apply was in fact paying off both in a dollar sense and in a societal sense.

And I'm pleased to serve with a Chairman who shares that view, because we're advocates of investing in what we think is a very significant payoff for all our taxpayers in our country, and indeed, because we're the leader in the world.

Thank you, Mr. Chairman, for giving me the time.

HUMAN CLONING RESEARCH

Mr. PORTER. Thank you, Mr. Hoyer.

Dr. Lenfant, we're going to give you a rest for just a minute, so I can ask Dr. Varmus several questions. Dr. Varmus, we understand you've been to the White House this morning discussing the human cloning issue. And today's radio reports indicate that the President intends to issue an executive order prohibiting human cloning in Federal research programs, and requesting a voluntary moratorium on private experimentation.

Are the news reports correct?

Dr. VARMUS. Yes, he actually has signed that order.

Mr. PORTER. Is the executive order thought to be necessary because the human embryo research ban in our bill does not cover the entire Government? Or did the White House lawyers disagree with the NIH position that the provision in our bill covers human cloning?

Dr. VARMUS. My understanding is that the former provides the bulk of the motivation, not all of it. The bill covers HHS and there's concern about, we want to make it perfectly clear that no Federal dollars in any agency can be used, regardless of the intent of the manipulation, if they're intended for research or for reproductive purposes, solely.

Mr. PORTER. The President's 1998 budget proposes to lift the human embryo research ban in our bill. And you cautioned last week against quick legislative action on cloning before ethical and scientific factors could be fully considered.

Is this executive order inconsistent with these views?

Dr. VARMUS. No. The intention is to have that order in place to reassure the public until the National Bioethics Advisory Commission, headed by Harold Shapiro, who was also in attendance this morning at the signing and discussion, can fulfill its responsibility to return an evaluation of the potential of performing human cloning and the ethical considerations around it.

Mr. PORTER. And does the White House, has the White House indicated whether the rest of the ban on human embryo research should be lifted, the portion that does not deal with cloning in our bill?

Dr. VARMUS. I think the position remains the same with respect to——

Mr. PORTER. Regarding the rest of it?

Dr. VARMUS. Correct.

LASER SURGERY FOR THE HEART

Mr. PORTER. Thank you, Dr. Varmus.

Dr. Lenfant, last September, the *Journal of NIH Research* reported on a laser technique called TMLR for patients with end stage heart disease. The laser essentially burns a series of small holes through the heart to allow the blood and oxygen to seep

through and into the heart muscle. Early results are promising in terms of increased blood flow and patient endurance, and the procedure is currently being tested in a clinical trial. But scientists readily acknowledge that they don't understand why TMLR works. Is it troubling to you that the FDA could approve a procedure drilling holes into the heart simply if it shown to be safe and efficacious, even if the reasons for its benefit are unknown?

Dr. LENFANT. Well, I think the procedure is being used in Europe. There is quite an extensive experience in Europe.

I do not think that the FDA has anything to do with the procedure itself, but rather the approval of the device to drill the holes inside the myocardium. That's what they are going to be concerned with. To my knowledge, the FDA is not getting involved with surgical procedure. In fact, that's a problem, that emerging surgical procedures which have doubtful validity, but there is nobody to regulate that, unless the HCFA gets into it because there is a reimbursement issue.

I think that we need to have the results of that clinical trial, which is going on. I have to say that we know very little about who is doing this clinical trial. We know it's sponsored by the company that makes the laser device. But I really don't know anything about the exclusion or the inclusion of the subject criteria that they have. We don't know for sure what the end points are.

I think that for something like that, I would hope that the end point would not be after six months, but rather after maybe two or three years. I think the verdict is still out on that one.

SLEEP CENTER

Mr. PORTER. Last year, we discussed a problem being encountered by the Sleep Disorders Center in the low number of research applications it was receiving. Has that situation improved over the last year?

Dr. LENFANT. Yes, yes, indeed. And I would say, it's to the tribute of the Director of that center, who is extraordinarily active, working with all the Institutes at NIH and developing all kinds of programs and things. For example, the research on melatonin that we were mentioning earlier, the bottom line is that we are indeed increasing the number of research grants and support. Last year, in 1995, the support at NIH was about $73 million. It was $76 million last year. This year, it's anticipated to be over $81 million.

So we keep on increasing, and I think the center is doing quite well. I don't know if Dr. Varmus would agree with that, but that's my opinion.

FUNDING FOR PUBLIC EDUCATION PRGRAMS

Mr. PORTER. Dr. Lenfant, as you know, this subcommittee has been concerned about administrative costs and has taken steps to limit these expenditures. But we want to be careful that we are not inadvertently limiting program activities.

Your Institute's public education programs are included in the admin costs line. How much is your public education budget?

Dr. LENFANT. Well, the public education budget is made of three components: paying the employees who work in there, and I would say that the number of employees has been reduced over the last

few years. At one time we had 39 employees, we are down to 34. The second component is the support of the contract program, which manages the development of brochures and things of that sort. And the third thing are direct costs within the Institute.

The total in 1995, taking that as a base, of these three components, was $10.5 million. This year it is going to be $8 million, is our projection. However, what you should know, is that the direct costs which were $3 million in 1995, are going to be less than $800,000 or $900,000 this year.

And I have to say that that is reaching a very, very critical point, especially at a time when there is increased pressure on the Institute to further develop some of its educational activities, not least from the sleep community. We have been mandated to develop a sleep disorder educational program. And basically, it is very difficult, if not impossible, to do.

Mr. PORTER. Have you considered displaying the public education activity separately in your budget so it is not artificially constrained when administrative costs are frozen?

Dr. LENFANT. We have considered that in other years a number of times. And I have to say that we really vacillate, sometimes for, sometimes against. And the reason is the following, that it is a relatively small amount of money. And it is going to be, you know, we are talking about, the whole thing is in the order of, well, in the happy days it was about $13 million, $15 million. Now it's down to half that.

And if you see that from a total of almost $1.4 billion, I think nobody's going to understand what that $10 million does by itself there. And that is the reason that sometimes we think we should do it, and some other time we say, well, no, we should not do it, we should leave it where it is. It is a very difficult thing. But the bottom line is that we are exceedingly concerned to see the reduction of our flexibility and therefore the loss of opportunity for further development of our educational program.

Mr. PORTER. Dr. Varmus, from a centralized NIH perspective, would you have any problem separately identifying public education activities in the mechanism table?

Dr. VARMUS. No, I wouldn't. In fact, I think I'd prefer it in the long run. One of the outcomes of the administrative review that we're undertaking in response to your suggestion, I hope will be a more uniform way to account for expenditures across the Institutes.

SERVICE CENTERS

Mr. PORTER. Dr. Lenfant, you've established three service centers which provide services to other Institutes in the area of procurement, committee management and technology transfer. How many Institute and center customers do you have for your three centers, and is there any other Institute competing with you to offer these same services?

Dr. LENFANT. Well, the first part of your question, in the procurement, we have three Institutes. In the technology transfer, we have four Institutes. In the committee management, we have four Institutes. And they are all different. And I can say that we have a few of other Institutes, not least the Office of the Director, who utilize our services for some of their functions.

It is very labor intensive, and we are having discussions with Dr. Varmus' office to see how we can better set that up. My reaction is that it has been very successful for the Institutes which are being served. And I have to assume that they agree with that statement, because if not, we would not have other Institutes coming and asking to be part of our service network, especially the Office of the Director.

GOVERNMENT PERFORMANCE AND RESULTS ACT

Mr. PORTER. Dr. Lenfant, you have the reputation of being a skilled Institute manager. How are you contemplating applying the analysis of the Government Performance and Results Act to your Institute's activities? Is it possible, for example, to link mortality and morbidity measures to the performance of your programs?

Dr. LENFANT. Well, first of all, that's an activity which is emerging at NIH, and we are working to set up these measures of performance.

The thing that I have to say, which I find interesting, is that we have done that to a point for many, many years. For example, you are familiar with our educational programs. And every so often, we do surveys to establish whether we have met our goals, which is to increase the number of people who are aware of their blood pressure, who keep it under control, or the number of people who do something about lowering of cholesterol, and so forth.

In addition, we also have done it to some of our clinical trials to assess whether the practicing community has actually implemented some of the recommendations or outcomes coming from these clinical trials. Whether the death rate would be an appropriate measure, in all honesty, I would have to think about that. I don't know.

But I think the whole thing is positive, but difficult. And we have to be very careful. Because research is not as predictable as building bridges or roads, or planting trees along the water.

LUNG VOLUME REDUCTION SURGERY

Mr. PORTER. Last year, we found ourselves in the middle of the dispute about HCFA's refusal to reimburse lung reduction surgery. We had hoped the controversy would be settled by a clinical trial of the procedure, which your Institute and HCFA have jointly agreed to support.

Instead, the outside groups seem to think that the trial you are developing is too narrow, and won't test the full range of procedures being used in the field. Can you review for us the status of this trial and how you are responding to criticisms of its design?

Dr. LENFANT. Let me answer the second question first, which procedures are being used. Today, there are three approaches to excising, if you want, a part of the lung, so that the rest can expand and work better. One is a sternotomy, that you open the chest in the middle and do what you want to do. The second one is video assisted. And the third one is a laser excision. The clinical study that we have designed includes the two first approaches, that is the sternotomy and the video assisted, but not the laser.

Why not the laser? Well, there are several questions, several reasons. The first one is that to do a serious study, you have to be able to compare this procedure with that procedure, otherwise, you can-

not determine what is best. But the problem is that the surgeons, while doing the laser excision, do not do any of the two other procedures. And therefore, if you were to include it, you would never know whether it's better or worse, because of the surgeon or because of the procedure. Do you follow me?

Mr. PORTER. Yes.

Dr. LENFANT. The second reason is that to have a clinical trial with the three procedures would be extraordinarily expensive. In fact, it would cost about three times what is underway. And the third reason, which is probably the most forbidding one, is that we know of two centers where they have a fairly large experience with laser excision. One of them has given up because of the number of complications. And they decided not to use it any more. And the second has not given up, but they have published a report to show that the number of complications is much higher than the two procedures which we are using.

So the study is done to answer specifically two simple questions. The first one, is excising a piece of the lung beneficial to the patient. And second, which patients would benefit.

As we went out designing the study, we thought that it would make no sense to include a procedure which at the outside was already so controversial. Of course, the people who do it don't think it's controversial. But the community at large does.

Now, the other question, which is, are we too rigid in our approach to clinical trials, we now have 18 centers which are involved with it throughout the country. And their job now is to develop the protocol which will be implemented in a couple of months. Some of the participants say, but we have the answer, we have the data, we don't think we have to go through the protocol.

The response of the Institute has been, fine, bring your data, we will have it independently assessed and reviewed, and if the independent review says, yes, these data should lead to excluding these kinds of patients, or making this change or that change, we will comply. But so far, that hasn't taken place.

The position of the Institute, Mr. Chairman, has been very clear. If new data becomes available as we proceed, we are prepared to modify what we are doing. But so far, we haven't seen any of that data.

Mr. PORTER. So the criticism that the clinical trial, which is expected to take seven years, is too long a time to be useful for HCFA's reimbursement decisions, if I understand what you're saying, you're saying you're going to review whatever data comes along in the meantime, and even if new procedures come along in the meantime, if there's data to support their efficacy, that would be included in your study.

Dr. LENFANT. That is correct. And I can tell you, that if we had included the laser excision in the design instead of taking 7 years, we were going for 10 or 12 years.

HEMOPHILIA

Mr. PORTER. I was hopeful that Mr. Miller would arrive. He's at a budget hearing where Alan Greenspan is testifying, and that's the reason he's unable to be here.

These are questions that Mr. Miller of Florida would have liked to have asked had he been here, and I want to ask them and have you answer them for me.

What are the latest developments by your Institute in the area of hemophilia?

Dr. LENFANT. Well, this year has been kind of a golden year, actually, in the sense that there have been some very significant advances. The first one, which is really novel and did not exist before, is that the recombinant DNA factor IX has been produced. The deficiency in two clotting factors, if you want, which are responsible for hemophilia, are factor VIII and factor IX.

We have had a substitute for factor VIII for quite a few years, and I'm going to come back to that. The one for factor IX, we didn't have. But now we have it. And it is my understanding that it's being reviewed now by the FDA to decide whether they can approve it or not.

Now, the second thing that has happened is that factor VIII, which I said we have had for quite a few years, was still including some human albumin in it in order to stabilize the product. And that in fact was responsible for some immune reaction when it was given to patients.

Now what is being developed, and is almost developed, is a new factor VIII which does not include any human albumin, and therefore would be much safer for the patient. And then the third thing is that a new animal model has been developed. We have had hemophilic dogs, now we have hemophilic mice. And the advantage of having these two species is that it's going to enhance the capability for gene therapy development and assessing the effectiveness of gene therapy a great deal.

Mr. PORTER. Representative Miller's son is a hemophiliac. And he would also like to ask, are there any new developments on hemophilia from any biotech companies that you may have heard about?

Dr. LENFANT. Yes, as a matter of fact, the recombinant DNA factor IX that I just mentioned is developed by a biotech company. As is often the case, the commercial outfits are picking up the result of the research which is conducted by the Institute. I have to say I don't know which company that is. But I could find out.

Mr. PORTER. Dr. Lenfant, thank you for your good testimony this morning, for your very candid answers and direct answers to our questions, and for the wonderful job that you're doing there at the Institute. And 50 years is a great milestone for the Institute. You've been its director for almost a third of its existence, and we appreciate the fine work that you're doing.

Dr. LENFANT. Thank you, Mr. Chairman.

Mr. PORTER. The subcommittee will stand in recess until 1:30.

[The following questions were submitted to be answered for the record.]

SELECTED AREAS OF RESEARCH

Mr. Porter: Identify 1996-1998 spending on asthma, sickle cell disease, cystic fibrosis, Cooley's anemia, transfusion medicine, tuberculosis, hemophilia, hypertension, sleep disorders, LAM, and cardiovascular disease. Separately identify direct and related spending (understanding that related spending may overlap several disease areas).

Dr. Lenfant: NHLBI funding estimate for these research areas are shown on the table below.

	1996 Actual	1997 Estimate	1998 Estimate
Asthma			
Direct	$50,246,000	$53,256,000	$54,553,000
Related	7,872,000	8,344,000	8,547,000
Total	58,118,000	61,600,000	63,100,000
Sickle Cell Disease			
Direct	41,468,000	43,957,000	45,029,000
Related	2,022,000	2,143,000	2,196,000
Total	43,490,000	46,100,000	47,225,000
Cystic Fibrosis			
Direct	15,871,000	16,833,000	17,242,000
Related	629,000	667,000	683,000
Total	16,500,000	17,500,000	17,925,000
Cooley's Anemia			
Direct	10,109,000	10,716,000	10,971,000
Related	4,541,000	4,814,000	4,929,000
Total	14,650,000	15,530,000	15,900,000
Transfusion Medicine			
Direct	34,500,000	36,584,000	37,512,000
Related	8,267,000	8,766,000	8,988,000
Total	42,767,000	45,350,000	46,500,000
Tuberculosis			
Direct	12,209,000	12,942,000	13,256,000
Related	243,000	258,000	264,000
Total	12,452,000	13,200,000	13,520,000

Hemophilia			
Direct	13,937,000	14,775,000	15,126,000
Related	3,938,000	4,175,000	4,274,000
Total	17,875,000	18,950,000	19,400,000
Hypertension			
Direct	117,420,000	124,470,000	127,487,000
Related	14,909,000	15,805,000	16,188,000
Total	132,329,000	140,275,000	143,675,000
Sleep Disorders			
Direct	14,395,000	15,839,000	16,251,000
Related	2,055,000	2,261,000	2,319,000
Total	16,450,000	18,100,000	18,570,000
Lyphangioleiomyomatosis (LAM)			
Direct	198,000	900,000	920,000
Related	0	0	0
Total	198,000	900,000	920,000
Cardiovascular Disease			
Direct	757,921,000	803,421,000	822,873,000
Related	38,894,000	41,229,000	42,227,000
Total	796,815,000	844,650,000	865,100,000

SPECIALIZED CENTERS OF RESEARCH

Mr. Porter: Identify the number and subject matter of research centers supported in 1997.

Dr. Lenfant: In 1997 the National Heart, Lung, and Blood Institute anticipates supporting 78 research centers:

	Number of Centers
HEART AND VASCULAR DISEASES	
•Ischemic heart disease	1
•Sudden cardiac death	4
•Heart Failure	5
•Ischemic heart disease in Blacks	2

•Pediatric cardiovascular disease	3
•Molecular genetics of hypertension	7
•Molecular medicine and atherosclerosis	5
LUNG DISEASES	
•Pathobiology of fibrotic lung disease	7
•Biology of lung development	5
•Cellular and molecular mechanisms of asthma	7
•Airway biology and pathogenesis of cystic fibrosis	4
•Acute lung injury	6
SLEEP DISORDERS	
•Neurobiology of sleep and sleep apnea	3
BLOOD DISEASES AND RESOURCES	
•Transfusion biology and medicine	3
•Hemostatic and thrombotic disease	3
•Hematopoietic stem cell biology	3
•Sickle cell disease	10
TOTAL	78

PUBLIC EDUCATION PROGRAMS

Mr. Porter: If you were to enhance your public education programs beyond your current activities, what would be your highest priority areas?

Dr. Lenfant: Enhancing beyond our current public education program activities is an exciting possibility. It has been shown that African Americans are often less knowledgeable about coronary heart disease (CHD) symptoms, risk factors, and methods of prevention than whites even when controlling for other factors such as sociodemographics, risk factors, and other variables. It is possible to increase many of our efforts. For example, we would be able to expand the nationwide community education campaign begun in our CHD in Blacks project to promote alliances for outreach and education among a variety of groups such as physicians, and other health care professionals, as well as community organizations such as hospitals, public health clinics, schools, historically black colleges and universities (HBCUs), and by using radio and TV health messages to reach African Americans. We would also expand our National Physicians' Network, developed in collaboration with the Association of Black Cardiologists, the National Medical Association, and HBCUs, which is currently comprised of 250 physicians who have a personal interest in improving the health of African Americans. Network members have pledged to provide physician and public education in their communities using materials that have been developed by the NHLBI. However, more support is necessary to sustain these efforts. We would

also be able to organize more special forums on cardiovascular health in the African American community similar to the very successful ones already conducted in collaboration with Howard University and Meharry Medical College in Nashville, Tennessee.

Moreover, we would be able to address the changing health needs of "emerging" populations such as Hispanics, Asian/Pacific Islanders and American Indians. Increasing population diversity provides an opportunity to respond to special needs. For example, for Hispanic Americans, the NHLBI would be able to continue a strong presence in the Latino community and fully implement a national dissemination plan for the educational materials developed as part of the "Salud para su Corazon" (Health for Your Heart), the model program now underway in the Washington, D.C., metropolitan area. Additional resources would also enable us to design culturally appropriate, education and outreach activities to reach Asian Americans and Pacific Islanders as well as American Indians and Alaska Natives.

SLEEP DISORDERS

Mr. Porter: Would sleep disorders be one of these areas?

Dr. Lenfant: Sleep disorders would continue to be a priority area of our public education programs. With increased funds and increased staff resources we could add more depth to the current educational efforts on sleep apnea, such as producing additional television public service announcements. With additional resources, we could also expand the program to take on professional education activities in other sleep disorders, such as restless legs syndrome and narcolepsy.

SALT INTAKE

Mr. Porter: Last year we were approached by the salt industry, which disagrees with your Institute's recommendations on dietary salt intake as a way to reduce hypertension. The industry asserts that scientific evidence does not support a universal recommendation for salt reduction--only for that segment of the population that is "salt sensitive." Your testimony mentions the limitations of population-wide prevention efforts. Do you think there is any scientific basis for revising the current guidelines on salt intake?

Dr. Lenfant: The current guidelines on salt intake are affirmed by several scientific groups that have recently reviewed the evidence relating salt intake and blood pressure levels. In 1995, the Dietary Guidelines Advisory Committee, a group of non-Federal scientists, convened by the U.S. Department of Agriculture and the Department of Health and Human Services, concluded that most people reduce their chances of developing high blood pressure by consuming less salt. This group supported the 2400 mg of sodium daily value listed on the food label. In 1996, the scientists of the American Heart Association's Nutrition Committee also were convinced by the strength of scientific evidence to concur with a target level of 2400

mg of sodium per day. However, we are continuously monitoring outgoing scientific studies related to this topic. In fact, our Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure is currently reviewing the latest research findings in this area, and will be providing advice to the Institute late this calendar year.

TRIAL OF HYPERTENSION PREVENTION (TOHP), PHASE 2

Mr. Porter: An article in the February 7 edition of Science magazine reported that NIH is conducting a large clinical trial in which patients are tested for mutants of a gene that regulates salt retention. If successful, this test would identify which patients would be most helped by a low-salt diet. Do you expect that someday a test like this will tailor the low salt diet guideline only to those patients who would actually benefit?

Dr. Lenfant: The large clinical trial to which the Science report refers is the Trial of Hypertension Prevention, Phase 2, sponsored by the NHLBI. The genetic sub-study was undertaken as an addition to the main protocol and results have not yet been reported. It is possible that genetic typing of this kind will help tailor guidelines on salt reduction if it can reliably and accurately distinguish those who are sensitive and those who are not. Other questions would need to be answered as well, such as how costly and difficult would it be to administer the test to the large number of people who should be tested because they are at risk. At the present time, the Institute is convinced that our advice to limit sodium intake for everyone is the best advice given our current scientific knowledge. However, if an accurate, reliable, easy-to-administer, cost effective test of salt sensitivity becomes available, the scientific community would undoubtedly consider another approach.

COST RECOVERY

Mr. Porter: Last September at the Sleep Disorders Research Advisory Board you mentioned that NHLBI was investigating the use of a cost-recovery system for the many documents you produce that are distributed by the Government Printing Office. Have you been able to establish such a system?

Dr. Lenfant: Since 1987, in fact, the support contract for NHLBI's national education programs has contained a cost-recovery clause. Several education products have been offered through the contract on a cost-recovery basis including the "Month Kit" of reproducible materials for public health program planners and the "Speaker's Kit for the Guidelines for the Diagnosis and Management of Asthma." In general, NHLBI materials have been free, but requests for 11 or more copies of a single title, or 1 copy each of 11 separate titles are assessed a flat $10 shipping and handling cost-recovery fee. Exceptions to the rule are considered on a case-by-case basis. These minimal cost recovery efforts have resulted in an average of $2,000-$3,000 per month recovered for reinvestment in the contract. Recently, NHLBI has repackaged and

produced for cost recovery the materials developed and used in the Child and Adolescent Trial for Cardiovascular Health (CATCH), a multisite research study funded by NHLBI to demonstrate the effectiveness of school-based health education for motivating heart-healthy behavior. The Texas Department of Health in partnership with the University of Texas CATCH site, and professional teaching, fitness, and parenting associations have purchased 400 complete sets of the CATCH materials at a cost of $99,000 for distribution to interested schools in the State of Texas.

Because the Administration encourages cost recovery as a positive aspect of furthering a Federal agency's ultimate mission of "creating a government that works better and costs less," NHLBI is currently in the process of developing and implementing a more aggressive cost-recovery effort. With the issuance of an updated NHLBI education materials catalog this year, the Institute will begin to recover costs for the printing or duplication and dissemination (not development) of nearly all of its education materials including clinical practice guidelines, working group reports, and patient/public education materials. Once the initial promotional or "seed copies" dissemination of any of these products is completed, all subsequent requests would be subject to cost recovery. It is hoped that this more aggressive cost-recovery effort will enable NHLBI to continue to develop and disseminate high-quality education materials to its target audiences.

SELECT PAY

Mr. Porter: Your Institute has a "select pay" policy in which you allocate 85 percent of your funding strictly by priority score and 15 percent according to programmatic needs as well as merit. How far beyond the payline do you go to accommodate programmatic needs?

Dr. Lenfant: For the most part, "select pay" awards were no further than 10 percentile points from the final payline. On occasion, the Institute will select an application further than 10 percentile points from payline if there are strong programmatic reasons for doing so. Recent "select pay" awards include: a grant to a new investigator to examine the neurogenic mechanisms by which sleep disordered breathing contributes to hypertension; a competing renewal award to an established investigator to identify regulators of smooth muscle gene expression in order to understand the mechanisms that underlie transcriptional control of smooth muscle cell differentiation and diversity; a grant to a new investigator to study the function and structure of novel human bone marrow cell adhesion molecules in order to gain understanding of basic mechanisms related to the growth, proliferation, and differentiation of normal and abnormal blood cells; a grant to another new investigator to assess estrogen replacement and cardiovascular disease outcomes in diabetic women.

The Institute uses the following criteria in making its decisions:

- innovative research as identified by the Initial Review Group or by the Institute staff
- high-risk research with a potential high payoff as identified by the Initial Review Group or by the Institute staff
- applications from new investigators in contrast to investigators with multiple grants
- research areas of interest with few grants supported by the NHLBI
- research of special relevance to minority and women populations
- research related to a possible Request for Applications (RFA)
- applications with a technical or methodological problem that is easily corrected by the investigator
- applications for continuing longitudinal follow-up of participants in observational studies or clinical trials, for which interruption in funding would compromise the long term success of the study, even if renewed at a later date
- applications from minority investigators and institutions and from women investigators.

Mr. Porter: Last September your advisory council discussed the expedited review system the Cancer Institute is using and seemed unenthused about adopting it. Have you made a decision about whether to use expedited review?

Dr. Lenfant: The September 1996 decision of the National Heart, Lung, and Blood Advisory Council (NHLBAC) regarding expedited review has not changed. At that time, the NHLBAC, after review of the results of staff analysis, concluded that the expedited review policy as proposed by the Cancer Institute would actually operate at cross purposes to the principles of "select pay" that the NHLBAC enthusiastically endorsed, because both policies would compete for the same money. The NHLBAC recognized that funding all well-qualified applications eligible for expedited review would leave little "select pay" resources available and the discretionary aspect of "select pay" would be compromised by emphasis on funding applications eligible for expedited review. In addition, the need to request and review letters from all eligible grant applicants would be a time-consuming task for both investigators and NHLBI staff, and an unnecessary step that might result in a delayed award.

Mr. Porter: The council also discussed interim support for investigators who have just missed the payline but who are likely to be funded in the next round. Why do you feel that interim support would not be useful for your Institute?

Dr. Lenfant: Our Council also considered an interim funding plan at its September 1996 meeting. The NHLBAC concluded that interim funding should be used sparingly, and reserved for special circumstances such as supporting particularly innovative or high-risk research; such "interim funding" support is now successfully accomplished as part of the NHLBI "select pay" policy. One of the disadvantages of implementing a highly-structured interim funding plan is that it has trade-off costs.

Even if the amounts provided for interim support are recovered from applicants who subsequently receive an award, nothing can be recovered from recipients of interim support who do not. Analysis suggests that a large fraction (approximately 40 percent) of the funds provided would be unrecoverable if interim support were provided to all applicants within 10 percentile points of the payline. The resources to support the program would have to be obtained either by denying funding to applications that otherwise would be paid or by imposing a uniform percent reduction on all grant awards. The former is viewed as undesirable by the NHLBI and its Advisory Council; the latter would undermine a basic tenet of NHLBI policy, a policy that is consistent with a previous mandate from the Congress, that is, to make awards at levels recommended by the NHLBAC. In fact, approximately 80 percent of our new and competing renewal grants are funded at Council recommended levels.

HYPERTROPHIC CARDIOMYOPATHY

Mr. Porter: Last June, the Wall Street Journal ran an article critical of one of your grantees who is conducting research on a rare disease called hypertrophic cardiomyopathy. At the time you indicated that some protocol irregularities had occurred and the researcher had been sanctioned. After a more complete review of the research, has NHLBI taken any further actions against the grantee?

Dr. Lenfant: This research involved an intramural study investigating the efficacy of pacemakers in children with hypertrophic cardiomyopathy (HCM). No further actions have been taken against the investigator.

After the publication of the Journal's article, a subcommittee of the NIH Clinical Center's Medical Board reviewed both the protocol irregularities brought to the Institutional Review Board (IRB) and the IRB's decisions and recommendations. The Medical Board concluded that the matter was handled appropriately and that no further action needed to be taken. In addition, the Institute conducted an in-depth examination of other protocols led by the investigator, including an extensive review of the children's pacing protocol. It was determined that this was an isolated incident, as no additional breaches of research procedure were found. On the basis of all of the deliberations, the Institute concluded that the incident did not result in harm to any patient nor warrant further action against the investigator.

Mr. Porter: Do you think the underlying premise of the research remains sound?

Dr. Lenfant: The scientific basis for this research was thoroughly examined by the expert panel; they concluded that the underlying premise for this research remains sound.

HCM is characterized by thickening of the heart walls which causes obstruction to blood flow from the heart. This obstruction is believed to be an important cause of patient symptoms and heart failure. More than 16 centers world-wide have confirmed that pacemakers improve symptoms and relieve the obstruction in adult and young patients (over 400 patients). It has also been reported by at least three centers that both in adults and children, pacemakers may reduce heart wall thickness.

Children with HCM have a higher mortality than adults, and the heart wall thickness and obstruction increases with body growth. About a third of the children who at present do not have obstruction, develop obstruction during this period. Current therapeutic options include drug therapy, pacemaker, use of alcohol injected into heart muscle to thin the heart wall muscle, heart operation, and heart transplantation. However, there is no uniform opinion as to how these patients should be managed. It therefore remains valid to investigate the question as to whether pacemaker therapy relieves obstruction, attenuates the wall thickness, and improves symptoms and exercise performance in children during the several years that the heart disease is anticipated to worsen.

PRIMARY PULMONARY HYPERTENSION

Mr. Porter: In the past year, the Subcommittee has heard from advocates concerned about a disease called primary pulmonary hypertension - a progressive, fatal disease. What is the state of science relating to this disorder?

Dr. Lenfant: Primary pulmonary hypertension (PPH) is a rare, often fatal disease of unknown cause characterized by abnormally high pressure in the pulmonary artery. The cellular events that lead to PPH are not understood. Scientists are pursuing several different avenues with the goal of identifying the causes and eventually, new treatments for this devastating disease. Understanding the basic functions of the pulmonary vascular cells, how they are regulated, and functions that become abnormal in PPH are some of the topics being investigated. The availability of new treatments such as prostacyclin and nitric oxide are resulting in increased survival for some PPH patients.

An important recent advance is the localization of the gene to a particular human chromosome for the familial form of PPH. Although familial PPH accounts for only about 6 percent of PPH cases, identifying the gene involved will provide exciting opportunities for understanding what goes wrong in PPH and what new treatment strategies may be applied to curing the disease. Understanding the genetic factors predisposing to PPH may also be important to identifying individuals susceptible to developing PPH after exposure to the new diet drugs recently released, such as fenfluramine and dexfenfluramine. Disturbing evidence suggests that these drugs may increase the risk for PPH as much as 23 times. Other major research directions concern understanding the relationship between inflammation and injury to pulmonary vascular cells and research on gene delivery to pulmonary vessels, two

areas that may lead to new therapeutic approaches. The Institute recently released a Program Announcement "Cellular and Molecular Mechanisms of Primary Pulmonary Hypertension" that seeks to stimulate and encourage new investigations into the cellular events underlying the disease. We are also sponsoring a major conference this year that will bring together experts from throughout this country for an in depth discussion of PPH. We are anticipating new ideas and research directions will emerge from this meeting.

Mr. Porter: What is the prevalence of this disease in the general population?

Dr. Lenfant: Because primary pulmonary hypertension (PPH) is so rare, it is difficult to give you a precise answer. Our best estimate, however, is that the prevalence of PPH is 1,000-3,000 cases in the United States. The prevalence may be increasing due to longer survival, as well as to additional new cases due to the recent release of new diet drugs that increase significantly the risk for PPH.

SLEEP DISORDERS CENTER

Mr. Porter: Has the Sleep Disorders Center developed a plan for collaboration between NHLBI and other Institutes?

Dr. Lenfant: Yes, as part of the NIH Director's National Sleep Disorders Research Plan, the Center has established mechanisms to foster scientific collaborations among the Institutes. Even prior to the Plan, the Institutes have been working cooperatively with the National Center on Sleep Disorders Research (NCSDR) to advance sleep research. Examples of collaboration include: joint sponsorship of consensus conferences, workshops, program announcements and requests for applications (RFA), as well as inter-organizational information-sharing through the NCSDR Advisory Board and Trans-NIH Sleep Research Coordinating Committee.

A most noteworthy collaborative effort in FY 1996 was the release of a new initiative on the molecular biology and genetics of sleep and sleep disorders, which is jointly sponsored by four Institutes (National Heart, Lung, and Blood Institute, National Institute of Mental Health, National Institute of Child Health and Human Development, and National Institute of Arthritis and Musculoskeletal and Skin Diseases). This initiative directly addresses one of the primary recommendations in the Research Plan. Applications responding to this solicitation will strengthen and expand ongoing sleep research across NIH. In addition, several Trans-NIH sleep related workshops have been conducted over the past few years addressing important areas such as melatonin and the interaction between the circadian and sleep/wake systems. The NCSDR is currently developing a cross Institute sleep training grant program announcement, which will target another critical recommendation in the Plan. Finally, the NIH Sleep Research Plan has identified a number of scientific areas where it is possible to increase support for sleep research in a collaborative manner.

SLEEP DISORDERS CENTER

Mr. Porter: Is the Sleep Disorders Center supporting any research on the association between sleep apnea and high blood pressure?

Dr. Lenfant: Yes, the National Heart, Lung, and Blood Institute (NHLBI) supports a range of projects looking at the relationship of sleep apnea to cardiovascular disease. For example, the Sleep Heart Health Study is an ongoing, multi center, epidemiologic investigation to determine if subjects with high blood pressure have sleep apnea; whether sleep apnea is a contributing risk factor for the development of cardiovascular and cerebrovascular disease; and how age, gender, and ethnicity influence the association between apnea, high blood pressure, and stroke. The NHLBI Specialized Centers of Research (SCOR) program in Cardiopulmonary Disorders During Sleep brings together experts on sleep, the heart, and the lung to perform basic research and translate new findings into clinical strategies including the treatment and prevention of sleep apnea and hypertension. Projects in this program are developing new diagnostic tools and investigating how the control of blood pressure is changed by sleep apnea. In addition, NHLBI supports other population studies and research using a variety of animal models to explore fundamental mechanisms linking sleep-disordered breathing to abnormalities in the cardiovascular system that can cause high blood pressure. Recent findings indicate that more than half the patients with sleep apnea have high blood pressure, and the risk of developing high blood pressure increases even if the sleep apnea is very mild. Research on the association between sleep apnea and high blood pressure is a priority area identified in the NIH Director's National Sleep Disorders Research Plan.

SLEEP DISORDERS

Mr. Porter: Dr. Lenfant, I've heard about the educational program of the National Center on Sleep Disorders Research. Do you have any evidence regarding its effectiveness?

Dr. Lenfant: The educational program of the National Center on Sleep Disorders Research (NCSDR) is still in its beginning stages; the first materials were produced in September 1995. Although it is too soon to evaluate impact, we do know that our messages are getting out. Since the program began, we have produced fact sheets for the public in the areas of sleep apnea (80,000 copies), restless legs syndrome (25,000 copies), narcolepsy (25,000 copies), and insomnia (50,000 copies), as well as an informative "Check Your Sleep I.Q." quiz (50,000 copies). We have also produced 45,000 copies of a document on sleep apnea for physicians. The materials have been disseminated widely through the NHLBI Information Center, through the NHLBI World Wide Webb home page, and through the efforts of other sleep organizations such as the American Sleep Disorders Association (ASDA), the National Sleep

Foundation, and the American Sleep Apnea Association. For example, the ASDA greatly extended our reach by reproducing the mass media materials and distributing them to every accredited sleep center. The sleep centers in turn have been using the materials extensively with the local media as well as internally. Additional publications on the issue of problem sleepiness are currently under development.

The first mass media campaign to increase awareness of sleep apnea was distributed in February 1996, and the second campaign was distributed in February 1997. The first campaign included two radio and one television public service announcement (PSA). We are able to track the airing of the television PSAs and have found that this one has been aired 6,586 times in the 9 months of 1996 that it was available. This airing frequency is comparable to the high blood pressure and cholesterol PSAs that were distributed in the same time frame. The first radio PSA campaign was well-received by the media who indicated they regard the topic to be important, the PSAs of high quality, and agreed to play them regularly. We have anecdotal evidence from a sleep center that used the PSAs with its local media that they resulted in an increase in the number of inquiries as well as new sleep apnea patients at the center.

PRIMARY PULMONARY HYPERTENSION

Mr. Porter: Primary pulmonary hypertension (PPH) is a rare disease with a research infrastructure comprised of many renowned and expert scientists. The research proposals generated are exciting possibilities for treatments and a cure for PPH, as well as having applications for other diseases. What is NIH doing to effectively use these opportunities and ensure funding is available in this area?

Dr. Lenfant: The National Heart, Lung, and Blood Institute (NHLBI) currently supports several exciting projects related to PPH. In addition, the Institute recently released a Program Announcement "Cellular and Molecular Mechanisms of Primary Pulmonary Hypertension" that seeks to stimulate and encourage new investigations into the cellular and molecular events underlying the disease. The NHLBI is also sponsoring a major conference this year that will bring together experts from throughout this country and from Europe for an in depth discussion of PPH. We are anticipating that new ideas and research directions will emerge from both the program announcement and the conference that will result in high quality research applications. We will carefully examine each of these applications for their scientific merit and attempt to support as many of them as possible.

Mr. Porter: PPH research in the area of gene therapy has progressed significantly. Does NIH plan to support further research in this area?

Dr. Lenfant: NIH intramural and extramural research on gene therapy is very promising. Some or all of this research may result in new treatments for PPH in the future. For example, the National Heart, Lung, and Blood Institute currently supports several innovative research projects on gene delivery to the lung. Although the major

focus of this research has been on delivering genes to lung airways for exploring potential treatments for cystic fibrosis and other lung diseases, this work is sparking researchers to investigate approaches for delivery of genes to the pulmonary vessels as well. Recent findings, for example, suggest that adenoviral-mediated gene transfer may hold promise as a way to direct genes to pulmonary vessels. This technique therefore represents a new potential strategy for treatment of primary pulmonary hypertension. However, the technology is complex, and much more needs to be known about the cause and progression of PPH before the promise of successful gene therapy for this terrible disease can be fulfilled. The Institute anticipates continued support of research in gene therapy for several lung diseases, including primary pulmonary hypertension.

COMPREHENSIVE HEART, LUNG, AND BLOOD CENTER

Mr. Bonilla: On page 29 of your budget justification you indicate that NIH has decided not to initiate a comprehensive centers program on heart, blood vessel, lung and blood diseases. You state that these programs are too expensive and desired results can be achieved through other avenues established at the NIH. Please elaborate on NIH's decision.

Dr. Lenfant: The NHLBI has supported a large centers program since the early 1970s. At that time we awarded Specialized Centers of Research (SCORs) to support basic and clinical research focused on high-priority problems in heart, lung, and blood diseases. The SCOR programs were designed to expedite the development and application of new knowledge essential for improved diagnosis, treatment, and prevention of disease. At the same time, the Institute was also developing an extensive program in demonstration and education research through the R18 mechanism. Its purpose was to take interventions that were generally accepted as beneficial and adapt them to other populations or settings. In 1983, responding to authorizing legislation, the NHLBI established National Research and Demonstration Centers (NRDCs) in heart and blood vessel, lung, and blood diseases and blood resources. The NRDCs were formed by integrating demonstration and education research into clinical and basic research supported by the SCOR mechanism.

In theory, it appeared that combining the basic and clinical research supported by the SCORS with demonstration and education research could be easily done. However, it soon became apparent that a comprehensive center required highly trained investigators with very different types of expertise, and that in most cases, such expertise was not to be found within a single institution. Also, many of the projects supported by the basic and clinical components of a comprehensive center were not yet ready to be translated into demonstration and education research. There was no identifiable synergistic effects resulting from combining demonstration and education research with a basic and clinical research program. Thus, the Institute elected to redirect center resources away from the comprehensive center concept back to supporting only SCORs. This permitted supporting demonstration and education research with other resources.

The Institute also found that it could achieve its programmatic objectives through a combination of mechanisms, such as regular research grants, Specialized Centers of Research, and cooperative agreements. Additional mechanisms of support are not needed.

Mr. Bonilla: Has the NHLBI considered a comprehensive center that would have a reasonable cost ($1 million each year for 2 years) and would leverage an equal or greater amount of state and private resources to fund the center?

Dr. Lenfant: Because the issue is not one of how to finance a comprehensive center but, rather, how best to orchestrate and oversee the research, the source of funds for such centers is not a major factor in our decision. Our experience has shown that it

is difficult for any one applicant to propose high-quality science in all areas of heart, lung, and blood diseases. This results in having to fund weaker science along with the stronger components. It has been the Institute's experience that a given institution may excel in one or more areas, but not all.

Mr. Bonilla: What would be the benefit versus risk of a cost effective pilot comprehensive center to address prevention and the integration of clinical and basic research of lung and heart diseases?

Dr. Lenfant: Inasmuch as size and complexity are the very issues that militate against the efficient and effective operation of comprehensive centers, we believe that a small pilot would not shed useful light on the matter.

HEART ATTACKS AND DIABETES

Mr. Bonilla: Last year, the NHLBI issued an alert to U.S. physicians indicating that diabetics suffering from blockages in two or more coronary arteries should undergo bypass surgery rather than angioplasty because of the markedly lower death rate at five years.

Are you confident that physicians, particularly in remote areas in the country, learned of this finding?

Dr. Lenfant: Yes, indeed we are. Even though major revascularization procedures, such as angioplasty and surgery are done in large medical centers, and not in remote rural areas, we always see to it that clinical alerts of important issues such as the one raised in your question are broadly disseminated. Among the methods used for dissemination of this particular clinical alert, we had a live press conference that was carried on the major TV networks as well as radio stations and the printed media. Additionally, we channeled this clinical alert through the National Library of Medicine and through a variety of other special media events designed to reach all physicians. Our file of news media clippings on this issue suggests that this story was carried all throughout the United States and that even physicians in remote areas were apprised of the finding that diabetics in need of revascularization are likely to have better outcomes if they undergo bypass surgery as compared to angioplasty.

Mr. Bonilla: Have you had any results to measure how broadly this practice is used?

Dr. Lenfant: We currently do not have that information. However, we will monitor data from the National Center for Health Statistics (NCHS) at CDC on the number of diabetic patients undergoing either type of revascularization, which will allow us to look at this issue indirectly.

Mr. Bonilla: Are there any new developments relating to angioplasty and diabetics?

Dr. Lenfant: The five-year follow-up results of the NHLBI-funded Bypass Angioplasty Revascularization Investigation (BARI) Trial comparing application of balloon angioplasty versus coronary bypass surgery in patients with multi-vessel coronary artery disease, was recently published in the New England Journal of Medicine (NEJM). The finding that diabetics in this study had superior five year survival with bypass surgery versus angioplasty was reported in a clinical alert in advance of the full NEJM report because of the concern that these results should be available to diabetic patients that require coronary revascularization and to their physicians as early as possible. The survival benefit observed in diabetics receiving bypass surgery is remarkable and was a surprise. Because diabetics are at high risk for infection and other procedural complications, many physicians expected the more invasive bypass surgery to pose a higher risk compared to angioplasty. The mechanism for the superior survival observed is not clear and has rekindled intense interest in understanding the role of this metabolic disorder in vascular diseases and heart failure.

Mr. Bonilla: What do you think the next five or ten years will bring in this area?

Dr. Lenfant: Cardiovascular medicine and interventional cardiology in particular are rapidly advancing. Catheter technology continues to evolve. All these advances are likely to affect the cardiovascular care of diabetic patients. For example, a coronary artery stent (an expandable metallic lattice tube inserted in the artery at the point of balloon dilation to keep the artery open) improves the initial result of angioplasty and reduces restenosis, may offer even greater clinical benefits for diabetics than in non-diabetic patients.

With the advances in catheter technology and better drugs more complete revascularization by percutaneous approaches is likely. The advantages of bypass surgery over angioplasty for diabetics may be likely to diminish with time. Further, novel surgical approaches which avoid splitting the breast bone have been developed and early results are encouraging with low procedural complications and hospital cost when compared to current open heart surgery, offering diabetics a less traumatic revascularization alternative with much less morbidity and more rapid recovery.

WOMEN AND HEART DISEASE

Mr. Bonilla: Yesterday, the AP published the Health Journal's article on heart disease having different symptoms for female sufferers. It states that "unfortunately, women historically have received different treatment: fewer diagnostic tests, fewer angioplasties, fewer bypass and less treatment with drugs. And while women cite breast cancer with its one-in-nine lifetime incidence as their biggest fear, heart disease kills one in two women more than all cancers combined."

I understand from this article that trends of treatment is changing as research reveals new discoveries for women and heart disease. I am surprised to learn that diabetes poses even more potent cardiac risks for women than men. Please explain why that is the case.

Dr. Lenfant: Rates of heart disease in women with diabetes are very similar to rates in men with diabetes, while rates in women without diabetes are much lower than rates in men without diabetes. Epidemiologic studies generally demonstrate that diabetes removes the "female advantage" of nearly uniformly lower heart disease rates than in men, but women with diabetes do not appear to be at higher risk of heart disease than men with diabetes. The mechanisms for the detrimental effect of diabetes on heart disease risk in both sexes appear to include several factors, particularly in regard to cholesterol levels and blood clotting systems.

Mr. Bonilla: The NHLBI is aiming two studies, WISE and WAVE, at improving diagnosis of heart disease and treatment. Do these studies address the diabetes factor related to women?

Dr. Lenfant: These studies were not designed to pursue the "diabetes factor" per se. However, the data collection plans will allow us to obtain information that should shed more light on the issue since 10-15 percent of the women being evaluated in both studies are expected to be diabetic.

The Women's Ischemia Syndrome Evaluation (WISE) Study will evaluate innovative diagnostic methods with the goal of improving the clinical utility of cardiovascular testing in evaluation of ischemic heart disease in women. Approximately 800 women will be evaluated. Innovative approaches include physiologic and functional measurements such as metabolism, perfusion, wall motion, or endothelial function, and assessment of epicardial coronary stenosis by arteriography. Diabetes, an important risk factor that may influence diagnostic evaluation, will be also evaluated. The Women's Angiographic Vitamin and Estrogen (WAVE) Trial will study the impact of hormone replacement therapy and antioxidant vitamins C and E, on the progression of coronary artery disease in 450 post-menopausal women with blockage in one or more of their coronary arteries. Diabetes will also be taken into consideration.

GENE THERAPY

Mr. Bonilla: Last September, a research team at the University of Chicago showed that genes can be injected into muscle tissue to cause the production of proteins needed to correct some blood disorders. Researchers claim this is a solid breakthrough and that the gene delivery technique will be tested in humans using the hormone gene that stimulates production of red blood cells.

It is assumed that this technique may be developed for the treatment of hemophilia and diabetes that are caused by the deficiency of some essential protein. What will NHLBI's role be in developing this technique?

Dr. Lenfant: The report of the University of Chicago researchers describing the development of a novel muscle-based gene therapy technique that produces long-term expression of therapeutic levels of erythropoietin (Epo) in mice is very exciting. In theory, this new approach to gene therapy may have the potential to treat a number of diseases that result from diminished levels of proteins that circulate in the blood.

However, many technically demanding hurdles must be overcome before this technique can be attempted in humans. For example, based on studies in mice, extremely high levels of the protein will have to be produced for such diseases as hemophilia and diabetes in humans. For a disease such as diabetes, techniques need to be developed that tightly regulate the production of the essential protein, insulin. The high levels of the Factor VIII protein required to treat hemophilia also presents a major obstacle.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION STUDY

Mr. Bonilla: According to The Journal of the American Medical Association published last month, the death rates from heart disease in the United States are declining mostly due to better drugs and other treatments and not because people were leading healthier lives.

The researchers' conclusions were based on a computer model they created to forecast trends in heart disease. The study stated that the computer model explains 92 percent of the decline in heart disease deaths in the 1980s.

However, two other researchers not associated with the findings said it failed to consider important factors such as the presence of diabetes, levels of physical activity and whether people took aspirin or hormones.

Are you familiar with this study and is it accurate?

Dr. Lenfant: Yes, I am quite familiar with the study and I believe that it is accurate. One can always question the assumptions that underlie a model and what factors to include or exclude is often a matter of professional judgment and frequently a subject of scientific debate. Publication of the article in The Journal of the American Medical Association suggests that the reviewers and the editor of the Journal considered the authors approach to be worthy of consideration by their readers. It does not mean that it is the final definitive word on the subject. Other investigators, employing different assumptions may come to different conclusions.

I should note that I do not think the exact percentages are as critical as the overall implication of the results; namely, that the progress we have been making and are continuing to make against the burdens of heart disease are the result of both better approaches to prevention and improved methods of diagnosis and treatment.

Mr. Bonilla: On page 2 of your testimony, you state that "we have gained valuable insight into the characteristics and habits that predispose people to develop cardiovascular disease and have raised public awareness of the importance of modifying these risks."

Do you agree with the statement of this study that better drugs and other treatments and not people leading healthier lives have resulted in a decline of death rates?

Dr. Lenfant: I do not think I can fully agree with that statement, because I believe that it too readily dismisses the important role of lifestyle changes in the decline of death rates. Even if we accept the conclusion of the authors of the article in The Journal of the American Medical Association that "only" one-quarter of the decline in coronary heart disease (CHD) mortality occurring between 1980 and 1990 could be attributed to prevention of CHD, that one-quarter amounts to nearly 32,000 lives saved each year—a substantial impact by any standard. In addition, the authors say that another 29 percent of the decline is associated with reduction of risk factors in patients with established coronary disease. Better drugs and other treatments to lower blood pressures and cholesterol levels have certainly been critical to saving the lives of people with established CHD, but so have healthier lifestyles. The advances in imaging technologies that I discussed in my opening remarks offer great promise for increasing the numbers of lives saved through prevention by demonstrating the development of disease before heart attacks and other life-threatening clinical events arise.

Our continued success in reducing coronary heart disease mortality has been a joint result of greater attention to prevention and improved methods of diagnosis and treatment, and further progress in both areas will be essential if we are to extend the present favorable trends into the future.

CHILD AND ADOLESCENT TRIAL FOR CARDIOVASCULAR HEALTH (CATCH)

Mr. Bonilla: It is my understanding that a soon-to-be-released study by NHLBI proves that young children can be taught behaviors that could help protect them against heart disease later in life.

The Child and Adolescent Trial for Cardiovascular Health (CATCH) supported by NHLBI is said to be the largest school-based health promotion study ever done in the United States. It involved 100 elementary schools in four states over a three year period and 5,000 children participated in the trial.

It would only seem logical to me that children can be taught such behaviors without a need for a study of this magnitude. Most school systems have physical education, anti-tobacco and drug education as well as nutrition counselors of some sort. What did trial reveal that we did not already know?

Dr. Lenfant: It is important to document that interventions are effective and can be conducted using existing school staff with minimal special training and school resources. The cost is high for such a study but if prevention programs are to be advocated in schools it is crucial to be certain you know that the program works and the strengths and weaknesses of its various components.

The CATCH trial assessed the outcomes of a four component school-based coordinated program promoting cardiovascular health in third, fourth, and fifth graders.

The components were the school food service program, the physical education program, the classroom curriculum, and supporting family-based education. Results showed that percentage of total and saturated fat in school lunches decreased and the intensity of the physical activity in physical education classes increased significantly in the intervention schools compared with control schools. Also, policy implementation for smoke free schools increased. Students participating in the interventions reported significantly more daily vigorous activity. Self-reported daily energy intake from total and saturated fat among students in intervention schools was significant. Other findings indicated sustained significant effects in improved knowledge, intentions, and social reinforcement for healthful food choices. Girls reported greater perceived reinforcement for healthful eating than did boys. The effects of the family component were more pronounced for minority and male students related to knowledge and attitudes related to diet.

CHILD AND ADOLESCENT TRIAL FOR CARDIOVASCULAR HEALTH (CATCH)

Mr. Bonilla: How much did this trial cost and how will the results be used?

Dr. Lenfant: The total cost of the trial was twenty-four million dollars. This included a three and half year feasibility study in the same communities where the main trial was conducted to be sure that all the food service, physical education, classroom curricula, and family-based programs developed for the intervention were culturally and linguistically appropriate and feasible for school staff.

The study results have been reported in numerous publications and presentations for education administrators, policy makers, and the scientific community. The Institute has packaged the program components, and they are available from our information center. A flyer describing the materials that has been mailed to all elementary schools in the country. In addition, the Texas Department of Health purchased one hundred thousand dollars worth of the CATCH intervention sets of materials and have made them available to any school in Texas. Since the CATCH intervention was shown to work using existing school staff with diverse groups of schools with very little additional school resources to implement, it appears to provide an important model of school-based health promotion that should be feasible and effective in other American schools.

Mr. Bonilla: Would you say it is difficult to measure the effectiveness of this study since you are not planning to track the behavior of these kids as they become adults?

Dr. Lenfant: We know that risk patterns in youth tend to track or persist over time. While a long-term follow-up into adulthood of the students in the CATCH study would be prohibitively expensive, we are currently following the cohort from sixth to eighth grade to look at the tracking of physiological and behavioral risk factors. The CATCH study is the only one to have data on Hispanic, African-American, and Caucasian youth from four diverse geographic locations in the United States.

FOLIC ACID

Mr. Bonilla: Last year, the Chairman asked you about Folic Acid and its role in preventing heart disease. You responded that you were in the process of developing a clinical trial but had to readjust your plans because Secretary Shalala initiated a food fortification program with folic acid. This put your plans of a clinical trial on hold.

What progress has NHLBI made on this front?

Dr. Lenfant: Secretary Shalala's food fortification program raised the issue of whether the usual amount of folic acid from food, as fortified, would affect the feasibility of a clinical study of the impact of lowering homocysteine levels on heart disease. A recent study testing the effect of different levels of folic acid shows that an increased dose of folic acid, above that resulting from the average diet, with fortification, can reduce homocysteine levels even further. Thus, a clinical trial is feasible even though folic acid is being added to food. Several proposals for conducting a clinical trial are now being considered.

Mr. Bonilla: What would you have done differently without the Secretary's involvement?

Dr. Lenfant: We would have had to conduct a dose-response study because the appropriate dose was not known. The prospect of the food fortification program had an influence on what doses were tested.

Mr. Bonilla: Do you think you will get the same intended results as you would have if you conducted the original clinical trial you had planned before the Secretary's initiative?

Dr. Lenfant: As it turned out, the doses of folic acid that had been proposed previously for a clinical trial would have had an effect on lowering the levels of homocysteine, but we did not know that without the study mentioned above.

MAGNETIC RESONANCE IMAGING ANGIOGRAM

Mr. Wicker: In the testimony, much discussion concentrated on the new non-invasive angioplast MRI. How new is this method?

Dr. Lenfant: The new non-invasive magnetic resonance imaging (MRI) angiogram that was discussed in my testimony is very new indeed. Images of the quality and resolution that I showed in my testimony would not have been possible as recently as one year ago. Although investigators have been trying to produce high resolution images of the coronary arteries for about the last 10 years, the constant movement associated with respiration and the beating of the heart, itself, have made this a difficult problem to resolve. However, continuous improvements in the computer software

involved in producing the images have now reached the point where MRI angiograms are closely approximating the results available from conventional angiograms. Even better images are certain to be possible in the very near future. Improvements in MRI angiogram quality can be expected not only from further improvements in imaging processing software, but also from the new MRI equipment that is about to be available.

Mr. Wicker: How widely is it used?

Dr. Lenfant: Because it is so new, it is only currently available in the very few selected sites that have been involved in developing improved image processing software. However, because the image resolution that I demonstrated in my testimony can be obtained with most of the magnetic resonance imaging equipment currently in place throughout the country by installing the new software and with modest changes in the equipment, it is likely that the number of sites offering the approach for diagnostic purposes will increase.

Mr. Wicker: If it costs $1,000 as opposed to the $8,000 cost of the older invasive method, why isn't it used by everyone?

Dr. Lenfant: The invasive method continues to be used because it was, until very recently, the only way to obtain images of the needed level of detail for guiding patient treatment. My point is that, in the past, we have focussed on diagnosis, but now we have an opportunity here that previously was not available to us. To use this technology for prevention, more specialized facilities and equipment are needed and will take time and money to put in place. As the availability of high quality images using magnetic resonance imaging (MRI) becomes more widely known, we are hopeful that usage of the MRI angiogram even before symptoms occur will enable patients and their doctors to prevent deterioration in their condition and delay or eliminate the need for an invasive angiogram. We are excited about the possibility that this new technology can be used in ways that will prevent or delay heart attacks.

STROKE BELT

Mr. Wicker: Dr. Lenfant stated during testimony that Mississippi is included in the region known as the stroke belt. What factors exist that cause states within the stroke belt to have higher rates of cardiovascular disease? (Ex: Is diet a major factor? Is heredity a major factor?)

Dr. Lenfant: While the exact causes of the higher stroke mortality rates in the Southeast are unknown, there is some evidence to suggest several possible explanations for this phenomena. The prevalence of obesity, especially among African American women in the Southeast, is higher than their counterparts who reside elsewhere in the nation. Obesity has been shown to increase the prevalence of high blood pressure which in turn causes more strokes. It is speculated that "Southern style" of cooking, which yields higher intake of fats and salt in the diet and lower dietary potassium in the Southeast, may contribute to the excessive age adjusted stroke mortality. Hypertension control rates for those who reside in the Southeast are not as good as their counterparts

residing elsewhere. There is a suggestion that average blood pressures are higher in this region than elsewhere. Whether this is the result of life style patterns or some other factor is unknown. Access to medical care may be a problem for males in the Southeast, especially African American males who use hospital emergency rooms as a source of primary care. The use of emergency rooms affords little opportunity for followup and long-term management of a chronic illness such as hypertension.

Mr. Wicker: I understand that NHLBI has been doing cardiovascular disease prevention work in the stroke belt during the past 10 years. In what areas of prevention have these programs concentrated?

Dr. Lenfant: The NHLBI has worked in the stroke belt to promote blood pressure control and other risk factor reductions. In 1990 and 1993-96, the NHLBI provided funding to state health departments in each stroke belt state to reduce the risk of stroke. Each state health department decided how to best approach the problem in their state. The funds from the NHLBI enabled them to establish key partnerships with private and public agencies to promote and carry out risk reduction programs in the community. Some states chose to promote programs in all the major risk factors, i.e., high blood pressure control, smoking cessation, weight reduction, healthy eating, and increased physical activity. Others chose to focus on one or more of these major risk factors.

Mr. Wicker: Approximately, how much money has been spent on these specific projects?

Dr. Lenfant: The NHLBI provided a total of $1,932,220 to fund the projects in the Stroke Belt Initiative.

WOMEN AND CARDIOVASCULAR DISEASE (CVD)

Ms. Northup: The history of research on women has not been very good, but has been improving. As you know, there are distinct differences in warning signs or symptoms of heart problems in women versus men. What is your agency doing to identify these differences and educate physicians and the public on these warning signs?

Dr. Lenfant: NHLBI is conducting several large-scale population studies to examine how middle-aged and older women who develop heart disease differ from women who do not and from men who do develop the disease. These studies have demonstrated that acute symptoms in women may differ in severity or character from those in men, and that typical evidence of heart problems in men, such as abnormal electrocardiography, may be more difficult to interpret in women. Other measures of underlying risk, such as measures of asymptomatic blockage or hardening of the arteries in the neck or leg, appear to identify women at risk for heart disease as well or better than they do men. Active investigation into the interpretation and application of tests in screening and diagnosis of women is ongoing and will continue. Because of differences in symptom presentation and test results in women compared with men, the Women's

Ischemia Syndrome Evaluation (WISE) study is examining innovative diagnostic methods for evaluating ischemic heart disease in women. The goal is to develop safe, accurate, and cost effective approaches for evaluating and diagnosing women with suspected ischemic heart disease.

Rapid Early Action for Coronary Treatment (REACT) is a study in 20 U.S. communities that is implementing and evaluating the impact of a community-based education program for recognition of acute cardiac warning signs and to encourage prompt seeking of medical care when experiencing symptoms. The program targets community residents, health care professionals, and patients. Many of the educational messages are specifically targeting women, to see if they change when and how women seek treatment. The study also will evaluate differences in symptom presentation, diagnoses, treatment, and case fatality rates in women versus men.

The National Heart Attack Alert Program of the NHLBI has addressed the issue of women and heart disease in a variety of publications for professionals and the public. These publications are disseminated in medical journals, professional meetings, and through the NHLBI information center.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Ms. Northup: Emphysema at its end stage is very restrictive for patients and also very costly. Do you have information from HCFA regarding the costs relating to emphysema and what percentage of Medicare beneficiaries have related illnesses?

Dr. Lenfant: No, I do not have specific Health Care Financing Administration (HCFA) data on costs related to emphysema or the percentage of Medicare beneficiaries with related illnesses. We know that approximately 2 million people in the United States have been diagnosed with emphysema, the majority of whom are over 55 years of age, there is no doubt that the costs to HCFA for providing care for these patients must be very high.

Ms. Northup: If so, how does this impact your research on this disease?

Dr. Lenfant: We have always considered emphysema an important health problem and support many research projects to determine the cause of the disease and ways to improve treatment as well as important initiatives in early detection and prevention. A major key to success will be smoking prevention, by increasing the proportion that do not smoke and helping smokers to stop. NHLBI supports many projects in this important area and are active participants in the Trans-NIH Tobacco Initiative to coordinate the smoking related programs. We also support research on the pathogenesis of the disease, including basic mechanisms of injury, repair and inflammation. Exciting new possibilities include tools from molecular epidemiology, to determine if some individuals are genetically susceptible to the damaging effects of cigarette smoking. Research on the treatment of emphysema, including a multicenter study to evaluate the effect of inhaled corticosteroids in preventing emphysema in

smokers, remains a high priority. We just initiated a program in cooperation with HCFA to evaluate the efficacy of lung volume reduction surgery (LVRS) in the treatment of end-stage emphysema. Through this program, we will work very closely with HCFA on cost of care for the emphysema patients participating in the LVRS study. We anticipate that this study will contribute enormously to our knowledge base of this chronic lung disease.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Ms. Northup: You mentioned in your justification that women are affected more strongly by smoking. Why is that and what research has your Institute done to show this?

Dr. Lenfant: It has long been suspected that women have different susceptibilities to the effects of smoking, both in the severity and type of disease induced. However, because women have different smoking patterns than men, this has been difficult to determine. The Lung Health Study, a multicenter study evaluating the effects of smoking cessation on lung function, was the first study to follow longitudinally a large population of women smokers. The Lung Health Study followed 5,887 smokers, thirty-seven percent of whom were women, ages 35-60 years old. They had pulmonary function abnormalities suggestive of early chronic obstructive pulmonary disease (COPD) on entry to the study. Results from this study have shown that women smokers had more difficulty quitting smoking, had more weight gain if they did quit, and had greater airway reactivity. Preliminary data have suggested that the pulmonary function changes were greater in the women compared to the men who continued smoking, especially if corrected for the lower number of cigarettes smoked per day by women. One possible reason may be that women have smaller lungs than men because women are generally smaller in size. In fact, some studies are suggesting that women may have smaller airways than men even when corrected for lung size. Smaller lungs and smaller airways could mean that the dose of tobacco smoke is higher for the number of cigarettes smoked. Women participating in the Lung Health Study continue to be followed for both the progression of COPD and possible development of lung cancer.

SLEEP DISORDERS

Ms. Northup: Please provide more details on the type of research you are doing on sleep disorders.

Dr. Lenfant: The National Heart, Lung, and Blood Institute (NHLBI) sponsors a comprehensive sleep disorders research program that includes basic research on fundamental mechanisms involved in the regulation and functions of sleep; patient-oriented research to understand the cause and improve the treatment of sleep disorders; and applied research to determine how sleep disorders affect well-being (that is, productivity and quality of life), with the goal of developing strategies to prevent and manage these impairments most effectively. This is a multi-disciplinary program

encompassing neuroscience, genetics, circadian biology, physiology, immunology, behavioral science, and epidemiology across all ages, genders and ethnic groups. The Institute supports research on the basic molecular, genetic, and physiologic mechanisms regulating sleep; abnormalities in sleep control causing cardiopulmonary disorders such as sleep apnea, high blood pressure, and stroke; genetic and developmental factors contributing to the incidence of sleep-disordered breathing and apnea of prematurity; treatments to prevent sleep apnea; and studies into the effects and treatment of other sleep disturbances such as insomnia.

The Institute is also supporting clinical and epidemiologic studies such as Sleep Heart Health Study, to explore the relationship between sleep apnea and high blood pressure and to determine whether this sleep disorder is a contributing risk factor for the development of heart disease and stroke. The NHLBI Specialized Centers of Research (SCOR) program in Cardiopulmonary Disorders During Sleep integrates basic and clinical researchers studying the effects of sleep abnormalities on breathing, cardiovascular function, behavior, and cognitive function in order to facilitate the transition of scientific advances into strategies for the treatment and prevention of sleep disorders. Finally, through the new Sleep Academic Award program, NHLBI is supporting research into educational interventions to enhance the sleep medicine skills of physicians and awareness of sleep disorder-associated health risks.

Ms. Northup: Do you measure how sleep disorders may affect productivity or lifestyle?

Dr. Lenfant: The NHLBI supports several clinical and applied research projects on how sleep disorders affect productivity and lifestyle. A longitudinal study in elderly men and women is examining whether sleep-disordered breathing causes depression and a decline in the health-related quality of life. Another epidemiologic study is investigating the etiologic link between sleep-disordered breathing and the rise in daytime sleepiness among postmenopausal women. The NHLBI supports a study of sleep-related behaviors affecting productivity in 600 primarily Hispanic women who are participating in the Women's Health Initiative (WHI) Observational Study in order to distinguish the role of sleep disorders in WHI outcomes. An important outcome of these epidemiological investigations will be quantitative data which physicians can use to evaluate the clinical significance of sleep-disordered breathing in specific patient populations. The Institute also sponsors research that will determine the effects of sleep fragmentation on daytime function, and whether light therapy can improve the alertness and cognitive performance of individuals working at night.

SLEEP DISORDERS

Ms. Northup: Your justification mentioned an ongoing collaboration with the Department of Transportation, but gave no details. Please elaborate on this collaboration.

Dr. Lenfant: In the FY 1996 Appropriations Bill for the National Highway

Traffic Safety Administration (NHTSA) of the Department of Transportation (DoT), Congress requested and provided funds for NHTSA to work with the National Center on Sleep Disorde s Research (NCSDR) to investigate the role of fatigue, sleep disorders and inattention in highway crashes. Based on this information, NHTSA and NCSDR are developing and evaluating an educational campaign to address the problem of sleepiness related highway crashes.

Starting in FY 1995, the DoT and NCSDR began collaborating by co-sponsoring a National Forum on Sleepiness and Traffic Safety with the National Sleep Foundation. In FY 1996, NHTSA and NCSDR developed a plan to initiate the new sleepy driver program. The program consists of 5 parts: establish an expert panel to analyze the role of fatigue, sleep disorders and inattention in highway crashes; investigate instances of fatigue-related events in motor vehicle operation; develop and test educational countermeasures; develop a strategy and materials for the education campaign; and evaluate and pretest the information and education campaign. An expert panel has been formed and they are currently working on its report, which is expected to be completed in the summer of 1997. The remaining phases of the project will be done by NHTSA, with oversight from a steering committee set up and chaired by the NCSDR. The plan was endorsed by the Sleep Disorders Advisory Board of the NCSDR. It is expected that dissemination of materials may start in late 1998. Lastly, ongoing discussions are underway for further collaborations and support for complimentary activities between NCSDR and NHTSA/DoT in this area.

LUNG VOLUME REDUCTION SURGERY

Ms. Northup: According to your justification, your Institute determined it was not appropriate to expand the LVRS trial, but you mentioned a possible review by a Data Safety Monitoring Board. Has the ongoing trial been monitored to this point, and when is the next likely review by this board?

Dr. Lenfant: The National Heart, Lung, and Blood Institute (NHLBI) awarded contracts for the LVRS program to 18 clinical centers and one coordinating center on December 20, 1996, following a national competition and review by an expert scientific panel. Since then, much work has been accomplished toward meeting our goal of protocol completion by summer, 1997. The first phase of the project is to develop the detailed protocol and manual of procedures. Several meetings have been held, and several more are scheduled to meet our very tight timetable. A weekly telephone conference of an Executive Committee assures that progress is being made toward the completion of the protocol.

An essential feature of every NHLBI clinical study is the active participation of a Data Safety Monitoring Board. The Institute has already identified participants for this Board, an independent group of scientists who will begin their work with a review of the protocol and manual of procedures. We anticipate that the Board will review the protocol in June 1997. Once patient recruitment begins, the Board will receive and review quarterly data reports and actively participate in on-site visits for assessment of quality. They will meet formally as needed, but at least twice a year, to discuss data

reports, data quality, patient safety, study progress and performance of the centers.

EXTENT OF CARDIOVASCULAR DISEASES AMONG MINORITIES

Mr. Stokes: As co-Chair of the Congressional Heart and Stroke Coalition, I am very concerned about the impact of cardiovascular disease on families across the country. I understand that cardiovascular diseases cause a death every 33 seconds in the United States.

It is shattering to think that in the span of this question and your response that more than three people could die from cardiovascular disease. According to the World Health Organization, heart disease is projected to replace pneumonia as the leading cause of premature death and disability worldwide by the year 2020. What is the extent of cardiovascular diseases among African Americans, Hispanics and other minorities?

Dr. Lenfant: As in the white population, heart disease is the leading cause of death in American Indians and in African, Hispanic and Asian Americans. Stroke ranks third highest in whites, African Americans, and Asian Americans and fifth highest in Hispanic Americans and American Indians. The decline in heart disease mortality is less steep in African Americans than in white Americans. It is not known how many persons among the minorities have cardiovascular disease, but hypertension and stroke are clearly major heath problems among African Americans, and stroke is a major problem in Asian Americans. In both men and women, mortality from coronary heart disease is higher in African Americans and whites under age 75, and prevalence is higher in African Americans in the younger adult age groups. But, rates of morbidity and mortality from coronary heart disease appear to be lower in the Hispanic, Asian, and American Indian populations than in whites.

Mr. Stokes: Is the onset of the disease earlier than that of the general population?

Dr. Lenfant: Prevalence rates for heart disease, heart failure, stroke, and hypertension are higher in African Americans than in whites at the younger adult ages, suggesting the onset of disease is earlier than for the general population.

CLINICAL TRIALS

Mr. Stokes: In the area of clinical trials, what specifically is the Institute doing to slow the rate and to reduce the burden of this devastating life threatening disease?

Dr. Lenfant: The Institute has several clinical trials addressing the treatment and prevention of hypertension with a particular focus on the African American population. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is comparing four commonly used antihypertensive medications for their effectiveness in reducing the rate of heart attacks in older patients with additional risk factors. ALLHAT has enrolled over 10,000 African Americans among the more than

26,000 patients entered to date. A second program supports a series of five coordinated grants through which investigators in five major cities are conducting trials aimed at improving hypertension control among inner-city minority populations. A third program, Dietary Approaches to Stop Hypertension, is conducting a series of carefully controlled dietary studies in persons with high normal or slightly elevated blood pressure, 50-60 percent of whom are African American, and is likely to report some important positive findings. A fourth trial, called PATHWAYS, is targeting another minority group, American Indians, in attempt to prevent obesity in childhood.

Trials focusing on heart disease in women are evaluating the effects of aspirin, antioxidant vitamins, and hormone replacement therapy on first or recurrent heart attacks or progression of coronary artery disease. The Activity Counseling Trial seeks to learn the best of several approaches to increasing physical activity through counseling delivered in doctors' offices and clinics, for both men and women. The Rapid Early Action for Coronary Treatment Trial, is targeting whole communities, including several with large minority populations, to reduce the time for seeking acute medical care. Other ongoing trials are addressing the use of antiarrhythmic drugs compared to an implantable defibrillator to prevent sudden cardiac death in high risk cardiac patients; beta-blocking medication to prolong survival in congestive heart failure; alternative strategies for the management of atrial fibrillation; and the use of an angiotensin-converting enzyme inhibitor to prevent recurrent heart attack and death following first heart attacks. All of these trials have minority representation.

MISSISSIPPI HEART STUDY

Mr. Stokes: What progress do you have to report with regard to the Mississippi Heart Study?

Dr. Lenfant: We have been working with the NIH Office of Research on Minority Health and three institutions in the Jackson, MS area (University of Mississippi Medical Center, Jackson State University, and Tougaloo College) to identify scientific priorities and implementation steps for an expansion of the ongoing Jackson component of the Atherosclerosis Risk in Communities (ARIC) study. We envision such a study, if successful in its planning and pilot phases, to become a community study in a predominantly African-American cohort similar to the Framingham Heart Study. Areas of scientific priority include: 1) studies of high rates of complications from hypertension in African-Americans, including stroke, renovascular disease, and congestive heart failure; 2) expanded studies of genetic factors related to cardiovascular disease in African-Americans; and 3) examination of cardiovascular disease and its risk factors in younger middle age (35-44) and older (70 and above) adults, to complement study subjects in the ongoing Jackson ARIC cohort.

RISK FACTORS

Mr. Stokes: It appears that most of the advances in cardiovascular diseases have been in the area of risk factor reduction. Yet, it is thought that risk factors account for only 50 percent of heart attacks. Would you elaborate on this assessment?

Dr. Lenfant: The 50 percent estimate is derived from statistical approaches that relate levels of risk factors in a population to occurrence of new heart attacks in that population. Unfortunately, we probably do not know all the risk factors, since it is clear that many people who are free of standard risk factors such as hypertension, hypercholesterolemia, smoking, diabetes, and family history still suffer heart attacks. Increased understanding of the biology of heart disease is helping to identify newer risk factors that may be responsible for heart attacks in people with widespread but asymptomatic atherosclerosis, or so-called "subclinical" disease. State-of-the-art measures of subclinical disease, now permit us to examine inflammatory and hemostatic factors that may be responsible for causing acute events, as well as genetic factors that may promote or retard this process. Since more than half of all heart disease deaths continue to occur outside the hospital, and are thus inaccessible to advances in acute medical treatment, risk factor identification and management before overt clinical symptoms occur are essential to continuing the impressive declines in morbidity and mortality from heart disease.

SMOKING AND OVERWEIGHT

Mr. Stokes: Smoking and overweight are major risk factors for heart attack, stroke, and, many other cardiovascular diseases. Yet, today, more of our youth are choosing to smoke and far too many people continue to lead a sedentary life style. Their life style choices dramatically increase their risk for cardiovascular disease, and worse premature death. Doctor, do you think that as a society that we are becoming complacent about heart disease, and if so, can you explain this false sense of security?

Dr. Lenfant: I do not think that society is becoming complacent about heart disease. Everywhere you turn there are magazine articles and television shows that focus on lower fat diets, weight control, exercise, and smoking cessation. Our citizens know these behavioral factors are important. The problem is that behavior change is not easy. People's habits are very hard to change. Brief changes toward more healthful behaviors are often followed by relapses back to the unhealthful practices. Not only do people have to be motivated and have the appropriate knowledge to engage in healthful behaviors, but society has to support healthful behaviors by offering healthful food, providing environments that promote physical activity, restricting use of tobacco products, and portraying role models engaging in healthful behaviors. When we become a society that provides an overall healthful physical and social environment, we will have come a long way toward preventing risk factors for cardiovascular disease.

MAJOR OPPORTUNITIES

Mr. Stokes: What major opportunities in heart disease research, research training, and outreach are on the horizon, and which of these will the FY 1998 budget allow the Institute to exploit?

Dr. Lenfant: Major opportunities in heart disease research include: identification of factors responsible for causing atherosclerotic lesions to rupture and produce heart attack and stroke, including processes related to inflammation and blood clotting; development of tests to identify unstable atherosclerotic lesions before they rupture; development and evaluation of screening tests for asymptomatic atherosclerotic disease to permit targeting of preventive efforts; identification of children at high risk of developing atherosclerosis based on non-invasive tests of cardiovascular structure and function; and identification of genes that interact with environmental and other risk factors to produce high risk of cardiovascular disease, or that are protective against cardiovascular disease. In addition, there are opportunities for expansion of efforts to understand heart disease risk factors in minorities. The FY 1998 President's Budget will allow progress in each of these areas.

In the area of intervention studies, the Institute has several clinical trials on treatment of coronary heart disease designed and ready to begin, and several intervention studies on prevention of cardiovascular disease under development that could be implemented in 1998. Because the epidemic of obesity in the United States is worsening, has an adverse impact on several cardiovascular risk factors especially among minorities, and is so difficult to treat once established, the Institute is developing a research program on prevention aimed at children or young adults. As our knowledge of both lifestyle and genetic factors in the causation of high blood pressure increases, there will be a need to further test the ability to reduce the incidence of this very common risk factor, especially in children and in broad population groups in the community.

ASTHMA

Mr. Stokes: As you know, minorities and children suffer disproportionately from asthma as compared to the general population. What can you tell us about the research that is underway and planned with regard to furthering our understanding of the relationship between respiratory viral infections and the development of asthma in young children?

Dr. Lenfant: A major issue in childhood asthma relates to the role of infections in the development and persistence of asthma. Recent epidemiologic studies have suggested that viral respiratory infections and exposure to allergens are the most important risk factors early in life that may lead to wheezing, prolonged alterations in airway function, and the development of persistent asthma. Since most children who develop asthma tend to be allergic and have a history of early respiratory infections, an interplay between respiratory infections and allergens may operate in the development of persistent asthma. On the other hand, it has been suggested recently that childhood tuberculosis and certain respiratory viral infections may actually protect against asthma and allergic disease. Differing exposures, their timing, and their frequency seem to be important in determining the role of infections either as protagonists or protectors in the onset and persistence of asthma.

To address these important issues, the NHLBI plans to announce programs to stimulate studies of the cellular and molecular mechanisms by which respiratory pathogens, including viruses, trigger or protect from the development and/or exacerbation of childhood asthma. These studies on the role of respiratory infections in the development of asthma may also shed light on whether respiratory infections have different consequences, depending on whether they occur early or late in life.

Mr. Stokes: Why is this research so vital?

Dr. Lenfant: This research is vital because asthma is a disease that often starts early in life, is not fatal if properly treated, but may require a lifetime of care. However, important clues into exactly what causes the disease are still missing. These studies should help to define the mechanisms by which both allergen exposure and viral infections produce changes in the structure and function of the lungs with lifelong consequences. This should lead to novel preventive and therapeutic strategies.

Mr. Stokes: It appears that African Americans and Hispanics also have a more severe form of asthma as compared to the rest of the population. Do we know why, and if not, what major research activities are underway to examine this relationship?

Dr. Lenfant: African Americans have a threefold and Puerto Rican Hispanics have a fourfold higher risk of dying from asthma than whites. African Americans also have higher hospitalization rates, indicating more severe disease. The reasons for these higher rates are complex and include a variety of risk factors such as environmental exposures, genetic inheritance, access to appropriate medical care, cultural health beliefs, and socioeconomic status. Current research is investigating how the complex interaction between environmental exposures, such as allergens and smoking, contributes to the severity levels of asthma in African Americans and whites. We support genetics studies that explore whether different racial or ethnic groups have different genes that control disease severity as well as variations in response to medications. The NHLBI Asthma Clinical Research Network evaluates new treatments as well as optimal ways to use existing treatments and has expanded minority recruitment by adding a clinical center in Harlem that serves a predominantly minority population. Several NHLBI supported studies are evaluating innovative educational programs to identify and overcome barriers to adequate asthma management in African Americans and Hispanics. These programs will help find ways to decrease the frequency and severity of asthma attacks among disadvantaged populations.

Future research activities will examine the role of risk factors specific to Hispanic populations. These studies will provide a complete picture of the factors associated with different types of asthma among Hispanics compared to other ethnic groups. Biologic, immunologic, clinical, and socio-cultural factors will be described in an effort to see which factors, or which combination of factors are the most important reasons for increasing asthma severity. This, in turn, will lead to more effective preventive educational and therapeutic interventions.

Mr. Stokes: Last year, you highlighted some of the studies underway in the area

of genetics to identify genes which seem to control susceptibility to asthma. What can you report to the Committee with regard to advances in this area of research?

Dr. Lenfant: Last year, I mentioned a search to identify all the genes that confer susceptibility to asthma. This multicenter study, called the Collaborative Study on the Genetics of Asthma, has collected the largest, most ethnically diverse, and best characterized sample of asthma families that exist to date. Early findings from these studies confirm that multiple genes may be involved in asthma and that they may vary between ethnic/racial groups. Examination of certain candidate genes support the concept that the pathophysiology of asthma may involve genetically determined changes in inflammatory and immune pathways. While this represents an important first step to dissecting the complex genetic relationships underlying susceptibility to asthma, a formidable task lies ahead to delineate the specific genes responsible for asthma that are suggested by these initial linked regions. The investigation of these genetic mechanisms should ultimately lead to a better understanding of the primary defect(s) in asthma, as well as to new and /or improved therapeutic and preventive measures.

GENDER DIFFERENCES

Mr. Stokes: Heart attack, stroke, and other cardiovascular diseases have remained the number one killer in the United States. To what extent are there gender differences in how the disease presents itself and the treatment provided by their health care providers?

Dr. Lenfant: The first form of coronary heart disease is most likely to be angina pectoris (chest pain) in women, and a heart attack, often a sudden death, in men. There are more visits to physicians' offices for cardiovascular diseases in women than men, and more cardiovascular surgery is performed on men (2.7 million in 1994) than women (1.9 million).

Mr. Stokes: What is the extent of the problem among men and women?

Dr. Lenfant: The rate at which heart attacks occur increases with age and is appreciably greater in men than women. Under age 65, there are an estimated 140,000 heart attacks per year in women and 550,000 in men. Over age 65 there are about 350,000 attacks in women 450,000 in men. Survival of a first or recurrent attack is about 65 percent, but it is a little worse for women than men. Serious manifestations of coronary disease are infrequent in premenopausal but not postmenopausal women. The incidence of stroke and congestive heart failure is greater in men than women. Survival after stroke and congestive heart failure is worse in men than in women. For congestive heart failure, survival is 25 percent for men and 38 percent in women after five years.

Morbidity and mortality risks of most cardiovascular diseases are greater in men than women, but because there are more older women than older men, women with these diseases comprise a larger share of the nation's cardiovascular disease burden. The total number of persons living with cardiovascular disease is 30 million women and

27 million men. There are about the same numbers of hospitalizations for cardiovascular disease each year in men and women. There are more deaths from these diseases per year in women, 495,000, than men, 450,000.

MINORITY HEALTH

Mr. Stokes: What major programs funded by your Institute are specifically designed to help reduce heart disease risk factors and to encourage healthy behaviors in minorities?

Dr. Lenfant: The Institute has several health education activities as part of its national education efforts to help reduce cardiovascular risk factors in minority populations. For example, the NHLBI has funded 11 state health departments in the southeastern U.S. with high stroke death rates. A large number of African Americans reside in these states. The objective of the projects were to implement health education activities to prevent and control risk factors of cardiovascular disease (CVD).

Another activity is the National Physicians' Network, a group of physicians and other health professionals who provide care to African Americans. This group has agreed to work with the NHLBI to conduct professional education training programs as well as community education programs in African American communities. Members of the Association of Black Cardiologists and the National Medical Association are the key participants in these activities.

The NHLBI has developed professional education and public education materials to help facilitate the professional education training and community outreach activities to reduce CVD risk factors and to encourage the adoption of healthy-heart behaviors. The NHLBI has also developed an extensive public education campaign targeting African Americans. A series of 39 one-minute radio programs were developed on issues of particular interest to African American audiences as part of NHLBI's "HealthBeat Radio Network." "HealthBeat" is distributed to more than 900 radio stations across the U.S.

For Latinos, the NHLBI has implemented the most comprehensive model program to increase awareness and knowledge about CVD prevention and to promote heart-healthy lifestyles among Latinos in the Washington D.C. Metropolitan area. The outreach program *NHLBI's Salud para su Corazón* (Health for your Heart) program has developed several products: A set of eight, easy-to-read, bilingual brochures on heart health issues such as preventing and controlling high blood pressure, cutting down on salt/sodium, learning your cholesterol number, lowering your blood cholesterol, watching your weight, cutting down on fat, staying active and kicking the smoking habit. In addition, the program has develop a bilingual recipe book and several media products including radio, TV, and newspaper pieces. The educational materials and products produced by the program will be used to expedite education activities in Latino communities across the Nation and to answer a variety of consumer requests.

In addition, NHLBI has an extensive research program on American Indians to

quantify epidemiologic risk and to develop CVD intervention strategies to prevent and control risk factors in this population. The Strong Heart Study and the Obesity Prevention in American Indians (PATHWAYS) programs are milestone efforts to profile risk and to design appropriate interventions for American Indians.

FUNDING FOR HEART DISEASE RESEARCH

Mr. Stokes: It appears that in constant dollars, the NIH budget grew nearly 36 percent between 1986 and 1996. In constant dollars, what was the growth in the Institute's total budget during this 10-year period, and what was it for heart disease and each of the other major disease components of the Institute's portfolio during this period?

Dr. Lenfant: In constant dollars, the NHLBI budget increased approximately 6.6 percent between 1986 and 1996. During this same period, the NHLBI Heart Program decreased by 5.5 percent, the Lung Program increased 30.6 percent, and the Blood Program increased 22.7 percent. There are a number of factors that contributed to this difference in the percent change in constant dollars between the Heart, Lung, and Blood Programs since 1986. First, special emphasis areas may affect the distribution of funding increases from year to year. For example, the AIDS budget increased 275 percent between 1986 and 1996 and approximately 96 percent of the AIDS extramural budget is funded from Lung and Blood Programs. In addition, a major factor in funding decisions and the allocation of resources between NHLBI programs is the relative scientific merit of the grant applications submitted to the Institute by investigators each year. The NHLBI attempts to fund grants of similar scientific merit in each of the three research programs, therefore, if a program receives a greater number of applications with high scientific merit scores this would have a major impact on the program distribution. Finally, I want to emphasize that research in one area often produces findings that are relevant to diseases with the purview of another program component. The benefits obtained from research frequently cross both organizational and scientific boundaries.

NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM

Mr. Stokes: Hypertension is the most critical stroke risk factor and is a leading cause of heart attack. The Institute is well known for its National High Blood Pressure Education Program. I think that Program began about 25 years ago. That was nearly a quarter of a century ago. Can you briefly highlight the major achievements that we have made in hypertension as a result of this long-term investment?

Dr. Lenfant: Since its inception in 1972, the National High Blood Pressure Education Program (NHBPEP) has been associated with some remarkable public health changes. Age-adjusted stroke mortality has decreased by nearly 60 percent. Coronary heart disease mortality has decreased by 53 percent. These declines in death rates are real and seen in all sectors of society, African Americans and whites, men and women.

Those hypertensives aware of their condition have increased from 51 percent in 1972 to 84 percent today. Hypertension treatment rates have doubled and controlled rates have increased three fold since the program began. Today, 75 percent of all Americans have their blood pressure (BP) measured every 6 months. Twenty-five years ago, only half the population ever had their BP measured. Today, more than 90 percent of the population understand the relationship of high blood pressure to stroke and coronary heart disease. Twenty-five years ago only one-quarter of the population knew of this relationship. Since the NHBPEP began, every state health department has developed some form of a hypertension control program and many have now expanded these efforts to other cardiovascular disease control efforts. In addition, 2,000 community groups have included hypertension control programs as part of their mission.

Hypertension control programs have been integrated into worksite programs, church-based programs, and school and youth programs and are now seen at community and sporting events. Physicians now treat hypertension more aggressively and begin treating high blood pressure sooner. Average blood pressure levels for all Americans have declined within the last decade, this means that some hypertension has been prevented. Many more Americans are alive today because of increased awareness, treatment and control of hypertension. This program has served as the model for other national health education efforts. It has been adopted by other countries, who have also experienced the declines in stroke and coronary heart disease mortality.

Mr. Stokes: What was the extent of hypertension at the time the Program was initiated, and what is the current situation?

Dr. Lenfant: At the time the NHBPEP began, 36 percent of adults in the U.S. had high blood pressure; today this number is 20 percent. At the time the Program began, only 51 percent of individuals with high blood pressure knew that they had high blood pressure. Today, 84 percent of hypertensives are aware that they have high blood pressure; moreover, 55 percent are being treated and have gotten their blood pressure levels under control.

RESEARCHERS

Mr. Stokes: What is the Institute doing to foster and strengthen the research capabilities of minority researchers and HBCUs in areas relevant to cardiovascular, pulmonary, and hematologic research?

Dr. Lenfant: The Institute has had a long standing commitment to improve and bolster the research capabilities of minority researchers. Since 1988, the Institute has supported the Minority Investigator Research Supplement program and last year awarded supplemental funds to support over 140 minority individuals. In addition, we support a career development award aimed at developing the research skills of faculty members at minority institutions, such as HBCUs, as well as minority faculty members at non-minority institutions. To interest minority students in research, the Institute supports the Short-Term training for Minority Students Program which provides

minority undergraduate and health professional students with short research training experiences.

Just recently within the last year, the Institute and the Office of Research on Minority Health collaborated to established the HBCU Research Scientist Award program. This program is intended to assist HBCUs to strengthen and augment their research capabilities through the recruitment of an established research scientist to the HBCU. This scientist, through support under the HBCU Research Scientist Award program, will strengthen the resources available for the conduct of research at the HBCU. Awards have been made to six different HBCUs and include Howard University, Meharry Medical College, Morehouse School of Medicine, Texas Southern University, Florida A&M University and North Carolina Central University. I am confident that as a result of this program, these HBCUs will be able to establish a greater research focus and increase the number of minority investigators involved in research.

INFANTS

Mr. Stokes: According to the budget submission, congenital heart disease is among the leading causes of death in children under the age of one. What do we know about how congenital heart defects develop?

Dr. Lenfant: With the advent of the powerful tools of molecular biology and molecular genetics, investigators have been able to study development of the heart in animal models at a time when the heart is no larger than a period on a printed page. At present we have about 55 grants, three program projects and three Specialized Centers of Research all studying various aspects of heart development. We have learned that genes expressed in the very early embryo in the hours before the heart begins to develop can determine certain forms of congenital cardiovascular malformations. A large number of other genes are required for normal development of both structure and function of the heart and some of these have now been identified.

Knowledge gained to date has enabled pediatric cardiologists to reorganize the classification of congenital heart disease in terms of embryologic development. In some cases, they have been able to identify a position on a chromosome associated with the human disease. This type of information is making it possible to screen families at risk for congenital heart defects and to provide more informative counseling. Gene therapy for these diseases is in the distant future. In the meantime, we can approach prevention by identifying environmental factors which may cause disease. To this end, we have initiated a grant program to study the roles of micro nutrients such as vitamin A and folic acid in the normal development of the heart and in perturbations of development resulting from excesses or inadequacies of micro nutrients in the maternal diet. Clearly more work remains to be done, but we are pleased to report that research in this difficult area is moving forward at a reasonable pace.

Mr. Stokes: How much is included in the FY 1998 budget request to study this problem and how does it compare to the current funding level?

Dr. Lenfant: The FY 1998 NHLBI budget includes an estimate of $18,850,000 for research on congenital heart disease. This is an increase of approximately 2.4 percent over the FY 1997 estimate of $18,400,000.

ORGAN DAMAGE

Mr. Stokes: High blood pressure is a leading cause of heart attack, congestive heart failure, and kidney failure. I have heard reports indicating that there may be susceptibility to organ damage that is associated with high blood pressure. What can you tell us about this relationship?

Dr. Lenfant: A vexing issue facing clinicians who treat hypertensive patients is that individuals with similar blood pressure levels often have different profiles with respect to the course of the disease and the extent of damage to crucial organs such as the heart, the kidney, and the blood vessels in the brain. The most serious problems that occur with high blood pressure are a result of damage to target organs. For example, an important but yet unanswered question about high blood pressure is why some hypertensives develop end stage renal disease while others develop stroke or heart failure or no major complications at all. New avenues for answering this question are now possible because evidence is emerging that genetic variations can increase or reduce susceptibility to the target organ damage that occurs with high blood pressure. Identification of genes that confer susceptibility to or protection from the complications of hypertension may lead to the development of new treatment and preventive strategies.

Epidemiological, familial, and animal studies strongly suggest that heritable factors play a significant role in determining which organ is susceptible to damage from high blood pressure. Two initial studies by groups at the Medical College of Wisconsin and the Brigham and Women's Hospital in Boston have clearly shown a genetic component involved in the development of kidney disease and stroke in hypertensive animal models. Therefore, a key area for research that should be encouraged is to determine why some individuals have greater organ damage brought on by high blood pressure than others. Importantly, the genes that predispose to susceptibility to target organ damage appear to be separate from those heritable factors that lead to the development of high blood pressure. It is possible to speculate that within a decade, clinicians may be able to use genetic data of the type just described to identify patients at risk for the complications of high blood pressure and initiate appropriate, complication-specific therapy.

HYPERTENSION AND CHILDREN

Mr. Stokes: It is thought that an estimated 50 million Americans age 6 and older suffer from high blood pressure. What is the extent of the problem in our youth, and have we unraveled the cause in this young age group?

Dr. Lenfant: There is no single agreed-upon definition of hypertension in

children. The 1996 Task Force Report on High Blood Pressure in Children and Adolescents defines hypertension in children and adolescents as an average blood pressure (BP) greater than or equal to the 95th percentile for age and sex measured on at least three separate occasions. By this definition 5 percent of all children and adolescents in the U.S. can be considered to have hypertension.

The causes of elevated BP in children are not well understood. Hypertension in some children may be a sign of an underlying disease (such as kidney disease), which is called secondary hypertension. In other cases elevated BP may represent the early onset of essential hypertension, which begins to emerge in later childhood and adolescence but which may have roots in higher than average BP in early life. Obesity is a major contributor to higher BP levels among children. In addition, there is evidence that low levels of physical activity and high sodium intake are associated with higher BP levels.

DIET AND BLOOD PRESSURE

Mr. Stokes: Earlier this year, the Institute reported the results of a study showing that a special diet can lower elevated blood pressure. Can you tell us more about this research?

Dr. Lenfant: The study was called Dietary Approaches to Stop Hypertension (DASH), which compared the effects of three dietary patterns on blood pressure in adults age 22 years and older who had high normal blood pressure or Stage 1 (mild) hypertension. The study found that a diet low in fat and high in fruits, vegetables, and low-fat dairy foods significantly and quickly lowered blood pressure by 5.5 points for systolic blood pressure and 3.0 points for diastolic blood pressure. For participants who had Stage 1 (mild) hypertension, the blood pressure lowering was double, similar to a level that a drug may achieve. The blood pressure reduction occurred without changes in other diet-related factors known to lower blood pressure, such as weight or intakes of sodium and alcohol, and was observed after only two weeks.

The study was conducted in 459 men and women, 60 percent of whom were African Americans. The diets were followed for 8 weeks. All meals and snacks were given to the participants who came to the research center to consume at least one meal per week day and took home meals and snacks needed until the next day or for the weekend. The diet was low in fat and included 9-10 servings of fruits and vegetables per day and 2-3 servings of low-fat dairy foods. Cereals, grains, legumes, nuts, and meat, poultry, and fish comprised the majority of other types of food provided. The foods are commonly available and no specialty foods were used. This diet potentially offers an additional nutritional approach to prevent and treat high blood pressure.

SLEEP DISORDERS

Mr. Stokes: Sleep apnea is one of the most common yet, most undiagnosed sleep disorders and is prevalent among African American men. What is the extent of

this problem in the United States?

Dr. Lenfant: Recent results from epidemiological studies supported by the Institute (NHLBI) have now clearly demonstrated that sleep apnea and accompanying daytime sleepiness is very common in the general population; with a prevalence of about 4 percent of the middle-aged adults and 25 percent of the elderly in this country. In addition, a recently published NHLBI sponsored study of genetic/familial sleep apnea has provided new evidence indicating that the prevalence in young African Americans is approximately twice that of Caucasians in the same age group. Preliminary findings from another NHBLI supported study also suggest that the prevalence of sleep apnea in elderly African Americans may be twice that of elderly Caucasians. Together these findings suggest a disproportionate risk of sleep apnea exists for African Americans. Further research is needed on ethnicity and age to confirm these findings, and to help target medical strategies which offset associated risks including systemic hypertension, cardiovascular disease, and ischemic stroke in these populations. The Institute has a particular interest in receiving applications for genetic epidemiological research on the relationship between sleep apnea and cardiovascular disease in African Americans.

Mr. Stokes: Can you tell us what the institute is doing to address this problem. What research is underway in this area?

Dr. Lenfant: The National Heart, Lung, and Blood Institute (NHLBI) sponsors a comprehensive sleep apnea research program that includes basic research to understand fundamental mechanisms of how breathing is controlled and why breathing stops during sleep apnea; patient-oriented research to improve the treatment of sleep apnea and the management of associated risks such as high blood pressure; and applied/behavioral research to determine how sleep apnea is detrimental to productivity and the quality of life with the goal of developing strategies to prevent and manage these impairments effectively. This is a multidisciplinary program encompassing sleep apnea studies in neuroscience, genetics, physiology, behavioral science, and epidemiology across all ages, genders and ethnic groups.

The ongoing, multi-center NHLBI Sleep Heart Health Study is an epidemiological investigation to explore the relationship between sleep apnea and high blood pressure and determine the population subgroups at greatest risk according to age, gender, and ethnicity. A sizable African American population is included in this study. The NHLBI Specialized Centers of Research (SCOR) Program in Cardiopulmonary Disorders During Sleep integrates basic and clinical research on the effects of sleep apnea on breathing, cardiovascular function, behavior, and cognitive function in order to facilitate the translation of scientific advances into strategies for the treatment and prevention of sleep disorders. Projects in this program are developing new diagnostic tools and investigating how the control of blood pressure is changed by sleep apnea. Finally, the NHLBI implemented a new program in FY 1996 to study the molecular biology and genetics of sleep and sleep disorders, which will also address this problem.

ISCHEMIC HEART DISEASE

Mr. Stokes: With regard to ischemic heart disease in African Americans, can you bring the committee up-to-date on the Institute's Collaborative Projects in Minority Health and Specialized Centers of Research?

Dr. Lenfant: The Institute currently supports two Specialized Centers of Research in Ischemic Heart Disease in Blacks. One such Center is located at Boston University and is studying blood vessel function and dysfunction relevant to cardiovascular disease in blacks. The other Center is located at the University of Texas Southwestern Medical Center in Dallas, Texas. This research center is attempting to understand the reasons for the excess morbidity and mortality from ischemic heart disease in blacks with diabetes. Additionally, the Collaborative Projects in Minority Health Program supports a group of three grants at the Allegheny University of the Health Sciences (formerly the Medical College of Pennsylvania) which investigate the role of increased insulin resistance and hyperinsulinemia in increased cardiovascular risk observed in African Americans. These projects use a well characterized multi-generational cohort of families and offer a unique ability for investigation in persons prior to development of disease as well as investigations of patients with documented heart disease. Through such efforts we hope to better understand and ultimately improve treatment of ischemic heart disease in blacks.

MINORITY REPRESENTATION IN RESEARCH AND RESEARCH TRAINING

Mr. Stokes: African Americans and other minorities continue to suffer disproportionally from a tremendous number of diseases and disorders--from cancer to cardiovascular diseases to AIDS to diabetes. It is thought that fuller participation of minorities in the biomedical research enterprise--from the conduct of research to research training to research decision making on the front-end, would help to dramatically close this long standing gap in health status. What is the Institute doing to increase minority representation in basic research and research training?

Dr. Lenfant: The NHLBI supports a variety of research training and career development programs to increase the number of underrepresented minority scientists involved in research. These programs target minority individuals from the high school level through the postdoctoral and investigator levels, and include the following: Research Supplements Program for Underrepresented Minorities, NHLBI Minority Institutional Faculty Mentored Research Scientist Development Award, NHLBI Mentored Research Scientist Development Award for Minority Faculty, Minority Institutional Research Training Program, and Short-Term Training for Minority Students Program. During the past year, the NHLBI implemented two new programs to encourage underrepresented minority populations to pursue careers in biomedical and behavioral research--the Biomedical Research Training Program for Underrepresented Minorities and the Historically Black Colleges and Universities (HBCU) Research Scientist Award.

NHLBI actively recruits underrepresented minorities by announcing its Research Supplements Program for Underrepresented Minorities in journals that are widely read in the minority science community. They include the Journal for Minority Medical Students, the Journal of the Student National Medical Association, the American Biology Teacher, Winds of Change, the Journal of the National Medical Association, the Journal of College Science Teaching, and The Science Teacher. Last September, the NHLBI held an innovative workshop to facilitate partnerships between minority-serving and nonminority institutions and to make them aware of the programs at the NIH available to support the partnership activities. Guidance developed as a result of this workshop is expected to enhance NIH-wide efforts to increase participation of minorities in biomedical research.

CLINICAL RESEARCH

Mr. Stokes: Clinical research is a critical component of the research continuum, as its findings are one of the most important means of determining what constitutes appropriate medical care or treatment. What portion of the Institute's budget is invested in clinical research and how does this compare with the basic research investment?

Dr. Lenfant: About 65 percent of the Institute's budget is considered basic research. On the other hand, approximately 25 percent is considered clinical research.

Mr. Stokes: Obviously, the relevance of clinical research findings are greatly enhanced when the study group is representative of the nation's population as a whole. What is the Institute doing to ensure minority representation in its clinical research programs?

Dr. Lenfant: In fiscal year 1990, well before the passage of the NIH Revitalization Act that mandated inclusion of women and minorities in all clinical studies, the NHLBI established and implemented procedures to ensure representation of minorities and women in all clinical studies. Our staff reviews research applications for appropriate representation of minorities. The NHLBI initial standard for evaluation is the composition of the population of the United States; by this standard, the total minority component should be approximately 20 percent. Any concerns the HSA has regarding the proposed study population are discussed with senior staff and possible solutions are then discussed with the applicant. The application is not presented to the National Heart, Lung, and Blood Advisory Council until all issues related to study population composition are resolved.

The NHLBI has developed a central database system for all study population data in order to evaluate trends and ensure compliance. Analysis of the aggregate data from the 459 NHLBI clinical studies active in fiscal year 1996 shows that 23.3 percent of study enrollees were minorities; they included significant numbers of Blacks, Hispanics, Native Americans/Alaska Native, Pacific Islanders, and Asians.

KNOWLEDGE "BOTTLENECK"

Mr. Stokes: The Director of NIEHS, Dr. Olden, spoke about a "bottleneck" when referring to the problems of identifying environmental hazards that contribute to human disease and illness. With regard to the diseases and disorders under the purview of your Institute, what are the most significant "bottlenecks in the Institute's knowledge base," and what are the health implications?

Dr. Lenfant: A perennial frustration has been our inability to understand the reasons for individual variations in the course and prognosis of disease. For example, we do not know why some sickle cell disease patients experience severe complications, while others have mild disease; why some persons with high blood pressure are especially prone to stroke, others to heart attack, and still others to kidney failure; why some, but not all, smokers die prematurely because of their habit. Fortunately, the new tools of molecular medicine and genetics now offer unprecedented opportunities for us to unravel these complex phenomena. Our ability to understand the genetic factors that make individuals susceptible to disease or, conversely, protect them from disease, will open the door to a host of new approaches to prevention and therapy and ultimately enable us to target our efforts where the payoff is likely to be highest.

For many years we have been well aware that there is much the individual can do to reduce risk of developing coronary heart disease. Although our society has witnessed beneficial trends with respect to some of these risk factors, there is still considerable room for improvement. A vexing problem is that many individuals do not make the necessary lifestyle changes until after a heart attack has occurred and irreversible damage is done. Now on the horizon are new techniques that may enable us to detect disease at very early stages, before conventional signs or symptoms become apparent. Such approaches will provide a powerful and cost-effective enhancement to our ability to prevent disease.

Mr. Stokes: To what extent will the FY 1997 Appropriations allow the Institute to address the "knowledge bottleneck" problem, and how much is included in the FY 1998 budget request for such?

Dr. Lenfant: The FY 1997 and FY 1998 budgets allow us to address a number of these issues. For example, recently the Institute initiated a new centers program in the Molecular Genetics of Hypertension. The centers will identify and map the genes responsible for hypertension in humans and animals, and undertake mechanistic studies to clarify the role of specific genetic mutations on the development and maintenance of high blood pressure. The Institute also has new initiatives to stimulate research in several areas, including: studies to advance our understanding of the molecular and genetic basis of sleep and sleep disorders; research on molecular medicine and atherosclerosis; research on the cellular and molecular mechanisms of primary pulmonary hypertension; studies on molecular biological approaches to cerebrovascular disease; and studies using cellular and molecular approaches on the development and progression of pulmonary lymphangioleiomyomatosis (LAM);

Mr. Stokes: In your professional judgement, is the proposed funding level adequate to address the "knowledge bottleneck," explain?

Dr. Lenfant: Yes, funding at the FY 1998 request level will allow the NHLBI to continue to support ongoing research to address the "knowledge bottleneck" as well as begin new research.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists cloning of adult sheep, and Oregon researchers cloning monkeys. These articles expressed excitement with regard to opportunities for advances in medical treatments, and concern with regard to misuse of the technology and the possibility of human cloning. As a leading researcher and as an Institute director, what is your professional opinion of this technology?

Dr. Lenfant: The science of cloning and tissue regeneration is still in the early stages. However, these experiments have broken important barriers in that they succeeded in returning mature, developed tissue cells, which ordinarily would not be capable of generating other types of cells, to a simpler, less-developed state in which they could generate all other types of cells--organ, blood, nerve, bone, and others--found in an embryo. They provide an important bridge to tissue regeneration and other biomedical technologies that are likely to be in high demand in the near future.

Mr. Stokes: This is another area where we must now be certain to examine and address the ethical, legal, and social issues of research on the front-end. As a leading researcher and as an Institute Director, what is your professional opinion of this technology and what are your most serious concerns?

Dr. Lenfant: These experiments in animal cloning raise a host of ethical concerns that the NHLBI shares regarding the possibility of misuse of technology and human cloning. To what extent cloning can or should be used, and under what circumstances, are just a few of the serious and complex issues that deserve thorough examination by the National Bioethics Advisory Commission.

Mr. Stokes: With regard to the diseases and disorders studied by your Institute, what are the most significant benefits that the cloning technology would yield?

Dr. Lenfant: Cloning technology brings the possibility of enormous benefits in the areas of tissue regeneration, large-scale production of protein-based drugs, and research on genetic diseases. A central problem of heart failure, which is affecting more Americans every year, is that adult heart muscle cells, once lost to disease, die and the other heart cells are too mature to grow replacements. Technology developed through these cloning experiments could one day enable us to take a sample of heart cells and return them to an earlier state in which they can grow new heart muscle tissue, or to

take some of the patient's nonheart cells and induce them to become heart cells. Such regeneration techniques, which we might never achieve without cloning research, could be used to repair and save a patient's failing heart, thereby eliminating the need for heart transplantation. Moreover, because the cells came from the patient, they would not create an immune reaction once they were treated and implanted in the patient's heart. Many advanced protein and hormone medications, such as the clot-buster drugs used to treat heart attacks, growth factors, and blood clotting factors needed by hemophilia patients, are now being produced through gene biotechnology in yeast, but production is low and the drugs are very expensive. New methods include inserting a human gene for these proteins into large animals such as sheep that can produce the drugs at higher volume in their milk. Cloning these sheep could boost production and lower the cost of these drugs considerably. Finally, cloning would enable researchers to create reproducible strains of experimental animals that have been given a key human gene. Cloning would allow more exact studies of diseases caused by a small gene defect or a combination of several gene defects. These techniques would cut the time needed to study and develop effective therapies for diseases such as cystic fibrosis, hemophilia, and congenital heart defects.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are currently underway, and what are the expected benefits to be achieved from this investment?

Dr. Lenfant: The following illustrates the range of important scientific questions that are currently being addressed in clinical trials:

- Implantable Total Artificial Hearts (TAH): Phased Readiness Testing. This study will establish the reliability, performance, and manufacturability of electrically powered, implantable TAH systems. The overall goal of the is to develop systems that are tether-free, have the potential for a 5-year life with high reliability, and provide a good quality of life for the recipient at a reasonable cost.

- Primary Prevention of Obesity in American Indians. This trial will evaluate an intervention to prevent schoolchildren from developing obesity, a serious health problem in the American Indian population.

- Antiarrhythmic Verses Implantable Defibrillator (AVID). This study will answer the important and timely question of whether the use of an implantable cardiac defibrillator will save the lives of patients who have been resuscitated from sudden cardiac arrest.

- Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). This study is comparing the effectiveness of new antihypertensive

medications versus more established drugs, a question of considerable economic and public health importance. It will also assess the benefits to be realized from lowering elevated serum cholesterol in elderly men and women.

- Beta-Blocker Evaluation in Survival Trial (BEST). This trial will determine whether the addition of beta-blockers to standard therapy reduces deaths in patients with moderate to severe congestive heart failure.

- Enhancing Recovery in Coronary Heart Disease (ENRICHD) Patients. This study will provide new information on the effects of educational and psychosocially supportive strategies designed to assist recovery from heart attack among patients at high risk, defined as those who are depressed, socially isolated, and/or who perceive themselves as lacking support from family and friends.

- Childhood Asthma Management Program (CAMP). This trial in young children with asthma will determine whether an intervention program can significantly improve growth of lung function, decrease utilization of health care resources and limitation of activity, and enhance school performance and attendance.

- Adult Hydroxyurea Patient Follow-up Study. This follow-up of adult patients who participated in the Multicenter Study of Hydroxyurea in Sickle Cell Disease will ascertain the long-term effects, if any, of hydroxyurea usage in this patient population.

- Human Umbilical Cord Blood Stem and Progenitor Cells. Collection, Storage, and Transplantation. This study will examine the efficacy and safety of cord blood stem cell transplants, a promising alternative to bone marrow transplantation.

Mr. Stokes: What major clinical trials that are ready to be implemented will the FY 1998 budget request allow the Institute to pursue, and what are the expected benefits to be achieved?

Dr. Lenfant: The NHLBI is poised to implement the following trials:

- Pediatric Arrhythmia Registry of Radiofrequency (RF) Catheter Ablation. This trial will establish a registry of young patients who have undergone cardiac catheterization procedures for the ablation of an arrhythmia using RF energy to determine long-term safety and efficacy of this procedure.

- Revascularization Prior to Noncardiac Surgery. This trial will determine the efficacy of preoperative revascularization in preventing deaths and heart attacks in coronary patients undergoing noncardiac surgery.

- Magnesium in Coronaries (MAGIC). This trial will establish whether early treatment of acute heart attack patients with intravenous magnesium--a simple,

inexpensive approach--reduces mortality.

- Clinical Network for the Treatment of Sickle Cell Disease and Thalassemia. This initiative would establish a network of clinical enters with sickle cell disease and Colley's anemia patients to assess effectiveness of specific interventions in reducing morbidity and mortality. The network would enhance progress in moving effective therapies, e.g., fetal mehoglobin enhancing agents, gene therapy, and iron chelation, from the laboratory to the patient bedside through rapid and systematic collaborative testing in phase III clinical trials.

CLINICAL TRIALS IN WOMEN

Ms. DeLauro: Heart attack, stroke, and other cardiovascular diseases remain the number one killer of American women. I know that your institute has done some research on hormone replacement therapy, but how many other clinical trials are you supporting that address women's health issues? How many exclusively focus on women?

Dr. Lenfant: Women are included in all sixty active NHLBI-supported clinical trials, and are the exclusive focus of 11 trials. In addition to the widely cited Postmenopausal Estrogen/Progestin Interventions (PEPI), several other trials are examining various questions about hormone replacement therapy (HRT). The multicenter Women's Angiographic Vitamin and Estrogen (WAVE) trial is assessing the effects of HRT and antioxidant treatment on coronary plaques in postmenopausal women who have angiographically documented coronary heart disease; the Estrogen Replacement and Atherosclerosis Trial (ERA) and the Women's Estrogen/Progestin Lipid Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) are comparing the effects of various HRT regimens on atherosclerosis. Two other trials are assessing, respectively, the role of HRT in preventing graft occlusion in women who have undergone bypass surgery and the potential use of HRT to control unstable angina.

In addition to the abovementioned WAVE trial, the NHLBI supports two other major studies of antioxidant vitamins. The Trial of Antioxidant Therapy of CVD in Women is assessing the preventive effects of vitamin C, vitamin E, and beta-carotene in women who have a history of CVD; the Women's Health Study is testing the effects of vitamin E, as well as low-dose aspirin, on prevention of heart attack, stroke, and cardiovascular disease (CVD) death in healthy postmenopausal women. In the area of smoking cessation, the Women's Health Initiative for Nonsmoking (WINS) is evaluating a relapse prevention program designed for women with coronary heart disease. The Institute also supports an evaluation of asthma treatment in pregnancy, and a trial of the efficacy of HIV immune globulin in preventing maternal-fetal transmission of HIV infection.

PRIMARY PULMONARY HYPERTENSION

Ms. DeLauro: One of the greatest assets of research done at the NIH is the

agency's ability to not just focus basic biomedical research on diseases afflicting the majority, but also to help alleviate the suffering of a few. Primary pulmonary hypertension, or PPH, is a rare disorder that affects less than 200,000 Americans. Yet, it is extremely deadly and affects mostly young people. What has NIH been doing to help develop a treatment and a cure for this disease?

Dr. Lenfant: Primary pulmonary hypertension (PPH) is indeed a very rare disease, estimated to affect between 1,000 and 3,000 individuals in the United States, but it has a devastating effect on patients, often young women, and their families. The Institute supports several research projects designed to investigate the functions of pulmonary vascular cells, how they are regulated, and what goes wrong in individuals afflicted with PPH. A potentially important advance this year is the localization of the gene for the inherited or familial form of PPH to a particular human chromosome. This finding will greatly facilitate the identification of the gene. Other major research directions concern understanding the relationship between inflammation and injury to pulmonary vascular cells and research on gene delivery to pulmonary vessels, two areas that may lead to new therapeutic approaches. The Institute recently released a program announcement "Cellular and Molecular Mechanisms of Primary Pulmonary Hypertension" that seeks to stimulate and encourage new investigations into the cellular and molecular events underlying the disease. We are also sponsoring a major conference this year that will bring together experts from throughout this country for an in depth discussion of PPH. We are anticipating new ideas and research directions will emerge from this meeting.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

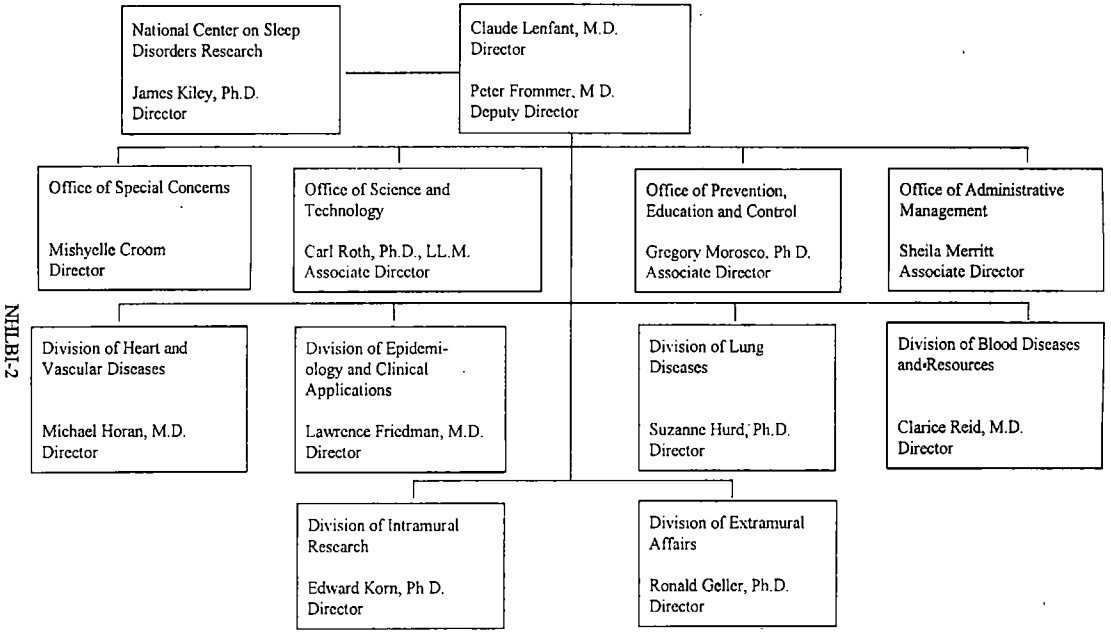
NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

FY 1998 Budget	Page No.
Organization chart	2
Appropriation language	3
Amounts available for obligation	4
Justification	5
Budget mechanism table	19
Budget authority by activity	20
Summary of changes	21
Budget authority by object	23
Administrative costs	24
Significant items in House and Senate Appropriations Committee reports	25
Authorizing legislation	34
Appropriation history	35
Detail of full-time-equivalent employment (FTE)	36
Detail of positions	37

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute
Organization Structure



NHLBI-2

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to cardiovascular, lung, and blood diseases, and blood and blood products, [$1,433,001,000] *$1,404,770,000*.

(Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, 1997, P.L. 104-208)

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$1,355,866,000	$1,433,001,000	$1,404,770,000
Rescission in accordance with P.L. 104-134	-872,000	0	0
Reduction in accordance with P.L. 104-208	0	-472,000	0
Subtotal, Adjusted Appropriation	1,354,994,000	1,432,529,000	1,404,770,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority	-3,506,000	0	0
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	-57,925,000	-61,577,000	0
Subtotal, adjusted budget authority	1,293,563,000	1,370,952,000	1,404,770,000
Unobligated balance, lapsing	-18,000	0	0
Total obligations	1,293,545,000	1,370,952,000	1,404,770,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1996 - $3,851,000; FY 1997 - $7,000,000; FY 1998 - $7,000,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research:
FY 1998 - $62,419,000

Note: Excludes $638,000 in FY 1996 and $650,000 in FY 1997 for royalties.

Justification

National Heart, Lung, and Blood Institute

Authorizing Legislation: Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act, as amended. Reauthorizing legislation will be proposed.

Budget Authority:

FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
834	$1,293,563,000	834	$1,370,952,000	834	$1,404,770,000	--	+$33,818,000

This document provides justification for the FY 1998 non-AIDS activities of the National Heart, Lung, and Blood Institute (NHLBI). Justification of NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

Introduction

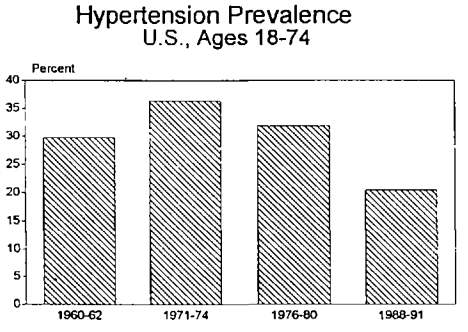
The NHLBI is now on the threshold of its 50th anniversary, a time when all Americans can celebrate the great advances in public health made possible in part through their longstanding investment in biomedical research The NHLBI supports outstanding and innovative basic and clinical research, provides the latest findings to physicians and the public, and trains the investigators who will become the 21st century's biomedical pioneers. Its leadership has also stimulated many private organizations and research institutions to contribute to this effort. As a result, substantial gains in the diagnosis, treatment, and prevention of heart, lung, and blood diseases have saved millions of lives and improved the quality of many more.

The 50th anniversary also challenges us to look ahead, because our work is far from complete. Fortunately, today we have more opportunities than ever to translate current knowledge into better strategies for care. New biomedical technologies are advancing our understanding of disease and health in ways that even a few years ago would have been impossible. The material that follows illustrates the considerable progress that has been made and the new directions that the Institute plans to pursue in the near future.

Story of Discovery: Hypertension

For the better part of this century, hypertension—high blood pressure—has been recognized as a serious threat to health. Actuarial data reported in the 1920s systematically documented that elevated blood pressure levels shortened life. In the late 1940s, the Framingham Heart Study began collecting longitudinal health information to improve understanding of risk factors for cardiovascular disease (CVD). Its findings, and those of subsequent studies, firmly established that hypertension strongly predisposes its victims to heart attack, stroke, and other life-threatening and disabling conditions.

When landmark research clearly demonstrated the benefits of lowering elevated blood pressure, the Institute launched the National High Blood Pressure Education Program to get the message out to health-care providers and the general public. The program has proved to be one of the most successful public health campaigns of this century The proportion of hypertensives aware of their condition has increased from 51 percent to 84 percent, the proportion on drug treatment has more than doubled, and the rate of adequate blood pressure control has increased from 16 percent to 55 percent. Even more remarkably, the estimated prevalence of hypertension has decreased from 58 million to 50 million Americans, which suggests that the disease is being prevented. Concurrently, death rates from stroke have declined about 60 percent, and deaths rates from coronary heart disease have been halved, undoubtedly due, to a considerable degree, to progress in control of hypertension



Source. National Center for Health Statistics.

The successes of this national effort have extended far beyond hypertension, because they formed a model for other research and dissemination activities to reduce CVD risk. Although recognition of high blood cholesterol as a treatable CVD risk factor developed a decade or more after that of hypertension, it involved the same scientific process of measuring risk factors—observing disease associations in large populations, establishing the biological plausibility of such observations, rigorously testing interventions in clinical trials, and moving the new knowledge into practice. Much evidence confirms that cholesterol education is having an impact.

These accomplishments are formidable, but the public health burden of CVD risk factors—particularly hypertension—is still substantial. Today, nearly 50 million Americans (25 percent of the adult population) have hypertension, defined as blood pressures of 140/90 mm Hg

or more, or are taking antihypertensive medications. Although drug treatment attenuates considerably the consequences of hypertension, it does not eliminate them entirely. For instance, new findings from the Framingham Heart Study have established that hypertension is the most important risk factor for congestive heart failure (CHF), a disease that has reached epidemic proportions in recent years. Scientists report that high blood pressure accounts for nearly 60 percent of CHF in women and almost 40 percent in men. Men were twice as likely, and women three times as likely, to develop CHF if they had hypertension. A separate study of elderly persons found a strong relationship between impaired cognitive function and blood pressure measured 20 years previously. After age and education were taken into account, every 10 mm Hg increment in systolic blood pressure was associated with a 7 percent excess risk of having intermediate cognitive function, and a 9 percent excess risk of poor cognitive function in old age.

Fortunately, research offers promising new opportunities to gain control over this "silent killer." For instance, two recent studies show that lifestyle changes can substantially reduce blood pressure in adults and can keep older patients off antihypertensive medication. The Dietary Approaches to Stop Hypertension (DASH) trial found that a diet low in fat and high in vegetables, fruits, fiber, and low-fat dietary products significantly and quickly lowered blood pressure. In individuals diagnosed with low levels of Stage 1 hypertension, the diet produced blood pressure reductions similar to drug therapy. The reductions, observed in men and women, whites and minorities alike, occurred within 2 weeks after participants began the diet The Trial of Nonpharmacologic Interventions in the Elderly (TONE) found that weight loss and reduction of dietary sodium safely reduced the need for high blood pressure drugs in older patients, while keeping their blood pressure under control. These findings have important implications for preventing hypertension from developing in healthy individuals and reducing treatment costs of patients with established hypertension.

Advances in molecular genetics and the potential to determine the genes responsible for complex traits open a new avenue for hypertension research. Understanding the genetic alterations that contribute to hypertension would be instrumental in determining the mechanisms behind this complex and prevalent disease. For the near term, this area provides great potential for advancing knowledge that will enhance our understanding of the causes and progression of hypertension, provide more targeted prevention, and improve diagnostic tests and therapeutic interventions. For the future, it may suggest a cure.

Story of Discovery. Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), a classification that includes chronic bronchitis and emphysema, is now the fourth most common cause of death in this country. About 15 million Americans currently have COPD, which makes breathing more and more difficult over the years as it slowly deteriorates lung tissue and constricts the airways. An estimated 95,000 people die each year from the disease or its complications. Of greatest concern is the fact that deaths from COPD have more than doubled in the last 20 years among both whites and blacks and in older age groups. Although white men still have the highest overall COPD mortality, their age-adjusted death rate appears to be leveling off while COPD deaths are still increasing among women and blacks.

Each year, COPD sends more than half a million people to the hospital and more than 14 million people to their physicians, costing the U.S. health care system several billion dollars. As yet, the only available treatments for patients in the end stages of COPD are supportive care—oxygen therapy, bronchodilator drugs, nutritional supplements, and exercise rehabilitation, all of which serve to maintain the patient's strength—rather than cure the disease. But researchers supported by the NHLBI have made significant strides in understanding the basic causes and mechanisms of this disease.

Population studies of the past 40 years have identified smoking as the number one risk factor for COPD—about 80 percent of patients are current or former smokers. While this strongly suggests that COPD is largely preventable—by not smoking—until recently it was not definitely known whether smoking cessation could help patients who were already in the early stages of the disease. Recent findings from the NHLBI-supported Lung Health Study, which examined the effects of smoking cessation on lung function, indicate that quitting smoking is the single most effective way to slow the progress of COPD. Smokers who began the study with mild COPD and quit smoking slowed the course of the disease, and after several years of not smoking, their age-related declines in lung function were almost as small as those of people who had never smoked. The study results also indicate that women are more strongly affected by smoking than men, suffering greater declines in lung function but also benefitting more noticeably from smoking cessation In both men and women, smoking cessation was more effective in slowing the long-term damage from COPD than any of the bronchodilator drugs used to relieve symptoms

Although smoking is the major risk factor for COPD, a small but important subset of patients who do not smoke develop clinical signs of COPD in their thirties or forties, 10 or 20 years earlier than most COPD patients. In the 1980s, genetic researchers discovered that these patients have an inherited defect in the gene for alpha-1-antitrypsin (AAT). AAT prevents the breakdown of elastin, a key lung protein that, as its name suggests, helps the tiny air sacs in the lungs expand and contract over and over again without collapsing. Progress in DNA technology and gene research may soon point the way to effective therapies such as replacement of the defective AAT gene or drug-based management of the delicate balance between elastin and the enzyme that breaks it down.

Advances in genetic and molecular research are expected ultimately to yield answers to the question of individual susceptibility to COPD, and facilitate development of innovative therapies for protecting the lungs or for stimulating repair of damaged tissue. In the near term, two new NHLBI efforts are expected to have a large impact on COPD treatment. The first is the National Lung Health Education Program, an outgrowth of the Lung Health Study. Its objective is to raise awareness among health-care professionals and the general public that lung health can be assessed by simple and inexpensive measurements of lung function; that reduced lung function, especially in smokers, predicts disability and premature death from many chronic lung and cardiovascular diseases; and that early detection of reduced lung function can prevent disease, facilitate effective treatment, and enhance quality of life.

The second project is a large-scale clinical trial, cosponsored by the Health Care Financing Administration, to test the efficacy of lung volume reduction surgery (LVRS) versus standard

nonsurgical medical treatment for advanced emphysema. The LVRS operation consists of removing part of the rigid, damaged lung tissue to allow the remaining functional lung more room to expand in the chest cavity. Which patients, if any, may benefit from this procedure will be determined by the trial.

Story of Discovery: Sickle Cell Disease

Sickle cell disease (SCD), the most common serious inherited blood disorder in the United States, is a problem of significant medical, psychological, social, and economic importance, particularly among the black population. The NIH-focused efforts on SCD research began about 25 years ago. Since that time, significant progress has been made, as evidenced by the fact that patients, who used to die in their 20s, are living into their 50s today. In fact, in 1977 SCD became the first human disease whose abnormality was shown to be at the level of a single nucleotide mutation in the gene. Breakthroughs that rapidly followed introduced gene mapping into prenatal diagnosis, and made it possible to use placental tissue rather than fetal blood samples for this purpose. This substantially increased the safety of prenatal diagnosis for SCD, and rapidly led to the application of molecular genetics for prenatal diagnosis of other inherited diseases.

Meanwhile, clinical research demonstrated the value of prophylactic penicillin in preventing major infections in infants and young children. Before that discovery, approximately 30 percent of SCD deaths occurred before 5 years of age, most in children under the age of 2, and the majority were due to pneumococcal infection. This work also provided the rationale for recommending that all newborns be screened for SCD. Infants at risk could then be referred for comprehensive care, and prophylactic penicillin therapy could be given by 3 months of age. This is now the standard of care. A followup study determined that this therapy can safely be discontinued in most children at 5 years of age, thereby decreasing the risk of promoting drug-resistant infections in this vulnerable population.

In 1995, the first effective therapy for SCD was confirmed in a landmark clinical trial of treatment with hydroxyurea, a common chemotherapeutic agent. Its administration in severely affected adult SCD patients not only reduces the frequency of crises and their attendant hospitalizations, but also reduces episodes of acute chest syndrome, a pneumonia-like complication, and the need for blood transfusions. The safety of use of this agent in children is under investigation.

We see a new era of optimism for treating and, indeed, curing SCD, because we are on the threshold of moving molecular medicine even closer to the bedside. Bone marrow transplantation and gene therapy offer great hopes for a cure. Bone marrow transplantation has been successfully used by NHLBI-supported investigators in children with severe symptoms and advanced disease Among children who received the bone marrow of a matched sibling, 90 percent were still alive 2 years later, and 73 percent were free of SCD at that time. Gene therapy research is also advancing, raising the possibility of inserting normal genes for hemoglobin production into the bone marrow precursor or stem cells and thereby enabling the production of normal hemoglobin. This approach is receiving active attention by many researchers around the country.

Research Highlights and Plans

New Directions in Heart Failure Research

Heart failure is the final common pathway of most primary cardiovascular diseases, including coronary atherosclerosis, hypertension, cardiomyopathy, myocarditis, diabetic vasculopathy, and valvular and congenital heart malformations. Current treatments may slow the course of these primary diseases, but do not abolish them.

Research advances offer clues for innovative approaches to understand and treat heart failure. To illustrate, healthy heart muscle cells could be grafted into a failing heart to enhance its pumping ability. Although this notion was once thought speculative, recent studies in dogs indicate that grafted heart muscle cells are able to survive indefinitely and work in concert with existing heart cells. Other preliminary work in rats found that grafted skeletal muscle cells "healed" areas of the heart muscle that had been damaged by heart attack. Further research should resolve pressing issues, such as which cell types best suit the needs of injured or weakened hearts

By adulthood, heart muscle cells have lost the capacity to reproduce, that is, to replace old or damaged cells. Several studies suggest that restoration of this capacity could serve as potential therapy for a variety of conditions, including acute heart attack and heart failure To accomplish this, scientists must define and remove the blocks to cell division and develop strategies to enhance function, so that optimal benefits can be realized. Such work may lead ultimately to practical alternatives to current methods of treatment such as heart transplantation.

A third area of considerable promise involves understanding the processes that lead to loss of heart muscle cells, a phenomenon that initiates and/or aggravates heart failure and leads to premature death. Recent studies indicate that apoptosis—"programmed death" of cells—is accelerated in heart failure. The stimuli for this process, its influence on neighboring cells and organ function, and the long-term effects of irrevocable cell loss have yet to be established in animal models or humans However, breakthroughs over the last several years identified the genetic factors that regulate apoptosis, and animal experiments indicate these gene pathways may be responsible for heart muscle cell following coronary obstructions or heart attack. Elucidation of the role of apoptosis could significantly influence ideas about the mechanisms of heart failure and open new routes to prevention and therapy.

Viral Infection and Restenosis After Coronary Angioplasty

Recent epidemiologic and pathologic evidence suggests that viral agents such as cytomegalovirus (CMV), a member of the herpes virus group, may play an important role in the initiation and progression of atherosclerosis. For example, NHLBI intramural researchers have found evidence of a potential role of CMV in the development of restenosis (renarrowing of the arteries) following coronary angioplasty. CMV DNA has been found in restenosis lesions, and its effects on a critical protein appear to contribute to abnormal thickening of the blood vessel wall lining, thereby leading to restenosis. Other studies have shown that prior infection with CMV is a strong independent risk factor for restenosis This finding raises tantalizing new questions about the role

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of infectious agents in restenosis, provides for powerful risk assessment approaches for patients undergoing angioplasty, and suggests that innovative therapeutic approaches (e.g., antiviral vaccines) may be feasible to reduce the risk of restenosis.

Cardiac Magnetic Resonance Imaging

In the past year NHLBI intramural scientists began an extensive project on the development of magnetic resonance imaging (MRI) for evaluation of the cardiovascular system. This program is devoted to the development of a noninvasive cardiovascular examination to reduce the risk and cost associated with other, more invasive, cardiac evaluation procedures such as coronary catheterization and trans-esophageal ultrasound. These studies have shown that MRI can provide an unprecedented high resolution view of the human heart in several seconds. The motion of the myocardium can be followed on a millimeter scale. Information on the regional function, proximal coronary vessel anatomy and blood flow, and perfusion of the myocardium has been obtained using hardware and software developed by a multidisciplinary team. Data collected through a complete contraction cycle in animal model systems have provided new information on the function of the heart as well as insight into clinical conditions. Methods have also been developed to evaluate the dynamics of blood flow in the major peripheral vessels of humans. These results demonstrate that MRI is a powerful new tool in the study of heart and cardiovascular disease. MRI shows great promise as a noninvasive diagnostic tool capable of replacing more costly and invasive approaches.

Childhood Asthma: Opportunities for Prevention Research

Accumulating evidence suggests that intrauterine, environmental (e.g., exposure to tobacco smoke, viral infections, and allergens), genetic, and developmental factors interact to influence not only the onset of childhood asthma but also its course and long-term consequences. Critical opportunities now exist for extending basic and clinical research findings into prevention strategies for this multifactorial disease.

Genetics of Asthma. Allergy and bronchial hyperresponsiveness are two important risk factors associated with the development of asthma. Individual genes affecting bronchial hyperresponsiveness in inbred mouse strains have been identified, and studies of human families have reported evidence for specific genes influencing asthma or allergy. Currently, a genome-wide search is under way to identify all the genes that confer susceptibility to asthma, with the NHLBI-supported Mammalian Genotyping Service involved in defining the regions of chromosomes that appear to influence the complex varieties of asthma typically seen in humans. Early findings from these studies confirm that multiple genes may be involved in asthma and that they may vary between ethnic/racial groups.

The opportunity now exists to complete the next crucial phase, namely, to narrow down the search to the precise genes that confer risk of asthma. Such genes will need to be examined carefully to determine their molecular, cellular, and physiological effects and to uncover genetic variations that may be involved in the development of asthma and allergy. With this information in hand, the specific gene–environment interactions that lead to asthma, and the mechanism by

which such interactions lead to the different clinical manifestations of asthma, can be explored. Identification of the genes responsible for asthma and allergy should lead to a better understanding of the primary defects in asthma and to the development of effective preventive strategies focused on individuals who are at risk but have not yet acquired the disease. Such progress will, in turn, open up new approaches for primary prevention—a considerable advance over current practice, which is limited to preventing symptoms in patients who have already developed the illness.

Inflammation and Asthma. Respiratory viral infections have long been thought to be a cause of asthma, particularly in young children. Studies indicate that different patterns of wheezing exist in young children with viral illness, and that respiratory viruses may actually protect some of them from developing asthma under some circumstances, while contributing to its exacerbations in others. In this view, asthma may be a result of an altered developmental pattern of both the lungs and the immune system. Additional studies have suggested that the initial encounter with antigen may be a critical point, and that this may occur in infancy.

Employing modern techniques of cell and molecular biology, we now have the opportunity to determine the molecular mechanisms by which viruses, individually and in combination with antigens, regulate such processes as airway inflammation and hyperresponsiveness. Transgenic animal models will provide exciting opportunities for examination of individual factors in the complex disease process, for determining just how altered cell biology relates to airway inflammation and asthma, and for identifying if there is a "pre-asthma" state in which exposures bring about asthma in genetically predisposed subjects. These studies should lead to the clarification of the basic mechanisms in asthma, potentially leading to new prevention strategies and therapeutic approaches.

Genetic Basis of Variability in Disease Complications

A vexing issue facing clinical medicine is that individuals with identical gene mutations or identical risk factor profiles vary with respect to the course of a disease and the extent of damage it causes. New avenues for answering this question are now possible because evidence is emerging that genetic variations can increase or reduce susceptibility to the target organ damage that occurs in many heart, lung, and blood diseases. Identification of susceptibility/protection genes would provide innovative approaches for the development of new treatment and prevention strategies, but this is a complicated task because it involves multiple genetic and environmental factors interacting in complex ways. However, resources (biological, informational, and technological) from the Human Genome Project, advances in analytical and statistical approaches, and new study designs now make it feasible to look for genetic factors that are responsible for the variability in damage caused by these diseases.

One area of considerable public health importance and great opportunity is the search for genetic factors that influence development of cardiovascular diseases. Enormous effort has been expended to understand the genetic and environmental etiology of CVD. Advances in molecular genetics make it possible not only to look for genetic factors that cause CVD, but also to discern genetic factors that prevent or retard progression of these chronic diseases. Just as susceptibility

genes may predispose many to disease, "protective" genes may confer a resistance to these disorders, even in the presence of a hostile environment. Identification of specific "protective" markers may not only improve understanding of the etiology of CVD, but also assist in the development of new drugs or other therapies to treat those who have the diseases.

Genetic Factors Affecting Response to Drug Therapy

Substantial variation exists in individual responses to drugs used to treat most diseases. Environmental factors and patient compliance account for some of these differences and have been the subject of extensive studies. Familial patterns of response to drug or nutrient administration have been observed, but until recently genetic factors contributing to variation in response received little attention. New advances in molecular genetics make it possible to look for genetic factors that influence response to a drug and to discern the reasons for these differences.

A better understanding of the genetic influence on the response to drug therapy for heart, lung, and blood disorders will lead to more effective treatments. When a genetic variant has a severe impact on drug response, or where the impact is modest but drug therapeutic levels are close to toxic levels, practical tests may be developed that will significantly reduce serious adverse drug effects. Such studies may also make possible a reduction in the costs of treatment by allowing less expensive drugs to be used when newer, more costly drugs will not offer significant additional advantages.

New Candidate Gene for Treatment of Premature Cardiovascular Disease

Much work is being done to identify genes that could be used to treat patients who have atherosclerosis or are at risk of developing it. NHLBI intramural researchers have identified a potential candidate for gene-mediated treatment of atherosclerosis: lecithin cholesterol acyltransferase (LCAT), an enzyme that chemically modifies cholesterol. LCAT transgenic rabbits (experimental animals that have abnormally high levels of LCAT) have a 7-fold increase in plasma levels of high density lipoproteins - the "good" cholesterol (HDL) and a marked reduction of low density lipoproteins - the "bad" cholesterol (LDL). When compared with control rabbits, LCAT transgenic rabbits placed on a high cholesterol diet were dramatically protected against the development of diet-induced atherosclerosis. To date, overexpression of the LCAT gene appears to offer more effective protection against diet-induced atherosclerosis than that of any gene reported. Scientists ultimately hope to extend this protection to humans through gene therapy or the development of drugs that increase plasma levels of LCAT.

Stem Cell Transplantation

The ability to transfer new genetic material into the bone marrow hematopoietic stem cell (the cell type responsible for producing a wide variety of important cells such as red blood cells, platelets, and lymphocytes and other white blood cells) could allow cures of a wide variety of congenital genetic disorders such as sickle cell disease, Gaucher Disease, and immunodeficiency syndromes,

as well as acquired disorders such as AIDS and certain forms of cancer. The Institute is moving rapidly to advance the state of stem cell transplantation science.

One area of great progress is the use of stem cells collected after birth from discarded umbilical cord blood. The Institute has initiated a 5-year, multicenter study of human umbilical cord blood transplants from unrelated, newborn donors. Scientists believe that transplants using stem cells from umbilical cord blood may be more effective than those from bone marrow. For bone marrow transplant candidates, particularly ethnic and racial minorities, the system for finding a matching unrelated donor can be a long, frustrating, and ultimately unsuccessful process. In contrast, research indicates that transplants using stem cells from umbilical cord blood appear to require a less precise match, and cause fewer severe reactions in recipients. Cord blood from related donors has been successfully transplanted in children worldwide. Cord blood from unrelated donors was successfully transplanted in 51 children in two previous studies. Researchers hope the further study will provide the necessary answers to scientific and ethical questions yet to be resolved.

The NHLBI has also supported a groundbreaking demonstration of the potential benefits of in utero stem cell transplantation—providing healthy unmatched marrow stem cells to an unborn child diagnosed (using chorionic villus biopsy) at 10 weeks gestation with a fatal inherited immune deficiency disease. This study demonstrates that the fetus can be successfully treated before birth, without the need for bone marrow ablative procedures or tissue matching and without rejection of the donor cells. These and other studies are expected to provide a powerful new approach to treat and cure diseases.

Perhaps the most exciting possibility for stem cell transplantation is gene therapy. NHLBI researchers are improving methods to purify stem cells and alter them genetically before transplanting them into patients with genetic disorders. The transplanted cells will supply a correct copy of the defective gene and may be the key to treating hereditary blood disorders such as sickle cell anemia, Cooley's anemia, and hemophilia.

NHLBI intramural investigators have made steady progress and have now completed pioneering clinical genetic marking trials, which have demonstrated successful gene transfer to primitive stem cells and long-term genetic modification of cells representative of all stem cell-derived lineages. The existence of stem cells in the peripheral blood, especially after treatment with cytokines, allows collection of greater numbers of stem cells for genetic modification than can be obtained from bone marrow, and may be especially applicable to treatment of congenital genetic disorders. NHLBI investigators have shown in clinical trials of cancer, Gaucher disease, and Fanconi anemia that these peripheral blood stem cells can be used as targets for genetic therapy. Further progress in the laboratory and in the intramural nonhuman primate transplantation facility has demonstrated better ways to make stem cells susceptible to gene transfer, elucidated problems and possible solutions to keeping stem cells alive during gene transduction procedures occurring outside the body, and examined the problem of immune responses against new gene products introduced into

stem cells and lymphocytes. The next several years will allow testing of these advances in new clinical trials, and further progress towards the goal of successful genetic therapy.

Sleep Disorders

The field of sleep research has witnessed a virtual explosion of interest and activity during the past several years. Unprecedented opportunities now exist to understand the normal functions of sleep; improve diagnosis, treatment, and prevention of sleep disorders; identify the effects of sleep loss on the waking function of the brain and other organs; and develop new ways to manage the sleep–wake function to optimize health and performance in the modern 24-hour society.

Recent advances in the cellular and molecular neurobiology of sleep offer particular hope for significant progress in understanding the basic mechanisms of sleep, sleepiness, sleep debt and their consequences. These approaches can expand, integrate with, and complement what has been learned about the regulation of sleep using traditional techniques. For example, genes have been identified that govern the biological "clocks" that regulate circadian rhythms. Although the propensity to sleep increases with duration of wakefulness, the timing, duration, and characteristics of sleep are strongly affected by the circadian pacemaker. Researchers can now explore the interaction between biological clocks and sleep–wake behavior, and thereby gain a more fundamental knowledge of sleep and its regulation in health and disease.

Lymphangioleiomyomatosis (LAM)

LAM is an uncommon disorder characterized by destruction of the lung; currently there is no effective therapy and the prognosis is poor. The abnormal smooth muscle proliferation associated with LAM is also characteristic of a number of other diseases (e.g., vascular restenosis, pulmonary hypertension), but the smooth muscle in these diseases may differ physiologically. In LAM, the abnormal and immature-appearing smooth muscle is characterized by the presence of tumor antigens similar to those found in the cancer melanoma. The fact that LAM is predominantly a disease of women in their childbearing years suggests a hormonal component in its initiation and progression. Scientists in the NHLBI intramural program have initiated a study of LAM to understand better the natural course and pathogenesis of the disease. Current studies are focused on determining the natural history and mechanisms of lung destruction in LAM; understanding the role of and rationale for hormonal therapies, and identifying their potential side effects (e.g. osteoporosis); and developing alternative therapies based on the unique presence of tumor antigens in the smooth muscle cells of LAM patients.

Innovations in Management and Administration

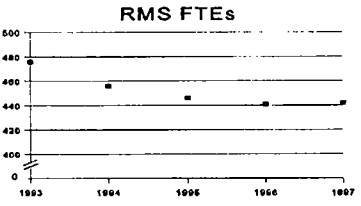
As an alternative to each organizational component developing its own capability to carry out certain functions, the Institute has taken a lead role at the National Institutes of Health in forming competitive service centers. These centers, which are located within an Institute, perform an administrative function for another NIH Institute, Division, or Office. The organization

purchasing the service can use its staff to perform other functions, thereby reducing its administrative cost. To date, the Institute has service centers in the areas of procurement, committee management, and technology transfer. In FY 1998, the Institute will continue to evaluate the way in which we plan and carry out our programmatic and business functions, while we provide proper stewardship over the resources entrusted to us.

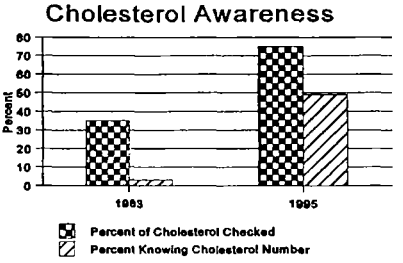
The Institute views the changes in administrative policies and procedures stimulated by the National Performance Review as positive. We have implemented numerous streamlining activities to simplify and expedite the review of grants and contracts. We have reorganized and increased utilization of teams for those tasks that can benefit from such an approach. We have delegated more authority to our managers and supervisors as they are delegated by NIH to us. We have increased our investment in information technology to reduce duplication of effort and expedite the analysis and transmission of data. We are implementing a new performance appraisal system that will reduce paperwork, while still providing appropriate feedback and recognition for our staff. We have simplified administrative procedures in property management, local travel, and messenger service. We continue to develop ideas for further change.

Education Programs

The Institute's highly effective public and professional education programs and information dissemination activities are funded in part from amounts made available to the Research Management and Support budget activity. However, with the rapid advances in information technology, the Institute is evaluating its efforts, and seeking a variety of new approaches to carry out its mandate, such as greater use of the World Wide Web.

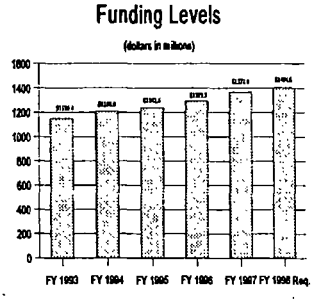


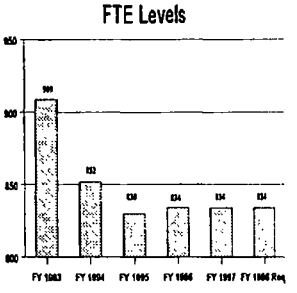
It is important to continue these programs since they are often the vehicle for translating the products resulting from our investments in research to improvements in public health. For example, the National Cholesterol Education Program, working with and through a variety of concerned organizations, has been very successful in its efforts to make the American public aware that blood cholesterol levels are a risk factor for heart disease. In 1983, 35 percent of the public had their cholesterol checked, and 3 percent knew their cholesterol number. In 1995, 75 percent had their cholesterol checked, and 49 percent knew their cholesterol number.



Budget Policy

The FY 1998 President's Budget request for the NHLBI is $1,404,770,000, excluding AIDS, an increase of $33,818,000, and 2.5 percent over the FY 1997 level. Included in this increase is $22,000,000 for the following NIH Special Emphasis Areas: (1) new approaches to the pathogenesis of disease; (2) new preventive strategies against disease; (3) therapeutics/drug development; and (4) genetic medicine.

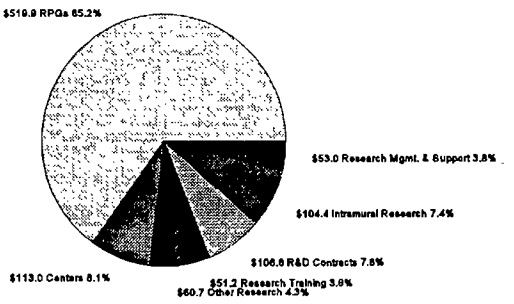




In the FY 1998 President's Budget request, the NHLBI would provide support for 709 competing research project grants (RPGs) and 3,026 total RPGs, an increase of 98 total RPGs over FY 1997. NIH policy links RPG average cost increases to total program budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for research project grants. In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs will increase by up to two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Products (GDP).

FY 1997 Request

(dollars in millions)



The President's Request also includes funds to support 78 research centers, 377 research career awards, 34 other research related awards, 42 cooperative clinical research grants, 189 research and development contracts, and 1,685 individual and institutional full-time-training positions. Also included in the President's Request is an increase in National Research Service Award stipend levels for trainees with up to two years experience.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	1,954	$621,028,000	1,975	$624,959,000	2,162	$671,806,000
Administrative supplementals	(79)	4,251,000	(80)	3,189,000	(80)	3,253,000
Competing:						
Renewal	261	89,298,000	330	117,120,000	289	103,655,000
New	366	86,231,000	464	113,097,000	416	104,622,000
Supplemental	4	1,208,000	5	1,584,000	4	1,400,000
Subtotal, competing	631	176,737,000	799	231,801,000	709	209,677,000
SBIR/STTR	142	25,404,000	154	30,215,000	155	31,203,000
Subtotal, RPGs	2,727	827,420,000	2,928	890,164,000	3,026	915,939,000
Research Centers						
Specialized/comprehensive	78	106,706,000	78	110,732,000	78	112,947,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research centers in minority institutions	0	0	0	0	0	0
Subtotal, Centers	78	106,706,000	78	110,732,000	78	112,947,000
Other Research						
Research careers	376	32,186,000	377	33,533,000	377	34,204,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	44	17,210,000	42	18,514,000	42	18,884,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	2,503,000	0	2,803,000	0	2,859,000
Other	17	3,107,000	34	4,687,000	34	4,781,000
Subtotal, Other Research	437	55,006,000	453	59,537,000	453	60,728,000
Total, Research Grants	3,242	989,132,000	3,459	1,060,433,000	3,557	1,089,614,000
Training	FTTPs		FTTPs		FTTPs	
Individual	248	7,267,000	248	7,367,000	248	7,514,000
Institutional	1,437	41,220,000	1,437	42,826,000	1,437	43,683,000
Total, Training	1,685	48,487,000	1,685	50,193,000	1,685	51,197,000
Research & development contracts	137	102,365,000	189	104,489,000	189	106,579,000
(SBIR/STTR)	(0)	(0)	(20)	(2,265,000)	(20)	(2,067,000)
	FTEs		FTEs		FTEs	
Intramural research	393	100,410,000	393	102,882,000	393	104,425,000
Research management and support	441	53,169,000	441	52,955,000	441	52,955,000
Cancer prevention & control	0	0	0	0	0	0
Construction	0	0	0	0	0	0
Total, NHLBI	834	1,293,563,000	834	1,370,952,000	834	1,404,770,000
(Clinical Trials)		(89,634,000)		(94,600,000)		(96,800,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Heart and vascular diseases program		690,597		722,014		741,175		19,161
Lung diseases program		239,854		251,589		258,280		6,691
Blood diseases and resources program		193,632		223,982		229,935		5,953
Center for sleep disorders research		15,883		17,530		18,000		470
Subtotal, Extramural research		1,139,966		1,215,115		1,247,390		32,275
Intramural research	393	100,410	393	102,882	393	104,425	0	1,543
Research management and support	441	53,169	441	52,955	441	52,955	0	0
Total obligations	834	1,293,545	834	1,370,952	834	1,404,770	0	33,818
Unobligated balance lapsing		18		0		0		0
Total, Budget Authority	834	1,293,563	834	1,370,952	834	1,404,770	0	33,818

Note: Includes 12 FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Summary of Changes

1997 Estimated budget authority		$1,370,952,000
1998 Estimated budget authority		1,404,770,000
Net change		33,818,000

	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$29,834,000		345,000
b. Annualization of January 1997 pay increase		29,834,000		238,000
c. January 1998 pay increase		29,834,000		627,000
d. Legislative proposal, 1.51% increase in the CSRS rate		5,671,000		86,000
e. Service and supply fund		8,500,000		220,000
f. Increased cost of laboratory supplies, materials, and other expenses		27,814,000		724,000
Subtotal				2,240,000
2. Research Management and Support:				
a. Within grade increase		30,872,000		438,000
b. Annualization of January 1997 pay increase		30,872,000		245,000
c. January 1998 pay increase		30,872,000		648,000
d. Legislative proposal, 1.51% increase in the CSRS rate		11,343,000		171,000
e. Service and supply fund		2,320,000		60,000
f. Increased cost of laboratory supplies, materials, and other expenses		7,198,000		187,000
Subtotal				1,749,000
Subtotal, Built-in				3,989,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute
Summary of Changes--continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	1,975	628,148,000	187	46,911,000
b. Competing	799	231,801,000	-90	-22,124,000
c. SBIR/STTR	154	30,215,000	1	988,000
Total	2,928	890,164,000	98	25,775,000
2. Centers	78	110,732,000	0	2,215,000
3. Other research	453	59,537,000	0	1,191,000
4. Research training	1,685	50,193,000	0	1,004,000
5. Research and development contracts	189	104,489,000	0	2,090,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes	393	100,382,000	0	-697,000
b. Special emphasis areas	0	2,500,000	0	0
Subtotal, intramural	393	102,882,000	0	-697,000
7. Research management and support	441	52,955,000	0	-1,749,000
Subtotal, program		1,370,952,000		29,829,000
Total changes				33,818,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Authority by Object

	FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	834	834	0
Full-time equivalent of overtime and holiday hours	3	3	0
Average ES salary	$120,400	$123,500	$3,100
Average GM/GS grade	10	10	0
Average GM/GS salary	$51,090	$52,520	$1,430
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$57,100	$58,700	$1,600
Average salary of ungraded positions	$48,350	$49,700	$1,350

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	35,540,000	36,931,000	$1,391,000
11.3	Other than Full-Time Permanent	7,971,000	8,272,000	301,000
11.5	Other Personnel Compensation	1,754,000	1,822,000	68,000
11.8	Special Personnel Services Payments	4,804,000	4,984,000	180,000
11.9	**Total Personnel Compensation**	**50,069,000**	**52,009,000**	**1,940,000**
12.0	Personnel Benefits	10,596,000	11,007,000	411,000
13.0	Benefits for Former Personnel	41,000	43,000	2,000
	Subtotal, Pay Costs	**60,706,000**	**63,059,000**	**2,353,000**
21.0	Travel & Transportation of Persons	953,000	927,000	-26,000
22.0	Transportation of Things	175,000	171,000	-4,000
23.1	Rental Payments to GSA	2,000	2,000	0
23.2	Rental Payments to Others	480,000	481,000	1,000
23.3	Communications, Utilities & Miscellaneous Charges	3,217,000	3,186,000	-31,000
24.0	Printing & Reproduction	738,000	686,000	-52,000
25.1	Consulting Services	681,000	640,000	-41,000
25.2	Other Services	3,768,000	3,666,000	-102,000
25.3	Purchase of Goods & Services from Government Accounts	71,197,000	70,734,000	-463,000
25.4	Operation & Maintenance of Facilities	1,988,000	1,997,000	9,000
25.5	Research & Development Contracts	91,092,000	93,107,000	2,015,000
25.6	Medical Care	6,275,000	6,240,000	-35,000
25.7	Operation & Maintenance of Equipment	2,006,000	2,008,000	2,000
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**177,007,000**	**178,392,000**	**1,385,000**
26.0	Supplies & Materials	10,228,000	10,263,000	35,000
31.0	Equipment	6,605,000	6,592,000	-13,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,110,626,000	1,140,811,000	30,185,000
42.0	Insurance Claims & Indemnities	215,000	200,000	-15,000
43.0	Interest & Dividends	0	0	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**1,310,246,000**	**1,341,711,000**	**31,465,000**
				0
	Total Direct Obligations	**1,370,952,000**	**1,404,770,000**	**33,818,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$35,540,000	$36,931,000	$1,391,000
Other Than Full-Time Permanent (11.3)	7,971,000	8,272,000	301,000
Other Personnel Compensation (11.5)	1,754,000	1,822,000	68,000
Special Personnel Services Payments (11.8)	4,804,000	4,984,000	180,000
Total Personnel Compensation (11.9)	**50,069,000**	**52,009,000**	**1,940,000**
Civilian Personnel Benefits (12.0)	10,596,000	11,007,000	411,000
Benefits to Former Personnel (13.0)	41,000	43,000	2,000
Subtotal, Pay Costs	**60,706,000**	**63,059,000**	**2,353,000**
Travel (21.0)	953,000	927,000	-26,000
Transportation of Things (22.0)	175,000	171,000	-4,000
Rental Payments to Others (23.2)	480,000	481,000	1,000
Communications, Utilities and Miscellaneous Charges (23.3)	3,217,000	3,186,000	-31,000
Printing and Reproduction (24.0)	738,000	686,000	-52,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	681,000	640,000	-41,000
Other Services (25.2)	3,768,000	3,666,000	-102,000
Purchases from Govt. Accounts (25.3)	52,176,000	51,638,000	-538,000
Operation & Maintenance of Facilities (25.4)	1,988,000	1,997,000	9,000
Operation & Maintenance of Equipment (25.7)	2,006,000	2,008,000	2,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**60,619,000**	**59,949,000**	**-670,000**
Supplies and Materials (26.0)	10,125,000	10,159,000	34,000
Subtotal, Non-Pay Costs	76,307,000	75,559,000	-748,000
Total, Administrative Costs	**137,013,000**	**138,618,000**	**1,605,000**

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Significant Items in House and Senate
Appropriations Committee Reports

1997 House Appropriations Committee Report language

Item

Cardiovascular disease - The House in its report 104-659, page 61 states that "The Committee recognizes the seriousness of heart attack, stroke and other cardiovascular diseases and is concerned that, despite progress, cardiovascular diseases have remained America's top killer of men and women since 1919 and a major cause of disability. The Committee believes that additional cardiovascular research is needed and encourages the Institute to enhance its research on cardiovascular diseases."

Action Taken or to be Taken - The Institute continues to support an innovative and expanding cardiovascular research program. Research initiatives planned in FY 1997 include: Specialized Centers of Research in Molecular Medicine and Atherosclerosis, Mitochondrial DNA Mutations in Heart, Lung, and Blood Diseases, Viruses in Restenosis and Atherosclerosis, and Development of New Gene Therapy Vectors and Delivery Systems for Small Business Technology Transfer and Small Business Innovation Research.

Item

Heart failure - The House in its report 104-659, page 61 states that " Heart failure kills more than 45,000 each year and is the leading cause of hospitalization for Americans age 65 and older. Because current treatment only slows the course of the underlying disease, the Committee encourages the Institute to conduct research in cellular and molecular techniques that offer promise for new methods to restore heart function."

Action Taken or to be Taken - In July 1995, the NHLBI issued a program announcement to encourage research on how the compensated, hypertrophied heart progresses to heart failure using molecular and cellular approaches. To date, the Institute has funded four applications submitted in response to this program announcement.

Item

Nutrient supplements - The House in its report 104-659, page 61 states that, "Elevated levels of homocysteine, an amino acid normally found in the body, appears to increase risk of heart attack, stroke, peripheral vascular disease and other cardiovascular diseases. The Committee encourages NHLBI to support research assessing the effects of folic acid, vitamin B6 and vitamin B12 in preventing cardiovascular diseases by reducing homocysteine levels."

Action Taken or to be Taken - The NHLBI has issued a Request for Applications (RFA) on homocysteinemia and atherosclerosis for grants to be awarded in FY 1997. In the last five years, a growing body of literature has related homocysteinemia to vascular disease and indicated that the relationship is independent of other risk factors. The RFA encourages research to understand the etiology of homocysteinemia and the pathogenesis of atherosclerosis and thrombosis associated with the condition.

Item

Asthma in Minorities - The House in its report 104-659, page 61 states that, "Children under the age of 18 and African Americans suffer disproportionately from asthma. Children have a 41 percent higher prevalence of asthma than the general population. African Americans up to age four and from ages 15 to 24 are six times more likely to die from asthma than their Caucasian counterparts. Intermediate findings of the NHLBI-sponsored study to develop, implement, and evaluate interventions to control asthma morbidity among African American and Hispanic children suggest that it is possible to develop a pattern of preventive and continuing care for populations which have traditionally been difficult to reach with preventive public health programs. The Committee urges the NHLBI to continue to make minority and children-related asthma research a high priority, and requests the Director to be prepared to provide an update on these efforts at next year's appropriations hearings."

Action Taken or to be Taken - The Institute supports basic, clinical, and demonstration and evaluation research to identify risk factors for asthma and asthma mortality and to promote effective management to reduce morbidity in high-risk populations. The NHLBI has also published "Asthma Management in Minority Children: Practical Insights for Clinicians, Researchers, and Public Health Planners."

Item

Asthma Management in Schools - The House in its report 104-659, page 61 states that, ". . . .The Committee encourages the development and evaluation of innovative model school programs to increase identification and appropriate referral of children with uncontrolled asthma, reduce exposure to known allergens and irritants, increase participation of students with asthma in all school activities, improve support to students for following their asthma management plans, and enhance communication between school and home."

Action Taken or to be Taken - Three contracts were awarded in FY 1995 to develop and evaluate model comprehensive programs for asthma management in schools. In FY 1996, the Institute developed and published a video and a pamphlet, "Asthma and Physical Activity in the School," to help school personnel encourage children with asthma to participate fully and safely in sports and physical activities.

Item

Hemophilia - The House in its report 104-659, page 62 states that, "Last year the Committee called upon NHLBI to strengthen its hemophilia research efforts in gene therapy and in seeking in a cure for this serious bleeding disorder. The Committee also called for a study of the scope of hemophilia vulnerability to blood contaminants and specifically Creuzfeldt-Jakob disease (CDJ). In light of the results of the Institute of Medicine study calling attention to the importance of research support to ensure a safe blood supply, the Committee encourages NHLBI to enhance its hemophilia research activities including the CDJ study. The Committee requests that NHLBI work collaboratively with CDC and FDA to address all hemophilia research, epidemiology, surveillance and patient outreach aspects necessary to ensure maximum safety and integrity of the U.S. blood supply."

Action Taken or to be Taken - The Institute has strengthened its hemophilia and hemophilia-related research in several areas. For example, it supports such activities as a new Specialized Centers of Research in Transfusion Biology and Medicine to improve the safety and efficacy of blood and blood components, and co-funded with the FDA and CDC a November 1996 workshop, Hemophilia 1996: Research for a Cure. The NHLBI participates with the CDC, the NIH Clinical Center, and the Armed Forces Blood Program and Resources Program in monthly conference calls, participated with the CDC in planning and designing epidemiological studies to determine if CJD is transmitted by blood, and participated in a November 1995 FDA meeting to plan a conference involving an International Working Group on Blood and CJD to be held early next year.

Item

Transfusion medicine - The House in its report 104-659, page 62 states that, ". . . .The Committee encourages the NHLBI to support research initiatives to improve the viability and function of transfused platelet. The Committee is pleased that the NHLBI is supporting the Viral Activation Transfusion Study (VATS) to determine if transfusion hastens the progression of HIV disease. The Committee also encourages the NHLBI to fund transfusion medicine initiatives to understand the basic aspects of immune responses following blood transfusion."

Action Taken or to be Taken - In 1996, the NHLBI sponsored a workshop on thrombopoietin (TPO), a platelet producing hormone. One of the centers supported under the Transfusion Biology and Medicine Centers program is focusing on studies to understand how blood transfusion affects the immune system of transfusion recipients.

Item

Cooley's anemia - The House in its report 104-659, page 62 states that, "The Committee continues to support the research efforts of NHLBI in the area of Cooley's anemia. . . . The Committee has learned that hormonal therapy as a medical treatment is becoming increasingly

necessary for patients who are now living through their teens. The Committee encourages the Institute convene a workshop of experts in the field to develop plans for research into the long term effects of this therapy."

Action Taken or to be Taken - In FY 1997, the NHLBI is planning a meeting on hormonal therapy for teenagers with Cooley's anemia to develop plans for research into the need for hormonal therapy and its long-term effects on patients with Cooley's anemia.

Item

National Center on Sleep Disorders Research - The House in its report 104-659, page 63 states that, "The Committee notes the continued development of the National Center on Sleep Disorders Research and the expansion of the Center's research portfolio. The Committee is pleased with demonstrated progress in the sleep disorders education campaign. The Committee recommends continued development of a plan for scientific collaboration among the National Center and other NIH Institutes through the implementation of the recently approved National Sleep Disorders Research Plan. The Committee encourages continued development of the National Center's research portfolio as outlined in the National Sleep Disorders Research Plan."

Action Taken or to be Taken - The NIH Director's Sleep Disorders Research Plan, prepared in collaboration with other NIH Institutes, is a major step toward a strong and dynamic NIH sleep research program. Under the auspices of the NCSDR, a wide variety of collaborative efforts are underway. These include: an NIH-wide solicitation of research on basic and clinical research on sleep and wakefulness, a jointly sponsored solicitation on the molecular biology and genetics of sleep disorders, and ongoing collaborations with the Department of Transportation.

Item

Sarcoidosis - The House in its report 104-659, page 63 states that, "Sarcoidosis is an inflammatory disease that can lead to scarring of the lung. Although the disease has been recognized for over 100 years, information on its incidence, prevalence risk factors, and natural history remains limited. Geographic and racial variations in the occurrence of sarcoidosis suggests that it may be caused by environmental factors or a combination of environmental factors and susceptible host. The Committee, therefore, encourages the Institute to explore environmental and genetic causes of sarcoidosis as an essential step toward identifying risk factors and improving treatment and prevention of the disease."

Action Taken or to be Taken - In FY 1995, contracts were awarded to ten clinical centers and one coordinating center for a case control etiologic study of sarcoidosis to determine the cause of sarcoidosis. A common research protocol has been developed and patient enrollment has begun.

Item

Primary pulmonary hypertension - The House in its report 104-659, page 63 states that, "Primary pulmonary hypertension (PPH) is a progressive, fatal disease affecting predominantly women--of

all ages and races-and involves deadly deterioration of the heart and lungs. The Committee encourages NHLBI to enhance its funding of PPH basic research, gene therapy, and clinical trials of promising pharmaceutical."

Action Taken or to be Taken - The NHLBI is releasing a program announcement in 1997 to stimulate basic studies of cellular and molecular mechanisms involved in development and pathogenesis of PPH. Currently, diagnosis of PPH is difficult. There is no cure, and treatment is limited.

Item

Clinical research - The House in its report 104-659, page 63 states that, "An impressive array of scientific opportunities in the areas of fibrotic lung disease, asthma, and lung development can be expected to lead to translation of basic science into clinical applications. The Committee recognizes the NHLBI has made significant contributions to clinical research through its Specialized Centers of Research programs. The Committee, therefore, encourages the NHLBI to continue its work in these areas."

Action Taken or to be Taken - In FY 1997, the NHLBI will initiate a multidisciplinary basic and clinical research program of Specialized Centers of Research in the pathobiology of fibrotic lung disease, pathobiology of lung development, and cellular and molecular mechanisms of asthma.

Item

Comprehensive Research - The House in its report 104-659, page 63, states that, "In its report accompanying the 1995 appropriations bill, the Committee encouraged the Director of the NHLBI to consider establishing a comprehensive research and demonstration center for heart, blood vessel, lung and blood diseases. The Committee requests an update from the Director regarding the status of this initiative."

Action Taken or to be Taken - The NHLBI has carefully considered the concept of a comprehensive centers program on heart, blood vessel, lung, and blood diseases, and has decided not to initiate such a program. The Institute experimented with this concept in the 1970s and early 1980s; we found that they were expensive, and created complex and difficult issues with regard to how the research was organized. The Institute feels that it can achieve the same results through single investigator projects, program projects, and Specialized Centers of Research.

Item

Lung reduction surgery - The House in its report 104-659, page 63 states that, "The Committee is pleased that NHLBI, in conjunction with the Health Care Financing Administration (HCFA), intends to conduct a clinical trial testing the efficacy of various lung reduction surgical procedures. The Committee encourages NHLBI to work with HCFA to ensure that the trial includes the full array of surgical options so that HCFA will have full and complete information on which to base its reimbursement decisions. Some of the surgical options the Committee urges the

NHLBI to consider evaluating in the trial include unilateral procedures, bilateral procedures, open-chest procedures, and procedures involving video-assisted thorascopic and low-energy contact laser technology and other laser technologies. The Committee further urges the NHLBI to review the number of patients involved in the trial. Approximately 5,000 individuals received this surgical procedure in 1995, but the trial, as currently designed, contemplates this surgery for only 1,500 individuals over a period of seven years. Further, the Committee urges NIH to consider conducting these trials at sites which have already demonstrated considerable expertise in performing lung reduction surgery."

Action Taken or to be Taken - The LVRS trial is designed to determine whether LVRS is efficacious compared to medical therapy and, if it is, to provide patient selection criteria as well as a standard to which other LVRS methods can be compared. The number of study arms must be limited so that sufficient patients are included in each one. Clinical trials are extremely expensive, and therefore are designed to include the minimum number of patients needed to obtain scientifically valid results to the questions asked. The LVRS trial data will be frequently reviewed by a Data Safety Monitoring Board, an independent scientific board with authority to recommend early termination if the data show a clear benefit or risk of surgery. Expertise in performing LVRS is among the criteria that were considered in evaluating proposals submitted.

Item

Fanconi Anemia - The House in its report 104-659 states that "The Committee is pleased to hear of the success of umbilical cord transplants in helping infants with Fanconi anemia. The Committee encourages the Institute to pursue additional research opportunities into this disorder."

Action Taken or to be Taken - The NHLBI has a very active and promising research program to determine the clinical efficacy of using umbilical cord blood transplantation to treat several genetic diseases, including Fanconi anemia, as well as certain acquired diseases. Recently, the Institute established a network of transplant centers, which will follow common protocols in transplanting cord and progenitor cells in treating adults and children with unrelated donor umbilical cord blood for high risk leukemia, bone marrow failure syndromes (for example, Fanconi anemia), immunodeficiency states, and inborn errors of metabolism. A coordinating center will manage donor searches, facilitate the distribution of cord blood units for transplantation, and collect and analyze data from this research. Several Institutes at NIH will continue to support related research, which will help continue and extend the excellent progress that is taking place.

1997 Senate Report Language

Item

Hemophilia- The Senate in its report 104-368, page 76-77 states that "Last year the Committee called upon NHLBI to strengthen its hemophilia research efforts in gene therapy and in seeking a cure for this serious bleeding disorder. The Committee also recommended the Institute conduct a study of the scope of hemophilia vulnerability to blood contaminants and specifically Creuzfeldt, Jakob disease [CJD]. In light of the results of the Institute of Medicine study calling attention to the importance of research support to ensure a safe blood supply, the Committee encourages the NHLBI to expand its hemophilia research activities, including the CJD study. The Committee also requests that NIH/NHLBI work collaboratively with CDC and FDA to address all hemophilia research, epidemiology, surveillance, and patient outreach aspects necessary to ensure maximum safety and integrity of the U.S. blood supply."

Action Taken or to be Taken - The Institute has strengthened its hemophilia and hemophilia-related research in several areas. For examples it supports such activities as a new Specialized Center of Research program in Transfusion Biology and Medicine to improve the safety and efficacy of blood and blood components, and co-funded with the FDA and CDC a November 1996 workshop, Hemophilia 1996: Research for a Cure. The NHLBI participates with the CDC, the NIH Clinical Center, and the Armed Forces Blood Program and Resources Program in monthly conference calls, participated with the CDC in planning and designing epidemiological studies to determine if CJD is transmitted by blood, and participated in a November 1995 FDA meeting to plan a conference involving an International Working Group on Blood and CJD to be held early next year.

Item

Bionutrition - The Senate in its report 104-368, page 77 states that "Diet is a major risk factor for heart disease, hypertension and stroke. The NHLBI has been a leader in research regarding nutrition as a prevention strategy for heart disease and hypertension. The Committee encourages the NHLBI to devote more attention to research and to educating the public on the relationship of obesity to hypertension since, according to data from the Framingham study, 70 percent of hypertension in men and 65 percent in women can be attributed primarily to obesity. Recently, NHLBI research has shown a relationship between homocysteine and heart disease and stroke. The Committee encourages further research by NHLBI on the role of folic acid, which affects homocysteine levels, to prevent heart disease and stroke."

Action Taken or to be Taken -. The NHLBI has issued a Request for Applications (RFA) on homocysteinemia and atherosclerosis for grants to be awarded in FY 1997. In the last five years, a growing body of literature has related homocysteinemia to vascular disease and indicated that the relationship is independent of other risk factors. The RFA encourages research to understand the etiology of homocysteinemia and the pathogenesis of atherosclerosis and thrombosis associated with the condition.

Item

Transfusion Medicine - The Senate in its report 104-368, page 77 states that "The Committee is pleased to see that the NHLBI plans to establish a network of umbilical cord blood banks transplant centers. These facilities will provide a resource for research designed to determine whether transplants to stem and progenitor cells from umbilical cord blood are a clinical acceptable alternative therapy for patients suffering from leukemia, aplastic anemia, combined immune deficiency, and inborn errors of metabolism. The Institute has also demonstrated its commitment to a safer and more efficacious blood supply by funding three specialized centers of research in transfusion medicine. The Committee encourages the NHLBI to support research initiatives to improve the viability and function of transfused platelet. The Committee is pleased that the NHLBI is supporting the viral activation transfusion study [VATS] to determine if transfusion hastens the progression of HIV disease. The Committee also encourages the NHLBI to fund additional transfusion medicine initiatives to understand the basic aspects of immune responses following blood transfusion."

Action Taken or to be Taken - In 1996, the NHLBI sponsored a workshop on thrombopoietin (TPO), a platelet producing hormone. One of the centers supported under the Transfusion Biology and Medicine Centers program is focusing on studies to understand how blood transfusion affects the immune system of transfusion recipients.

Item

Primary pulmonary hypertension [PPH] - The Senate in its report 104-368, page 77 states that "PPH is a progressive fatal disease whose mostly female victims are of all ages and races, involves deadly deterioration of the heart and lungs, and literally robs these people of their very life's breath. The Committee urges the Institute to expand its support of research devoted specifically to PPH gene therapy, basic research, and clinical trials of promising pharmaceuticals."

Action Taken or to be Taken - The NHLBI is releasing a program announcement in 1997 to stimulate basic studies of cellular and molecular mechanisms involved in development and pathogenesis of PPH. Currently, diagnosis is difficult, there is no cure, and treatment is limited.

Item

Asthma - The Senate in its report 104-368, page 78 states that "The Committee supports development and evaluation of innovative model school programs to increase identification and appropriate referral of children with uncontrolled asthma, reduce exposure to known allergens and irritants, increase participation of students with asthma in all school activities, improve support to students for following their asthma management plans, and enhance communication between school and home. An example of this is the Open Airways for Schools Program supported by NHLBI."

Action Taken or to be Taken - The Institute supports basic, clinical, and demonstration and evaluation research to identify risk factors for asthma and asthma mortality and to promote

effective management to reduce morbidity in high-risk populations. The NHLBI has also Published "Asthma Management in Minority Children: Practical Insights for Clinicians, Researchers, and Public Health Planners."

Item

[Minority and children-related research] - The Senate in its report 104-368, page 78 states that "The Committee urges the Institute to continue to make minority and children-related (asthma) research a priority, and it requests that the Director be prepared to provide an update on these efforts at next year's hearing."

Action Taken or to be Taken - The Institute supports basic, clinical, and demonstration and evaluation research to identify risk factors for asthma and asthma mortality and to promote effective management to reduce morbidity in high-risk populations. The NHLBI has also published "Asthma Management in Minority Children: Practical Insights for Clinicians, Researchers, and Public Health Planners."

Item

Sarcoidosis - The Senate in its report 104-368, page 79 states that "Although the disease has been recognized for over 100 years, information on its incidence, prevalence, risk factors, and natural history remains limited. Geographic and racial variations in the occurrence of sarcoidosis suggest that it may be caused by environmental factors of a combination of environmental factors and a susceptible host. The Committee, therefore, encourages the Institute to explore environmental and genetic causes of sarcoidosis as an essential step toward identifying risk factors and improving treatment and prevention of the disease."

Action Taken or to be Taken - In FY 1995, contracts were awarded to ten clinical centers and one coordinating center for a case control etiologic study of sarcoidosis to determine the cause of sarcoidosis. A common research protocol has been developed and patient enrollment has begun.

Item

Cooley's anemia - The Senate in its report 104-368, page 79 states that "The Committee continues to strongly support the research efforts of NHLBI in the areas of Cooley's anemia Hepatitis is a major concern of Cooley's anemia patients and the problem warrants further research into hepatitis C and other strains aimed at developing vaccines. The Committee has learned that hormonal therapy as a medical treatment is becoming recognized as more and more of a necessity for patients who are now living through their teens. The Committee requests that the Institute give consideration to convening a workshop of experts in the field to develop plans for research into the long-term effects of this therapy."

Action Taken or to be Taken - In FY 1997, the NHLBI is planning a meeting on hormonal therapy for teenagers with Cooley's anemia to develop plans for research into the need for hormonal therapy and its long-term effects on patients with Cooley's anemia.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
				> $1,320,759,000		> $1,353,573,000
National Heart, Lung, and Blood Institute	Section 425	42§285 b-8	a/		b/	
National Research Service Awards	Section 487(d)	42§288 (a/)	a/	50,193,000	b/	51,197,000
Total, Budget Authority				1,370,952,000		1,404,770,000

a/ Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208)

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1989	1,015,471,000 1/	1,018,903,000	1,056,603,000	1,045,985,000
1990	1,039,846,000 2/	1,090,930,000	1,091,597,000	1,087,524,000 3/
1990 Sequester				-15,170,000
1991	1,112,502,000	1,135,589,000 4/	1,137,235,000	1,126,942,000 5/
1991 Sequester				-15,000
1992	1,209,924,000	1,202,398,000	1,190,396,000	1,188,593,000 6/
1993	1,245,396,000	1,228,455,000	1,228,455,000	1,214,793,000 7/
1994	1,198,402,000	1,277,880,000	1,277,880,000	1,277,880,000
1995 8/	1,266,961,000	1,259,590,000	1,259,590,000	1,258,472,000 9/
1995 Rescission				-1,098,000
1996	1,279,096,000 8/	1,355,866,000	1,263,189,000 8/	1,355,866,000
1997	1,320,555,000 8/	1,438,265,000	1,344,742,000 8/	1,432,529,000 10/
1998 8/	1,404,770,000			

1/ Excludes funds for AIDS research and education ($39,032,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

2/ The 1990 request excludes funds for the National HIV program ($42,651,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

3/ Excludes enacted administrative reduction of $3,740,000.

4/ Excludes $44,476,000 in NRSA training programs not considered.

5/ Excludes Section 514 reductions of $31,708,000.

6/ Excludes Section 214 and 513 reductions of $9,398,000 and enacted rescission of $1,407,000.

7/ Excludes Section 215, 511, and 513 reductions of $13,662,000.

8/ Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.

9/ Excludes procurement reform, rent, and salary and expense reductions of $1,118,000.

10/ Excludes enacted administrative reduction of $472,000.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	10	10	10
Office of Special Concerns	4	4	4
Office of Science and Technology	44	44	44
Office of Prevention, Education, and Control	34	34	34
Office of Administrative Management	43	43	43
Division of Heart and Vascular Diseases	65	65	65
Division of Epidemiology and Clinical Applications	77	77	77
Division of Lung Diseases	28	28	28
Division of Blood Diseases and Resources	29	29	29
Division of Intramural Research	393	393	393
Division of Extramural Affairs	105	105	105
National Center on Sleep Disorders Research	2	2	2
Total, NHLBI	834	834	834

	Average GS/GM Grade
1993	10.0
1994	10.5
1995	10.4
1996	10.4
1997	10.4
1998	10.4

Note: Includes 12 FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	4	4	4
ES-5	2	2	2
ES-4	9	9	9
ES-3	1	1	1
ES-2	1	3	3
ES-1	3	1	1
Subtotal	20	20	20
Total - ES Salary	$2,334,496	$2,408,000	$2,470,000
GS/GM-15	68	68	68
GS/GM-14	83	83	83
GS/GM-13	77	77	77
GS-12	69	69	69
GS-11	79	79	79
GS-10	10	10	10
GS-9	40	40	40
GS-8	56	56	56
GS-7	85	85	85
GS-6	20	20	20
GS-5	22	22	22
GS-4	20	20	20
GS-3	11	11	11
GS-2	4	4	4
GS-1	2	2	2
Subtotal	646	646	646
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	25	25	25
Senior Grade	11	11	11
Full Grade	14	14	14
Senior Assistant Grade	1	1	1
Subtotal	52	52	52
Ungraded	149	149	149
Total permanent positions	673	673	673
Total positions, end of year	867	867	867
Total full-time equivalent (FTE) employment,end of year	834	834	834
Average ES level	4	4	4
Average ES salary	$116,725	$120,400	$123,500
Average GS/GM grade	10.4	10.4	10.4
Average GS/GM salary	$49,458	$51,090	$52,520

TUESDAY, MARCH 4, 1997.

NATIONAL INSTITUTE ON DRUG ABUSE

WITNESSES

ALAN I. LESHNER, M.D., DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

RICHARD A. MILLSTEIN, DEPUTY DIRECTOR

DONNA M. JONES, BUDGET OFFICER

LAURA ROSENTHAL, EXECUTIVE OFFICER

DR. HAROLD VARMUS, M.D., DIRECTOR, NIH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

We're pleased to welcome Dr. Alan Leshner, the Director of the National Institute on Drug Abuse. I apologize for being late. I was stuck on a phone call that I couldn't get off of.

Dr. Leshner, why don't you proceed with your statement right away?

INTRODUCTION OF WITNESSES

Dr. LESHNER. Thank you, Mr. Porter. Let me just introduce the people I brought with me. Donna Jones, NIDA's Budget Officer; Laura Rosenthal, our Executive Officer; Richard Millstein, our Deputy Director; you know Dr. Varmus and Mr. Williams from the Department.

OPENING STATEMENT

I'm very pleased to tell you that we've had another outstanding year in drug abuse research and its application. As you know, NIDA supports over 85 percent of the world's research on the health aspects of drug abuse and addiction. And we do that through a very comprehensive and broad ranging research portfolio.

Because NIDA plays such a dominant role in drug abuse research, we've come to understand that doing great science by itself is not enough. And we know that if our scientific findings are not both useful and used, we're not fulfilling our mission. And that's why NIDA and its staff are continuously holding discussions not only with the scientific and professional communities, but also with policy makers and the general public.

We do that both to share the results of NIDA-supported research, and to get input from the users of our findings about the information that they need to do their jobs. Our ongoing series of town meetings across the Nation exemplifies NIDA's commitment that our research both be useful and used.

As just one example, we recently brought together community leaders and leading scientists at a town meeting in San Francisco to help confront the emerging drug problem of methamphetamine. And as one result of that town meeting, NIDA has launched a major methamphetamine research initiative to increase our knowledge about this drug's effects and what to do about them.

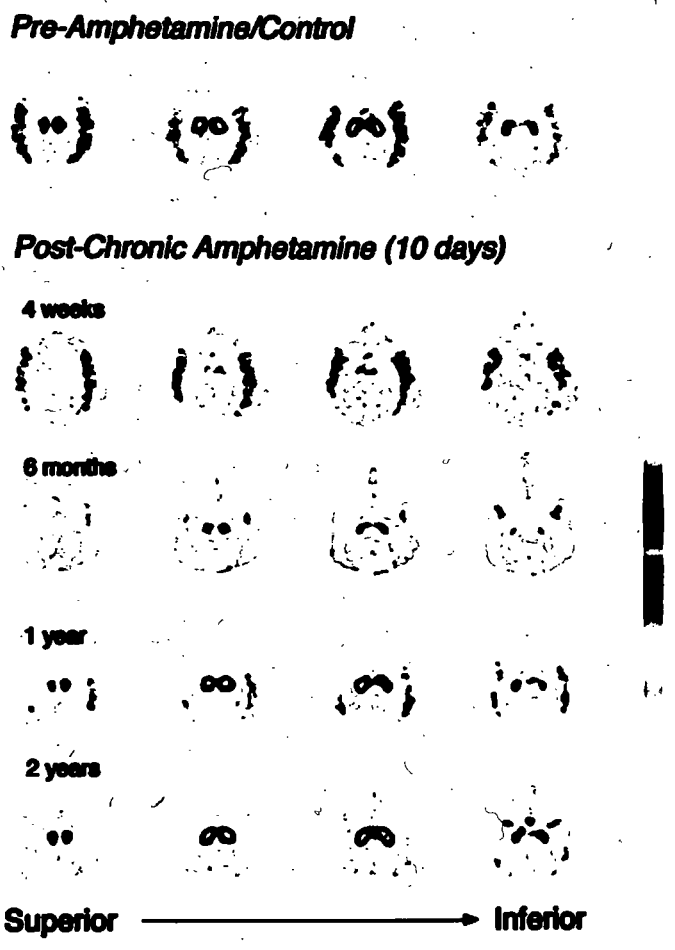
I'd like to share with you just one of the very important new findings described at that meeting. Last year, I showed you brain images showing your brain on drugs, and then I showed some brain scans of persistent effects of chronic cocaine use on general brain metabolism that last at least four months after the addict has stopped using cocaine. Well, research published this year demonstrates just how pervasive, how devastating and how long-lasting other brain changes can be after chronic heavy drug use. And they're adding important specificity to the kinds of more general effects that we discussed last year.

I'm going to use the case of methamphetamine. We know well that acute use of both methamphetamine and amphetamine produces very dramatic changes in brain function, particularly through the release of the neurochemical dopamine, and that spike in dopamine release is how the amphetamines produce their psychoactive effect.

Well, we now also know that long-term amphetamine use produces dramatic changes in dopamine activity that persist long after the individual stops using the drug. And the effects are not limited to the toxic effects of amphetamines, since those effects in fact recover over time. This poster to my left shows the effects of 10-day exposure to heavy doses of amphetamines on the brain's ability to synthesize, to produce this substance dopamine. These are positron emission tomography "PET" scans, of verdant monkey brains.

[The information follows:]

Striatal FDOPA Activity



And the top row shows you in white and red normal levels of compound fluoro-dopa, or fluoro-dopa activity, an index of the ability to synthesize dopamine. Red, yellow, and white are more activity, blue is less activity there. The second and the subsequent rows show a dramatic decrease in dopamine synthesis capacity that lasts at least a year after amphetamine dosing was stopped. So what you see there is the pre-amphetamine on the top row, amphetamine for 10 days, and then after you stop giving amphetamine, four weeks, six months, by a year it's coming back. The important point is it will recover by two years. And that bottom line is basically similar to the top line.

Mr. PORTER. Excuse me, it's just 10 days of the use of amphetamines?

Dr. LESHNER. That's right, it's 2 injections a day for 10 days.

Mr. PORTER. And that has an effect for at least a year?

Dr. LESHNER. Yes, sir.

What's important about this is that these persistent brain changes are accompanied both by severe amphetamine addiction and by dramatic changes in social and emotional behavior processes that also persist for a very long period of time. And of course, it's not surprising that there are these behavioral effects, since we know dopamine is critically involved in social and emotional behavior processes, including particularly the regulation of human mood states.

Turning to a very different domain, we've also been working very hard to try to improve the prevention of initial drug use, particularly among young people, which I know you know is a major problem in this country. In September we held the first national conference on drug abuse prevention research, bringing together over 500 researchers and community practitioners. And as a result of that meeting, in the next few days, we will be releasing the first ever science-based guide to drug abuse prevention.

We'll be sending this guide to thousands of practitioners, community anti-drug coalitions and other lay leaders all over the country. This user-friendly booklet articulates the principles that we've learned from prevention research, and it gives practical guidance on how communities can apply these principles to address local drug problems. It even includes science-based checklists of criteria against which communities can evaluate local programs.

NIDA is also working to continue to improve drug treatment approaches. We've mounted a new Institute treatment initiative this year that, among other things, is taking behavioral and pharmacologic therapies that our studies have shown to be effective in small-scale laboratory studies and evaluating them in real life, large, multi-site clinical trials. Behavioral approaches such as cognitive behavioral therapy and contingency management therapy that have been studied in academic settings but have not been applied very broadly in the real world will be further evaluated.

We will also continue to develop new medications to restore a degree of normalcy to brain function and behavior, so that other therapies and rehabilitative measures, such as counseling and psychotherapy, can be more effective than they are now. Although behavioral and pharmacologic treatments can be extremely useful

when employed alone, NIDA-supported research has taught us that integrating both types of treatment is the most effective approach.

In fact, these integrated approaches are typically essential to restoring an addicted individual to normal functioning.

We've also made tremendous progress in one of NIDA's top priority areas, the development of an anti-cocaine medication. One of the most promising and consistent basic science findings of the last year or so is that stimulating one of the brain's dopamine receptors, called the D–1 dopamine receptor, seems to suppress cocaine craving and cocaine seeking behavior.

We're now in discussions with chemists from academia, from other NIH institutes and from industry to develop and acquire dopamine D–1 stimulating compounds that we can examine as potential medication.

In addition, to expedite the path from these types of basic science findings, to actual changes in clinical practice, NIDA has just funded the first three grants of its Strategic Program for Innovative Research on Cocaine Addicts—SPIRCAP—program, which is that program I mentioned last year that we were inaugurating, to force the collaboration between basic scientists and clinical scientists to do the kind of translational research that I know many institutes have been talking with you about.

These are just a few of the past year's findings in NIDA's new initiatives. Some others are spelled out in my full statement. I hope that they make clear that NIDA-supported research is providing us with a solid scientific foundation to better ensure that our Nation is equipped to respond not only to the problems of today, but to the challenges of tomorrow.

To paraphrase a recent report by the Institute of Medicine of the National Academy of Sciences, the success of our national investment in addiction research will be measured in lives saved and reclaimed and the development of our youth into productive and healthy adults, and in the restoration of families and the security of communities. This same Institute of Medicine report applauded NIDA's past successes and stated the Institute of Medicine's belief that we're working in the right direction and are well on our way to meeting these important societal goals.

To meet the challenges and opportunities now presented to us, NIDA requests $358,475,000 for fiscal year 1998. A hallmark of this request is the $30 million increase proposed by the Administration. This is a part of the Administration's cross-cutting efforts to combat drug abuse, which has been increasing in some populations.

I would be pleased to answer any questions.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute on Drug Abuse

Mr. Chairman and Members of the Subcommittee, I am pleased to share some very exciting scientific findings with you today and to tell you about our plans for the future. Research supported by the National Institute on Drug Abuse (NIDA) has made extraordinary progress in providing science-based approaches and solutions to one of our Nation's most serious public health problems--drug abuse and addiction.

NIDA supports over 85% of the world's research on the health aspects of drug abuse and addiction through its comprehensive research portfolio which incorporates many diverse fields of scientific inquiries. Twenty years of research has shown that drug abuse is a preventable behavior, and drug addiction is a treatable disease of the brain. This is not a slogan, but fact based on scientific evidence.

The hallmark of the FY 1998 NIDA request is a $30 million (9%) increase proposed by the Administration for drug abuse research at NIDA. This $30 million is part of the Administration's crosscutting effort to combat drug abuse which has been increasing in some populations.

In this past year we have made significant strides throughout our entire research portfolio, but nowhere have the accomplishments been more fruitful, insightful and applicable to other areas than those findings made in basic research. We have learned not only how drugs affect the brain in ways which impact an individual's behavior, but also that behavioral and environmental factors may modulate brain function. One of our most significant breakthroughs has been our identification of areas of the brain that are specifically involved in the phenomenon of craving. Research converging from many laboratories using positron emission tomography (PET) scans shows that when addicts experience craving for a drug there is a high level of activation in specific areas of the brain, particularly in the amygdala, an area of the brain that appears to be involved in all emotional memories. Since craving is probably the single most important factor which can lead to relapse, understanding the systems that mediate this phenomenon provides the foundation for developing effective treatments to prevent or reverse the addiction process.

At cellular and molecular levels, a series of recent basic scientific discoveries points to one common reward pathway in the brain where all drugs of abuse act. The data now suggest that, independent of a drug's initial site of action, every drug--be it nicotine, heroin, cocaine, or amphetamine--appears to increase the levels of the neurotransmitter dopamine in the brain pathways that control pleasure.

This knowledge about the dopamine system is paving the way toward the development of a medication to treat cocaine addiction. As we progress towards this goal, we are unraveling the mechanisms of addiction and finding that dopamine appears to play a pivotal role in the entire addiction process. We know that the dopamine transporter is the major site for cocaine's action. We also know that there

are multiple dopamine receptors and that each responds differently to various compounds. One of our most promising findings is that stimulating one of the dopamine receptors D1, has been shown to suppress not only drug seeking behavior, but relapse as well. This suggests that D1 activation may prevent intense craving and ultimately prevent relapse. It is through the discovery of these types of incremental, yet significant, advances that we will accomplish one of our ultimate goals--effective, long-lasting strategies for breaking the cycle of addiction.

Every achievable goal must begin with a single objective. One of our first objectives toward truly understanding the addiction process was achieved when researchers actually visualized in exquisite detail what drugs do to the brain. Last year I showed you, literally "your brain on drugs." That same sophisticated brain imaging technology is now giving us even greater insights into how drugs exert their addictive effects such as craving and relapse, as well as the long-term detrimental effects of chronic drug use.

We can now actually see many of the dramatic changes in the brains of drug abusers that persist after chronic drug use. At the cellular level, NIDA researchers have shown in animals that chronic morphine use can cause marked structural changes in dopamine neurons located in a brain region known to be involved in addiction. Chronic use of morphine resulted in a dramatic change in the size and shape of the dopamine cells. We have seen that other addictive drugs affect the brain's reward pathway as well. Put simply and succinctly, addiction means that the brain has changed both structurally and functionally. These studies reinforce the principle that a major goal of any effective treatment strategy should be to address these biological changes, and reverse them, or at least compensate for them.

In addition to seeing these structural alterations in the brain we also see evidence of lessened cognitive and behavioral abilities. For example, drug use by adolescents can result in long-lasting cognitive defects, such as attentional and memory deficits. We also know that drug abuse can impact the health of a developing fetus and child. The immediate consequences of prenatal drug use may include premature birth and alteration of the newborn's brain function. Although more research needs to be done, NIDA researchers studying the potential long-term consequences of prenatal drug exposure to a child's development are now finding that these children may suffer from learning disabilities and other neurologic deficits that are only manifest in later years.

Nowhere are the effects of drug abuse and addiction more devastating than among our Nation's youth. In response, NIDA has declared a major Children and Adolescents Research Initiative. The main focus is prevention. We view prevention in two contexts: (a) prevention of initial drug use and (b) prevention of the health consequences of drug use for the individual, his or her offspring, and society.

NIDA research has helped identify important factors that put young people at risk for or protect against drug abuse. We will continue to rely on basic behavioral and social research to understand the biological, psychological, and environmental factors and their combinations involved in a person's first use of drugs and the risk for subsequent progression to abuse and addiction. For example, we will continue to look at the roles that decision-making processes and peer pressure have on a child's susceptibility to drug-taking behaviors. This will allow us to develop the

most effective prevention strategies.

We at NIDA recognize that doing great science is not enough if the results are not shared with those who could directly benefit from our country's investment in research. This past September we shared this culmination of prevention research findings with community members from across the country at our National Conference on Drug Abuse Prevention Research. We have just produced the first research-based guide to drug abuse prevention. This is a user-friendly guide which provides science-based prevention principles and practical guidance on how these principles can be applied by the community to address local drug abuse problems.

In addition to identifying risk and protective factors to be used in prevention strategies, research shows that addiction is eminently treatable. Addiction treatment has been shown to be effective in reducing drug use and HIV infection, diminishing the health and social costs that result from addiction, and decreasing criminal behavior.

Acknowledging that the path leading from new findings to actual changes in clinical practice can be very long, NIDA has mounted a new Treatment Initiative to more rapidly apply our basic findings in real life settings. This initiative will take behavioral and pharmacologic therapies that are shown to be effective in small scale studies and evaluate them in large multi-site clinical trials. NIDA will also strive to improve existing treatments and to develop new improved approaches. Translating fundamental findings into treatments that address not only addiction itself, but processes like the neurobiologic basis of drug craving, is an important part of this initiative.

For several years a major focus of NIDA's treatment research program has been on developing new medications to restore a degree of normalcy to brain function and behavior so that other therapies and rehabilitative measures, such as counseling and psychotherapy, can be more effective. Although behavioral and pharmacologic treatments can be extremely useful when employed alone, integrating both treatments, in ways specific to an individual's needs, is likely the best way to treat addictive disorders.

Building upon our neuroscience findings, we are continuing to develop new candidates for potential medications. During the past year, we have identified several compounds that show promise as long-acting cocaine treatment medications. One compound in particular works on the dopamine system and seems to reduce cocaine taking in monkeys. Of significance, this compound suppresses the desire for cocaine, while not affecting other pleasurable activities controlled by the dopamine reward pathway, such as eating.

Another major public health problem that NIDA is addressing when designing or evaluating treatment approaches is the spread of infectious diseases, such as HIV infection, hepatitis and tuberculosis. Drug abuse is currently the fastest growing vector for the spread of HIV in the United States. Approximately 30 percent of AIDS cases reported through June 1996 were related to use of illegal drugs. NIDA-supported studies have developed effective outreach strategies that result in positive behavior changes by intravenous drug abusers that are preventing the spread of the HIV infection. Importantly, NIDA research shows that AIDS risk reduction and successful behavioral changes are being achieved even among those who continue

to use drugs.

NIDA is addressing yet another emerging drug problem--methamphetamine abuse. One of the tools NIDA uses as an early warning system to monitor drug trends is its Community Epidemiology Work Group. This system has alerted us to significant increases in methamphetamine use in selected areas which may be spreading across the country. NIDA is taking a proactive multi-faceted approach to tackling this problem. We have launched a major research initiative to increase our knowledge about the effects of this drug, to use this research to develop prevention and treatment programs geared toward the unique characteristics of the methamphetamine abuser, and to disseminate this research information.

As a first step in this initiative, we recently sponsored a regional town meeting in San Francisco, an area particularly hard hit by this menacing drug. This conference brought together the country's leading experts on methamphetamine to share the most up to date information available as well as to develop strategies to combat this problem.

Methamphetamine, like amphetamine, is a drug of abuse with pronounced effects on the central nervous system including psychomotor activation and mood elevation. Research on animals has suggested substantial brain toxicity after prolonged methamphetamine exposure. In this panel you can see evidence of a substantial decrease in dopamine synthesis in the brain following chronic administration of amphetamine. The functional and behavioral consequences that result from this are among the problems addressed in NIDA's Methamphetamine Research Initiative.

This Initiative, along with our Children and Adolescents and Treatment Initiatives, are areas that NIDA will emphasize this year. Of course, none of these initiatives, nor any part of our research agenda, is developed in isolation. NIDA staff continuously engage in discussions with the public health community, including scientists, practitioners, policymakers and the general public. NIDA also uses other mechanisms like the town meetings we have been hosting across the country to carry out our goal of having science replace ideology as the foundation for drug abuse prevention, treatment and policy strategies. We acknowledge commendation by this committee last year for our dissemination efforts, and will continue these timely exchanges of information.

Mr. Chairman, over twenty years of NIDA-supported research provides us with a solid scientific foundation to ensure that our Nation is equipped to respond not only to the problems of today, but to the challenges of tomorrow.

A summation of why NIDA is committed to conducting and supporting research into this complex and troubling disease is well articulated in a recent report issued by the Institute of Medicine of the National Academy of Sciences. It states: "In the final analysis, the value of the nation's investment in drug abuse research is measured in lives saved and reclaimed, in the success of each young person who stays in school and joins the work force, and in the happiness of each child nurtured by his or her parents rather than abused or abandoned by them." While these are not my words, they eloquently express the reason that the National Institute on Drug Abuse exists.

To meet the challenges and opportunities now presented to us, NIDA requests $358,475,000 for FY 1998. I would be happy to answer any questions at this time.

RELATIONSHIP WITH ONDCP

Mr. PORTER. Thank you, Dr. Leshner.

Mr. Hoyer has another subcommittee that he has to attend, and I'd like to recognize him first. Mr. Hoyer.

Mr. HOYER. Thank you very much, Mr. Chairman. That's very thoughtful of you.

Doctor, thank you for the report and it is indeed, as you said at the outset, a hopeful report. I think all of us are very hopeful that we will sort of get a magic formula by which we can suppress the desire that you speak to in your larger statement; the craving for drugs, particularly for those who have been on and are off. Obviously recidivism is a major, major problem for the medical side of the question, as well as for the law enforcement side of the question.

Just a couple of questions. First of all, in my other subcommittee, the Treasury, Postal Subcommittee, General McCaffrey's Office of National Drug Control Policy, is budgeted there. Would you tell me what interface you have with ONDCP and General McCaffrey?

Dr. LESHNER. I will. We have been very fortunate, I think, to develop a fairly close relationship with ONDCP and with Director McCaffrey in particular. He has the unique characteristic of being very interested in science, and therefore, he has been known to track me down on vacation and ask literal scientific questions. He's met with Dr. Varmus and has been very interested in much of what we're doing.

Our relationship is informational, primarily, that is, we brief him probably every few weeks on whatever issue is in front of him at the moment. Our staff went down recently, for example, to talk about the science of prevention, in particular, and they've been very interested in our medication development program.

VACCINE DEVELOPMENT

Mr. HOYER. I'm glad to hear that. Of course, one of the things I was struck with in my first meeting with General McCaffrey before he'd been confirmed but after he'd been named by the President, was his emphasis on prevention and rehabilitation. This is a four-star general, the most decorated soldier in America right now who is living, and he does not like to refer to the war on drugs. He sees prevention and rehabilitation as a major, major component, as you know.

Toward that end, in your statement you refer to both identifying genetic markers for proclivity to use, as well as suppression of further desire. How far away do you think we are to, I know you referred to this, but to perhaps, I guess, an inoculation? What am I looking for? The word?

Dr. LESHNER. A medication? A vaccine?

Mr. HOYER. Vaccine. In effect, is that conceptually what we're looking toward?

Dr. LESHNER. Well, let me give you a slightly longer answer than you might want, but I'll try to keep it brief. Actually, the problem of developing appropriate medications, and I need to say, I don't think we'll ever have a magic bullet, so anyone who's waiting for that, I apologize. The cycle of addiction is from a clinical perspec-

tive complex, obviously. There's an issue of initial drug use, there's an issue of once an individual becomes addicted, which I believe is a different, and qualitatively different state. Then there's the issue of how do you keep someone off drugs once they're off. I believe that we may actually need different pharmacological approaches for each of those stages, and worse, more stages.

There has been a lot of interest, and NIDA has made a number of grants, actually, in three different places, to look at the potential for developing some kind of a vaccine based approach. We actually have a company called Immunologics that just got a very large grant from us in order to further the development of a potential vaccine.

I don't think we're at a point yet where we really understand the complexity of how that might be used. That is, that it might be that for some individuals you would want to give them this vaccine which has been preliminarily developed, in animals, of course. That might help control their initial drug use.

It's much more complex. An even more complex ethical issue is what you do for the long term with vaccinating somebody. Technologically, I would say that we're beginning to get close. That is, we have in fact in rodents developed a model where antibodies have been produced to block cocaine, and they do in fact block cocaine's entry into the brain. They do in fact block cocaine's initial psychomotor effect, that is, they block the stimulant effect of cocaine.

What we don't know is if they would also block craving for someone already addicted, for later drug seeking. So at most, I think, a vaccine approach will be an initial stage. I think we'll need other kinds of medications, particularly to deal with the craving, which is the most difficult and the most complex aspect for an addict.

ALCOHOL AND SUBSTANCE ABUSE

Mr. HOYER. Doctor, the last question, and I again apologize for having to leave to be on the other subcommittee, but we're going to hear from the National Institute of Alcoholism and Alcohol Abuse. Clearly, very closely related. I was interested to see in the paper today that although parents and teenagers or young people differed on a lot of things, in terms of drug use and what parents are telling students or their kids and what kids were hearing, they agreed on one thing overwhelmingly, that alcohol abuse was the major problem that confronted young people.

Clearly, without getting into the political definition of alcohol and tobacco versus cocaine and heroin and making an analogy there, which I'm not making at this point in time, but clearly there is an analogy; presumably all these substances have a similar effect and are driven by similar drives which lead to addiction or overuse. Am I correct on that? And if that's correct, I presume there's a great deal of cooperative effort between the two Institutes.

Dr. LESHNER. Well, there are both similarities and differences among individual drugs. It's true that many, many abusable substances have common effects, particularly on the dopamine system in the brain. We do work very closely with the National Institute on Alcoholism and Alcohol Abuse. And we have a lot of programs

that we do together and things that we study together. At the same time, there are separate sets of issues that pervade it.

But the questions of adolescent substance use are very broad and cut across issues of value as well as issues of science. And they are pervasive, as you suggest.

To answer your question, there are similarities and there are things that are different, including the nature of the metabolic effects that are going on with the use of different substances.

NICOTINE ADDICTION

Mr. HOYER. I said that was going to be my last question, but one thing occurs to me, Mr. Chairman. Alcohol is obviously a legal substance. What do we do, and this is going to be a controversial question, what do we do with respect to nicotine? We don't have a National Institute for Nicotine Addiction.

Dr. LESHNER. We actually study nicotine addiction. We coordinate, of course, with other institutes, the National Cancer Institute, the National Heart, Lung, and Blood Institute who study other aspects of nicotine and smoking. We actually are responsible for the primary research on the addictive properties of nicotine.

Mr. HOYER. Mr. Chairman, you've been generous to me in time, and I appreciate that very much, and for recognizing me first. Thank you.

Thank you, Doctor.

Dr. LESHNER. Thank you, sir.

DRUG ABUSE BUDGET INCREASE

Mr. PORTER. Thank you, Mr. Hoyer.

Dr. Varmus, I think I want to begin with a question to you. And this is not a hostile question, but merely one to determine how you reach conclusions. The NIH budget specifically identifies, as Dr. Leshner has said, a $30 million or 9 percent increase for non-AIDS drug abuse research.

In general, you've tried to avoid disease-specific increases and have instead constructed your budget on the basis of six areas of emphasis. But only $17 million of the $30 million non-AIDS increase for NIDA is associated with these six areas. Do you see any inconsistency in the way your budget provides such a large proportionate increase to drug abuse?

Dr. VARMUS. The extra money for the Drug Abuse Institute represents an Administration decision that there ought to be more emphasis placed in that area of research. The Drug Abuse Institute was slated for substantial monies, which you've seen represented in the areas of prevention and neuroscience. The increase is more than it might have been had there not been a coordinated decision by us, in collaboration with the Department and the White House, to make a special push this year to try to advance medications development and other topics that Dr. Leshner will discuss.

Mr. PORTER. Do I understand then that this was not in your original proposals sent to the Department?

Dr. VARMUS. That's correct.

Mr. PORTER. And came from the White House instead?

Dr. VARMUS. It was a coordinated decision to go ahead and do this.

ALASKA NEEDLE EXCHANGE

Mr. PORTER. Thank you.

Dr. Leshner, there's been a great deal of publicity recently about research on needle exchange programs, and in particular, a study NIDA is supporting in Alaska. First of all, can you summarize what we know and what we do not know on the basis of existing studies about the effectiveness of needle exchange programs in preventing the transmission of AIDS?

Dr. LESHNER. Well, I think if you look at the converging evidence as summarized now by a large number of reports, pretty much whatever measures we use are indicating that in the context of a broad set of prevention activities, needle exchange can be an effective vehicle for reducing the spread of blood-borne infections, including HIV, hepatitis virus and other kinds of blood-borne infections.

The question that's more difficult to demonstrate, of course, is the question of how it affects drug use. And I should say that there is no evidence that it increases drug use. It is a very effective strategy for bringing people into treatment. Somewhere, in our various studies, somewhere between 15 and 25 percent of the people who come to those programs in fact enter into treatment.

Mr. PORTER. Now, can you describe the needle exchange study you were sponsoring in Alaska and the reasons it has been opposed by Public Citizen?

Dr. LESHNER. I'll try. The needle exchange grant at the University of Alaska is actually a, what we might think of as a second generation project. That is to say, it's comparing the efficacy of two different approaches to providing sterile needles.

I should make clear that in any studies of this kind, and in any of the studies of needle exchange that we are doing, we recognize, and the protocols are created in such a way that the first attempt by all investigators is to get people into treatment and to get people to stop using drugs. The best prevention strategy, of course, for the spread of blood-borne infections, is for people to stop injecting drugs. However, we know that we're nowhere near as successful as we might be, and therefore, these are public health approaches that are being studied in a way to deal with this public health problem that goes beyond just an individual's drug use.

Having said that, a question that needs to be asked is not really whether or not using sterile equipment is a good idea. There's no question that the use of sterile equipment prevents the use of blood-borne infections. The question here is, what is the best way for making sterile equipment used; that is, how to do that. Each of the studies NIDA supports in this domain includes a formalized protocol of outreach, education, counseling on drug use, counseling on treatment, and then after that doesn't work, then the study starts.

This particular study, is a randomized trial, comparing the efficacy of a needle exchange program, supported locally. We don't provide the needles. It compares the efficacy of that approach to the approach of having people buy needles in a pharmacy, which in Anchorage, Alaska, are quite available.

The questions that have been raised about the study had to do with whether in fact one needed to demonstrate that using clean needles works. We never thought the investigator was demonstrating that. What we thought the investigator was demonstrating is which is the most effective technique for it. And as you know, Dr. Varmus asked a group to look at that. And they came to a similar conclusion.

Other than that, there was some discussion about the provision of hepatitis B vaccine. And we have made provisions to ensure that every individual in the study has access and is encouraged to get vaccinated against hepatitis B.

Mr. PORTER. And Dr. Varmus recommended you proceed with the study after making a change in its design?

Dr. LESHNER. A subset of the subjects in the study would receive free vaccine from the Indian Health Service or from other local service providers. A subset would not have had access to free vaccine. Dr. Varmus recommended, and we concurred fully, that we should provide vouchers for those individuals who would not get free vaccine, to make sure that everybody would be as encouraged as possible, if that's the correct phrasing, to get that vaccination.

DISEASE SPECIFIC BUDGETS

Mr. PORTER. Dr. Varmus, regarding my first question to you, I wonder if you would submit for the record a list of all those areas in the budgets of NIH that were suggested, either by the Secretary or by the White House that weren't contained in your original budget that are disease-specific? Would you do that for us?

Dr. VARMUS. I should perhaps point out that these are areas that were in the budget, not as an expansion, that we initially intended to ask for.

Mr. PORTER. And quantify them for us, too.

Dr. VARMUS. Sure.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH DISEASE-SPECIFIC BUDGETS

The following information is provided in response to Mr. Porter's request that NIH identify and quantify areas in the NIH budget that were suggested either by the Secretary, DHHS, or by the White House. It is important to note that these areas had already been identified by NIH and that the increases resulted from a coordinated decision by NIH, in conjunction with the DHHS Secretary, and OMB.

NIAID's FY 1998 budget for Non-AIDS research included an increase of $3,000,000 for the support of Hansen's disease research at the Hansen's Disease Center, to be funded through a reimbursable agreement with the Health Resources and Services Administration.

In the FY 1998 budget, NIDA received a total of $30,000,000 for Non-AIDS drug abuse research. Of this amount, $17,000,000 was for NIH special areas of emphasis as follows: Biology of Brain Disorders, $5,000,000; Preventive Strategies, $5,000,000; Therapeutics/Drug Development, $5,000,000, and Advanced Instrumentation, $2,000,000. In addition, an amount of $13,000,000 was included in NIDA's FY 1998 budget for research on drug activity.

The FY 1998 passback level includes $15,000,000 for third party payments to the Clinical Center in addition to appropriated funds. The collection of third party payments is consistent with initiatives currently underway at NIH to encourage public and private insurance support of costs of patients who participate in NIH-sponsored clinical research.

NEEDLE EXCHANGE

Mr. PORTER. Thank you.

The Secretary of Health and Human Services has recently submitted a report to Congress on needle exchange programs. Can you describe her major conclusions?

Dr. LESHNER. Secretary Shalala's conclusions were basically similar to the conclusions that I just mentioned, which is that on the basis of the studies done to date, on the basis of the report of the Institute of Medicine and the recent NIH consensus conference, we were to pull together all of those data. The best models of this came from Yale. But the best models indicate that needle exchange programs can reduce the spread of blood-borne infections by as much as 33 percent.

Secondly, the Secretary's report acknowledged that needle exchange programs are an effective vehicle for getting people into treatment. She did not draw a firm conclusion on the issue of whether or not needle exchange could reduce drug use, although she recognized that there are not data suggesting that it increases drug use. I believe that's accurate.

MEDICAL USE OF MARIJUANA

Mr. PORTER. Dr. Leshner, the medical use of marijuana and the Federal Government's position on it have generated considerable controversy. The National Drug Policy Director has ordered that an 18 month review of the science be conducted by the Institute of Medicine. And NIDA has recently convened a two-day workshop on the issue.

At the moment, is scientific opinion truly divided on the medical benefits of marijuana for particular conditions?

Dr. LESHNER. Let me just clarify. First, the workshop that we just held, which I helped organize as an NIH-wide event, actually was not a NIDA-specific event, because of course, any research that would be conducted likely would come from another NIH Institute. NIDA would only provide support in the form of providing the marijuana itself. If the research were for a particular medical indication, the appropriate Institute would do that.

This workshop, in fact, represented the joint efforts of 10 NIH Institutes, centers and divisions. Certainly in my experience, second to some of our neuroscience efforts, it was the most collaborative thing we've done.

I would say that a reasonable conclusion, and again, all of this has to be seen in the context of the broad public health discussion that's going on at the moment, is that the existing data base is relatively thin for smoked marijuana. That is, there is not a large body of data suggesting smoked marijuana is a viable medication for any particular indication. There are a lot of anecdotes, and we can come back to that if you'd like.

However, there are indications for which THC, tetrahydrocannabinol, the main psychoactive ingredient, have been approved, such as AIDS-wasting, and nausea associated with cancer chemotherapy. Therefore, given the extensive nature of the discussion going on, I think it would be a reasonable question whether additional research should be done. That was in part a reason that

NIH held this workshop and the workshop hasn't submitted its report to us yet.

But what we did was to have experts in each of those areas summarize the literature, and give us advice, particularly about clinical trial issues. You can imagine how complex it is to do research on a medical indication for a smoked preparation that has psychoactive properties to it.

Mr. PORTER. And you have a marijuana farm in Mississippi that provides your research marijuana supply?

Dr. LESHNER. We do. On contract to the University of Mississippi, NIDA maintains a farm that grows research-grade smokable marijuana. The majority of it is used either for those remaining compassionate use IND patients who receive smokable marijuana from the Government through the FDA, and for research purposes in our research grants. We do have, as you would imagine, a large number or fairly large number of grants looking at the pharmacokinetics of smoked marijuana.

Mr. PORTER. How many grants is that?

Dr. LESHNER. We probably have five to seven grants using smoked marijuana. Let me just give you one example of the kind of research I'm talking about. This is on the top of my head, last week I was at our own intramural research program, where an investigator was looking at individual differences in blood levels of marijuana after smoking, and after a very controlled smoking experience, virtually an identical by all external measures, the blood levels were phenomenally different among all individuals, and that has to do with the smoking which affects the absorption through the lungs.

So that's the kinds of studies that we do, and of course the abuse potential.

Mr. PORTER. Thank you.

Mr. Miller.

METHADONE TREATMENT

Mr. MILLER. Thank you. Just a couple questions.

Understanding the idea of where we're going five or ten years in time, methadone has been the treatment for heroin, right?

Dr. LESHNER. It's one of the medications for heroin, yes.

Mr. MILLER. Is that the most commonly used one?

Dr. LESHNER. It is, yes.

Mr. MILLER. It's been around a long time, has it?

Dr. LESHNER. Actually, methadone was first developed in the early 1970s.

Mr. MILLER. But is it fairly common? I know in my community, at least there was a place that heroin addicts——

Dr. LESHNER. One hundred and twenty thousand people are on methadone.

Mr. MILLER. Is there a waiting list to get on?

Dr. LESHNER. Yes, sir, in some places, not everywhere.

Mr. MILLER. How is that funded normally?

Dr. LESHNER. Methadone treatment is typically funded through the State, not through the Federal Government. Some of it comes through the block grant to the States that is administered by the Substance Abuse and Mental Health Services Administration.

But every State has to decide for itself whether or not it will in fact use methadone. And not every State does. And of course, not every country does. There's a lot of ideology out there about methadone as a compound, and a fair amount of misunderstanding. But it is a rather effective medication for, again, a subset of individuals. And typically, when combined with psychotherapy of some kind.

COCAINE MEDICATION

Mr. MILLER. Would the goal be with cocaine to do something similar?

Dr. LESHNER. Actually, my hope is not to have a substitute medication. Methadone is a substitute medication, it does not produce the same level of euphoria that heroin does, in contrast to popular misunderstanding about it. And what it does do is occupy the same receptors. So it is a similar compound in the sense that it is working on the MU opiate receptor in the brain. And it does have some abuse potential, that is, if you could get it out on the street and inject it, you could get a high from it, not the same high as from heroin, because it's absorbed less readily.

In any event, we are hoping that we can develop a compound that will actually work on the craving end rather than on the literal substance specific addiction. But I can't promise you that yet. I can tell you that we do have compounds that fit different categories for cocaine, some that would compete, as does methadone, for the same receptor. Some that might knock cocaine off its receptor, so it's just working in a different way. And some that might actually work on a craving itself, as opposed to the specific compound.

Mr. MILLER. So is that true for other types of addiction? Your goal, five or ten years, if you could choose what you could accomplish five years from today.

Dr. LESHNER. If I could decide what to walk out of the National Institute on Drug Abuse's having done, it would have been finding an anti-cocaine medication, sir. I think that's the biggest single need in this country's fight against addiction. We have nothing for overdose, we have nothing to get people to stop using the drug, and we have nothing to keep them not using the drug. And it's why we have put so much effort into this particular issue, since crack cocaine is in fact one of the most serious problems.

Mr. MILLER. Do you have any clinical trials right now?

Dr. LESHNER. We have 26 compounds in advanced clinical trials, and we have about another 8 or 10 compounds sort of lined up waiting to go into clinical trials. That's a part of, by the way, expanding on Dr. Varmus' answer, that's a part of what this initiative is, is to try to accelerate the rate of medication development. For example, we're screening the libraries of pharmaceutical companies. We have about 12 strategies, I promise not to give you all of them.

But we're trying to use converging strategies here.

SUCCESSOR DRUGS OF ABUSE

Mr. MILLER. What are other drugs that are going to be successor drugs to crack cocaine?

Dr. LESHNER. Well, we worry about it. We're very worried about methamphetamine. That's why we went and had that town meeting in San Francisco. It was an interesting experience for me that here on the east coast, you almost never hear about methamphetamine. But methamphetamine has now replaced cocaine in San Diego as the drug most likely to draw people into treatment.

That's a little statistic most people don't know. It's a regional problem. We were astounded, I was astounded, not everyone was, Ms. Pelosi was there, she was not astounded.

Actually, we had representatives from five state authorities who came to find out about methamphetamine and what to do. We have the same problem, we have no medication for methamphetamine, although we've made a lot of progress in understanding its neurobiology. And that will help us.

Mr. MILLER. Well, all this research has a lot of personal benefit but also economic benefit.

Dr. LESHNER. Yes, sir.

Mr. MILLER. Crime issues, as you mentioned, AIDS issues and all that. So I find it interesting and obviously very supportive, as does everybody on this committee. So thank you, sir.

Dr. LESHNER. Thank you. Thank you for saying so.

Mr. PORTER. Thank you, Mr. Miller.

Mrs. Northup.

NICOTINE ADDICTION

Mrs. NORTHUP. Dr. Leshner. I'm sorry, Mr. Chairman, I was a few minutes late, so if this is repetitive.

Does tobacco fall under the category of addictions?

Dr. LESHNER. Nicotine does. We do study nicotine addiction.

Mrs. NORTHUP. Do you study the relationship between people that start using nicotine at an early age, and then become drug addicted to something else later on? Do you recognize that as a gateway drug? Does it increase the chances of that happening?

Dr. LESHNER. It's a very important question. I'm a scientist, and so I feel that I should be very precise when I speak about the relationship of one drug to another drug. The term gateway, as used by some people, not by all people, implies direct causation. The data that we have are correlational.

What they show are unequivocally that the odds on someone who uses tobacco or alcohol at an early age becoming addicted are incredibly higher than someone who does not use those drugs. That is between 65 times higher, and 85 times higher. However, that's a correlation, that's not a literal cause. That does not mean that if you smoke cigarettes, you will become an addict. It just means that the risk of it is substantially higher.

The obverse is also true, that is to say, if you don't use alcohol, tobacco or marijuana by the age of 21, the odds on you ever becoming addicted to a substance is almost zero. It is not zero, but it's almost zero. However, again, that is not literal causation. It's sort of a funnel, if that makes sense. There's a funnel of all people who smoke, and the odds are very high, are much higher if you smoke than if you don't smoke.

Mrs. NORTHUP. How much research have you done into the pathological reasons for that and the habitual user? In other words, do you have a rebellious child, or do you have any sort of evidence that the pathological, you were talking about here increases in dopamine that are created by the addiction. Does that then sort of draw a person, pathologically, to fulfilling a craving and the drugs seem to do that, then they get hooked in there even faster? I know that's a real novice way of explaining it.

Dr. LESHNER. It's absolutely not a novice way, it's actually very sophisticated. Almost every abusable substance, nicotine, marijuana, cocaine, heroin, causes an increase in dopamine secretion and a spike not dissimilar from the one, sadly you missed last year that I showed. We have come to believe, and I need to be cautious about this, because I think this is early in our understanding, but there appears to be some commonality to the brain mechanisms of addiction.

At a minimum, there are certainly these similarities. What I don't know is whether in fact having one addiction makes you predisposed to have another addiction, literally. All I can tell you is there is some cross sensitization, across drugs. If you are addicted to heroin and then you go off, cocaine can prime you back to craving heroin. Then the reverse, of course, is amphetamines and cocaine.

So there is some commonality, but I think we should be very careful about it.

Mrs. NORTHUP. So are you saying that there is at least some indication of it creating a pathological interest or a possibility towards other addictions?

Dr. LESHNER. I think, being careful, I need to say I don't know. But I myself believe from my reading of the literature that we are beginning, and we're in an early stage, to understand, and behaviorally of course, that there ought to be some kind of commonality, some common essence to the phenomenon of addiction.

Mrs. NORTHUP. Do you have any pathological studies as to why a 13 year old that picks up a cigarette is going to become addicted compared to a 21 year old? Does it happen that that's pathological, that your incidence of creating these dopamine trails are more inclined to occur with earlier cells, earlier in life, than later in life? Or is it that if you have the tendency towards that, that you just tend to gravitate towards tobacco earlier?

Dr. LESHNER. We don't know, is the answer. People have sadly not studied developmental changes in those particular brain systems. But we have actually, as an Institute, been posing this question recently.

Mrs. NORTHUP. Are you doing those things? They're so important to me.

Dr. LESHNER. We have a lot of studies going on, not only on the psychosocial risk factors, but the biological vulnerabilities and the biological risk factors for not only the abuse of a specific drug, but for drugs generically. And again, I don't want to be promissory, but there are some data to suggest that there are genetic components to the vulnerability to becoming addicted. We haven't made a lot

of progress, in our case, in identifying any of those genes, of course. But there are familial differences and suggestions that there are individual differences and age differences.

Mrs. NORTHUP. The statistics show, I think, 85 percent of smokers become addicted, is that right? Fifteen percent of alcohol users become addicted. So there would have to be some genetic or physiological reasons——

Dr. LESHNER. There's no question in my mind——

Mrs. NORTHUP [continuing]. Why you're inclined to become addicted.

Dr. LESHNER. I actually believe that most people are ultimately susceptible to being addicted. That doesn't mean everyone will be. It just means that given enough drugs for a long enough period of time, I believe people can in fact be made addicted. That's, again, not totally clear.

Mrs. NORTHUP. That's all at this time.

Mr. PORTER. Thank you, Mrs. Northup. Mr. Stokes.

AIDS AND DRUG ABUSE

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Leshner, always a pleasure to see you.

Dr. LESHNER. How are you, sir.

Mr. STOKES. Dr. Leshner, AIDS continues to take a devastating toll on people worldwide. In the United States today, it's the leading cause of death among people in the 25 to 44 year old age group. These individuals are probably in the most productive period of their lives.

Tell us what portion of the AIDS–HIV toll is attributable to drug abuse.

Dr. LESHNER. Actually, I think we have just reached the point where intravenous drug use, directly or indirectly, is over 50 percent of the cause of new cases of AIDS. In fact, these two pandemics are totally intertwined. Our research program reflects the connection between the two of them, I hope. It's our intention that it reflect that.

A very large percentage of women who are infected with AIDS, I think the latest number is 55 percent, and 64 percent of children infected with AIDS are drug-related. There's no question that these are totally intertwined pandemics.

Mr. STOKES. Can you tell us what major research initiatives you now have underway and what you are planning for fiscal year 1998?

Dr. LESHNER. We have just about a third of our Institute's total budget, $116 million, that is devoted to HIV–AIDS. Our program runs the gamut from treatment approaches to using AIDS prevention as a part of treatment, so that we affect the public health aspect of AIDS, not just the individual's aspects of AIDS, of course. So treatment is one.

Outreach to active drug users is another. As I said earlier, not everyone who uses drugs is willing to enter into treatment. We have to change the risk behaviors of those out of treatment individuals.

We have a variety of studies looking at the medical consequences of the intersection between the two. We have some studies on the

epidemiology of the intersection. We have a pretty broad program that spans almost everything from the molecule to managed care. And much of it is focused towards outreach to active drug users in order to reduce the public health problem as well as the problem for the individual.

Mr. STOKES. How much of your Institute's budget is invested in AIDS–HIV drug abuse research?

Dr. LESHNER. I would say that a third of our budget is attributed to HIV–AIDS, and comes through that route. However, because of the intertwined nature of the two epidemics, it's difficult to give you a more accurate description. Much of the treatment research that we support is of course of great significance, because drug treatment is the best prevention for the spread of HIV–AIDS.

Mr. STOKES. It would seem to me that this is probably an area in which there ought to be significant outreach. Is this the case?

Dr. LESHNER. Well, there has been. NIDA and CDC, have very extensive outreach programs. We have had a number of multi-site studies looking at the most effective AIDS outreach techniques. And I'm pleased to say that they've been extremely successful in reducing AIDS risk behavior, even in active drug users, by 35 to 50 percent. And that's very significant. That's not only sharing needles. That's using bleach, that's re-using needles. And again, the implication of that goes beyond just the individual.

COMPARING UNITED STATES DRUG ABUSE

Mr. STOKES. In terms of understanding the nature and the extent of the drug abuse problem in the United States, how do we compare with other nations throughout the world?

Dr. LESHNER. Well, at the moment, we have probably as a percentage as high an overall drug abuse problem as most countries. I'm sorry to report, most countries are trying to catch up. We are at great risk. NIDA has done some international work, trying to come to understand emerging drug problems and see how we can help other countries prevent their drug problems, such as China and countries in southeast Asia and Russia, and countries within Eastern Europe.

But at the moment, particularly because of the crack epidemic, we have very high levels of relative drug use in this country. Most other countries have predominantly heroin problems.

DEMOGRAPHICS OF ADDICTS

Mr. STOKES. What is the extent of the problem in the United States across racial and ethnic populations?

Dr. LESHNER. The distribution across racial and ethnic groups, if you just take large groups, is about equal, the percentage of addicts who are Caucasian, who are African-American, or Hispanic. However, as adults, minority group individuals are heavily over-represented in the population of addicted individuals.

It's been informative that in younger people, actually, minority individuals begin using drugs later than Caucasian individuals. That may be tied to socioeconomic status, obviously. That's probably the most likely cause. But there are substantial differences in the demographics.

MINORITY RELATED RESEARCH

Mr. STOKES. Doctor, can you bring the Committee up to date on targeted research and research training that is currently underway to further advance knowledge across racial and ethnic populations?

Dr. LESHNER. Well, we, as you would imagine, maintain a very large program that's geared towards understanding the particular problems of various cultural and ethnic groups. We spend about $67 million a year focused on specific, particularly minority populations.

One of the things that's been most important, and I won't take very long with it, is that we've come to understand the need for culturally appropriate prevention and treatment programs. It's obvious once said. However, it's unfortunately not frequently done.

The places where we've learned this, for example, are in traditional therapeutic communities. Those ethnic groups that don't like confrontation don't do very well in some of those, and they've had to be modified. This is a result of the kind of research that we support that's looking at a focus on the specific needs and the specific problems of different ethnic groups. It's a large part of our portfolio.

Mr. STOKES. Can you tell us, what is the plan for fiscal year 1998, and how much is included in your fiscal year 1998 budget request for this activity?

Dr. LESHNER. Our total best estimate of minority-related research is about $76 million for fiscal year 1998. Some of that is devoted to our focused efforts to increase the number of minority investigators that NIDA supports. We believe it's very important for a variety of reasons to have a larger number of minority investigators. As far as we can tell, we've been quite successful at recruiting additional minority investigators in the last few years.

So we spend, actually, probably on the order of $3 million or $4 million a year just on targeted recruitment activity to bring minority investigators into the pool of researchers.

Mr. STOKES. Thank you, Doctor. I suppose I'm at the end of my time, Mr. Chairman.

Mr. PORTER. You actually have two more minutes if you'd like.

Mr. STOKES. Maybe we can get in another question here.

Dr. LESHNER. Sure.

NEEDLE EXCHANGE PROGRAMS

Mr. STOKES. Earlier on, as I came in, you were about to talk a little bit about needle exchange. And of course, my concern is, to what extent are there needle exchange programs in the United States, and whether or not the Institute has any major research underway in this area.

Dr. LESHNER. We have about 15 grants at the moment on the efficacy of needle exchange, and on various aspects of the use of needle exchange as a device to prevent the spread of blood-borne infections. There are many needle exchanges operating, either legally or illegally, in this country. Those are of course not supported by the Federal Government and are not supported by our Institute as part of the Government.

The decision whether or not to have needle exchanges and to fund them is done at the State and local level.

Mr. STOKES. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. PORTER. I have about three or four more questions. Do other members have additional questions they would like to ask?

Mr. STOKES. I have a few more.

COCAINE MEDICATION DEVELOPMENT

Mr. PORTER. Let's see how fast we can talk.

Finding an effective treatment for cocaine abuse, which you referred to earlier, Dr. Leshner, has been a Federal priority since at least 1988. And now, almost 10 years later, although some promising research leads have been identified, there still is no medication to treat cocaine abuse. Do you find that record disappointingly slow, or is it unreasonable to assume that we're going to be able to find something, say in 10 years?

Dr. LESHNER. Well, NIDA's medication development program actually came into being in 1992. And so our focused effort has really only ramped up then. I think the truth is that it's only been in the last two to four years that we've had the fundamental neuroscience to give us the molecular targets at which to approach medication development.

As I hope I've made clear, we've had unbelievable advances in understanding the ways in which drugs of abuse affect the brain and produce addiction. But that's really come in the last three to five years. Those targets are why we're so optimistic now that we have an opportunity to come up with these medications, and we're doing what we call strategic medication development, that is, focusing in on real biological targets, rather than screening thousands of drugs and hoping.

So, we are optimistic. I would like the drug yesterday.

PREVENTION PROGRAMS

Mr. PORTER. With reports of increasing drug abuse among teens, it's especially important to have good information about which prevention programs are effective. Your Institute supported research which indicated that, contrary to popular perception, the DARE program is not effective. What types of prevention programs do work, according to your research?

Dr. LESHNER. Let me just make clear, we believe the DARE program is an evolving program. So any study done of a particular program as a snapshot in time ought to be viewed carefully. And I will tell you that we have been working with DARE to help them evolve their approaches according to the scientifically based principles we have been talking about.

I think that there are again a number of principles one could delineate. But one of the most important ones, which will sound obvious, is persistence, that is, if you begin a program early in middle school, you need to have another program later and another one later. It needs to involve not only one mode, like media, or basketball games or whatever, it has to be a much more comprehensive kind of a program.

As I mentioned earlier, we have our new guide that we're sending out to only 100,000 of our closest friends, which will delineate the kinds of principles we were talking about, based again on the scientific research we've supported.

BUPROPION

Mr. PORTER. Your budget justification mentions pending FDA approval of a drug, Bupropion, as the first non-nicotine prescription drug. Is this drug thought to be more effective than the transdermal nicotine patches currently available?

Dr. LESHNER. I think it's a fundamentally different approach. Bupropion is typically used as an antidepressant. It works on the norepinephrine system in the brain. It is used to treat the dysphoria that occurs during withdrawal from nicotine addiction and to treat the craving. We also are trying a compound, by the way, for cocaine addiction. I'd give it about a B minus. I don't know yet whether it will be better than the transdermal patch. It may be that it needs to be used in combination.

Mr. PORTER. Was the drug developed with NIDA financial support?

Dr. LESHNER. A lot of research has been done on the drug supported by NIDA. But I don't know, the research done by the pharmaceutical company was done before I came to NIDA. I don't know the degree of relation.

Mr. PORTER. Mr. Miller.

COCAINE MEDICATION DEVELOPMENT

Mr. MILLER. On cocaine, are the pharmaceutical companies involved in this? Is there much of a market for them? Nicotine you see a market for the product, as a motivation. Is there a market for cocaine?

Dr. LESHNER. Actually, there isn't a market for cocaine. No, there is not. It's been a terrible problem for us. It's why we've developed our own medication development program and worked so hard with pharmaceutical companies to make their lives easier so they will become more interested. You will recall that Dr. Varmus a couple of years ago changed the CRADA policy so that there was a change in the pricing laws. It brought about six more companies into collaboration with our Institute, when they began to see financial incentives to help. So the market is a very big issue for us.

Mr. MILLER. Thank you.

Mr. PORTER. Mrs. Northup.

PREVENTION PRINCIPLES BOOK

Mrs. NORTHUP. Yes, I'd like to go back to some questions about drug use. You know, in here, I noted somewhere you mentioned that you all had actually created a book that was a very user-friendly guide to the prevention principles. I'd like to see a copy of that, if you could have that sent to my office.

Dr. LESHNER. We will.

PRENATAL DRUG USE STUDY

Mrs. NORTHUP. Also, you've done a study on the neurological effects of prenatal drug use. I'd love to see that, too.

EFFECTIVENESS OF PREVENTION PROGRAMS

Mrs. NORTHUP. Now, to go back to questions, I think especially following the line of my earlier question about creating the dopamine trail or whatever, it's pretty clear that prevention is really important. And in terms of the use of your budget, that's really important. I know that you say that's one of your goals, but I'd be interested in knowing what percentage of the $30 million are actually going to prevention strategies.

I also know that you've talked about these guides to prevention. Have you created a best practices sort of scheme that is then communicated to the Department of Education and Health and Human Services through appropriate agencies that they oversee, so that best practices are actually in effect in their programs?

Dr. LESHNER. Let me start with the second part, if I may. We have worked very closely within the last year or so with the Department of Education and the Drug Free School program. And of course, within the Department, Secretary Shalala has been a very strong supporter of our prevention program, and of our principle of using science to increase the effectiveness of prevention approaches.

So we've had very good, actually, cooperation. We are planning a very broad dissemination of these principles that have been derived.

What we are not doing, just to be clear, what we are not doing is endorsing one or another extant program. Because we think that what we get from science is principles, not a program that necessarily would work in all sectors.

Mrs. NORTHUP. Let me then ask it a little bit differently. Do you look at existing programs, for example, the DARE program that we have seen some disappointing statistics from. Do you do a different kind of analysis, examining how they address the medical research that you might do, and do you propose changes to make them more effective?

Dr. LESHNER. We do some studies looking at the efficacy of existing programs. But candidly, we're not very interested in the yes-no question for a particular program. We're more interested in, "does it work; why does it work; what's the essential element that might make it work."

However, having said that, we do have a number of relationships, particularly with very large programs like DARE or the Partnership for a Drug Free America, where we work collaboratively, and some days they think we bother them too much. But we do in fact try to take the science we support and make sure it's used.

INFORMATION DISSEMINATION

Mrs. NORTHUP. In my opinion, one of the most critical parts, lowering the use of drugs among teenagers, is real clear information. It's amazing the sort of conventional wisdom these kids pass

around to each other about how marijuana helps you concentrate more and longer and better and all those things. I wonder how much you do to disseminate the clear effects of these drugs, so that their own pass-around information doesn't take root.

Dr. LESHNER. Well, I think your fundamental point is a very important one. We have learned the hard way that hyperbole and exaggeration is the worst form of drug prevention. So we have been working hard to provide science-based information. We are now, I think, on our second millionth copy of our brochure on marijuana facts for teens and marijuana facts for parents. So that in fact it's all science-based.

Mrs. NORTHUP. You can send a few of those copies over, too.

Dr. LESHNER. We will, we'll be happy to.

PREVENTION INCREASE

Mrs. NORTHUP. Also, I don't think I got an answer about the $30 million that's in prevention. If you don't have that, could you please provide that?

Dr. LESHNER. Sure, I will.

[The information follows:]

Dr. Leshner: Fifteen to twenty percent of the $30 million increase that NIDA has requested will go to prevention research.

Mrs. NORTHUP. Okay.

Mr. PORTER. Thank you, Mrs. Northup.

Mr. Stokes.

NEEDLE EXCHANGE AND AIDS

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Leshner, one follow-up question on needle exchange. As a researcher, and as the Director of the National Institute on Drug Abuse, in your professional judgment, what should our Nation be doing with regards to AIDS–HIV and needle exchange?

Dr. LESHNER. I do believe, sir, that needle exchange can be an effective part of a constellation of HIV prevention programs. I believe that the statement that needle exchange can reduce the spread of blood-borne infections, including HIV, is wholly supported by the data.

MEDICAL MARIJUANA CONCERNS

Mr. STOKES. Okay. Doctor, the debate continues to focus on marijuana, especially as it relates to the use for medical purposes and the implications for contributing to increased drug abuse. What are your concerns regarding this matter?

Dr. LESHNER. My concern is that the question be resolved through science, and that the question not be resolved through political decision one way or another. I would like to have questions like this handled, just as we do for any other compound that's purported to be a medication. I would like to have it resolved through scientific study. We do that for all other kinds of medicines in this country. That's my own belief.

DRUG ABUSE COSTS

Mr. STOKES. Doctor, last year the Institute indicated that drug abuse costs the Nation an estimated $67 billion, and that new estimates under development would incorporate data reflecting each of the following major components: drug-related criminal justice expenditures, crack cocaine, AIDS epidemic, medical and social costs associated with the resurgence of TB and hepatitis, and prenatal exposure to drugs.

Doctor, what is the cost of drug abuse to the Nation?

Dr. LESHNER. Sadly, we don't have a figure better than that 1990 number of $67 billion. I can tell you that a study done by the Center for Addiction and Substance Abuse at Columbia University tried to do the analysis you're referring to just for New York City, and found the number of $20 billion. The number, in my own belief, is substantially higher than $67 billion. We're in the process, we have a study that we've contracted for jointly with NIAAA that's looking at it, and the results are not yet quite in.

EFFECTIVE DRUG TREATMENTS

Mr. STOKES. I hope you will share that with us whenever you have that data.

Doctor, what can you tell us this year that you could not tell us last year with regard to how close we are to having an effective treatment for any of the major drugs of abuse, like cocaine, and equally important, treatments that do not themselves create another adverse dependency?

Dr. LESHNER. I would like to say that we have very effective behavioral forms of treatment for drug abuse. They're not panaceas that work identically for all individuals. But there are a number of clinical trial documented efficacious treatments. Sadly, they're not used as broadly in the real world as we would like. That's a part of our treatment initiative.

But in the last few years, we've seen tremendous development in the techniques of psychological therapies like cognitive behavioral therapy, family therapies that work particularly well for young people. We are in the process of having these manualized, we're putting them into manuals so they'll go out to the field.

But there are treatments that can be very effective. It's a big task, of course, to find the right treatment for the right individual.

COCAINE CRAVING

Mr. STOKES. I understand that cocaine craving studies have been conducted, and two studies have used brain imaging techniques to determine which areas of the brain are activated during craving. Can you tell us anything about this?

Dr. LESHNER. There has been, as one chart showed, we are very interested in using the wonderful tool of brain imaging to help us understand what's going on in living, breathing individuals who are awake and craving. There has been a convergence of evidence now from three discrete laboratories, beginning to lay out the brain circuits involved in craving, and some of the mechanisms involved in craving.

So there's been tremendous progress, particularly in the last year, three separate papers have been studied identifying a particular site of the brain called the amygdala, part of a circuit where craving is involved. And of course, the frontal lobe of the brain is activated during craving.

So we have made a lot of progress in the neurobiology, the basic neurobiology, without yet a great deal of specificity. But again, we have a number of grants underway to look at that.

Mr. STOKES. Thank you, Dr. Leshner.

Mr. Chairman, I have a few additional questions which I'll submit for the record.

Mr. PORTER. Thank you, Mr. Stokes.

Each of us has additional questions we would like to submit for the record.

Dr. Leshner, thank you for your good testimony and the fine job you're doing at NIDA. We appreciate your coming here and testifying today, and we want to work very closely with you on one of the Nation's most serious problems.

Thank you.

Dr. LESHNER. Thank you, sir, for your support. Thank you all.

Mr. PORTER. The committee will stand briefly in recess.

[The following questions were submitted to be answered for the record.]

RELATIONSHIP BETWEEN MARIJUANA AND ABRUPT TERMINATION OF PREGNANCY

Mr. Porter: A research finding announced last fall suggests a relationship between exposure to marijuana and abrupt termination of pregnancy in the very early stages. What is the likely frequency of this event? Is there any information about the level of exposure necessary to trigger pregnancy termination?

Dr. Leshner: The study in question used mouse embryos at very early stages (8 cell or 3 day stage of development.) A cannabinoid antagonist blocked the embryotoxic effect of the cannabinoid, suggesting the effect was due to activation of cannabinoid receptors (Yang, Para, and Day Biology of Reproduction Oct. 1996). It is not really possible to extrapolate to the human situation in terms of the frequency of the event and the level of exposure that might be necessary to trigger pregnancy termination and Federally-funded research in this area is restricted.

Current research shows that the use of marijuana (cannabis) during pregnancy is not associated with premature delivery (abruptio placentae). A copy of an abstract of a recent article (The Impact of Cocaine and Marijuana Use on Low Birth Weight and Preterm Birth: A Multicenter Study, Shiono, Klebenoff, Nugent, Cotch et al., Am J Obstet Gynecol. 1995 Jan; 172 (1pt 1):19-27) is attached.

We are not aware of any published or unpublished reports of frequency or the exposure level(s) that could trigger or cause abruptio placentae in women who smoke marijuana during pregnancy. In fact, pharmacologically marijuana (cannabis) or its active chemical constituent, tetrahydrocannabinol (THC) is not a vasoconstrictor (unlike cocaine or amphetamines), that could result in abruptio placentae.

RESEARCH

Ms. Northup: You mentioned that your institute did 85% of all research on drug abuse worldwide. Who does the other 15%?

Dr. Leshner: According to a 1988 Report, "Defining the Scope of Alcohol and Drug Abuse and Mental Illness Research," the National Institute on Drug Abuse supports approximately 88% of the World's research on drug abuse and addiction. The remaining 12% of the research is attributed to other Department of Health and Human Service Agencies, Department of Veterans Affairs, the National Science Foundation, Department of Justice, the US Department of Agriculture, other governments, U.S. state governments, industry and private philanthropical organizations.

CRAVING

Ms. Northup: How do you believe your Institute's research on craving of drugs can be used in prevention research?

Dr. Leshner: For many years, physicians and other clinicians have reported that drug-addicted patients say they crave drugs. And, patients say that they went back to using drugs after having stopped because of strong feelings of drug craving. This makes the study of craving an important priority area for the National Institute on Drug Abuse. Clearly, if craving is one of the causes of relapsing to drug abuse, then finding solutions to limiting craving feelings, both with behavioral and pharmacological therapies, will serve as important preventive measures to drug abuse and addiction. Craving research can further prevention research by making available more accurate information about the causes of craving, or differences in cravings across different kinds of drugs, or increased craving when drugs are less available. This information can then be used in family, school and community based prevention efforts.

PREVENTION RESEARCH

Ms. Northup: Please provide the percentage of your budget which is focused on prevention research versus behavioral research? Why is there more of a focus on behavioral research?

Dr. Leshner: NIDA supports a comprehensive portfolio on all aspects of drug abuse and addiction, including prevention and behavioral research. These two areas however should not be looked at as discrete areas but as overlapping. Basic behavioral research plays an important role in the development of effective prevention programs. Basic behavioral research leads to an understanding of the biological, psychological, and environmental factors and their combinations involved in a person's first use of drugs and the risk for subsequent progression from abuse to addiction. For example, NIDA's Children and Adolescents Research Initiative investigates the roles that decision-making processes and peer pressure have on a child's susceptibility to drug-taking behaviors.

Since behavioral approaches are often the most frequently administered treatments for addiction and remain the only available treatment approaches for many drugs of abuse, NIDA supports a large number of grants in this area. Behavioral interventions also serve as adjuncts to pharmacological treatments, addressing concomitant interpersonal and environmental problems and facilitating medications compliance. Considerable progress has been achieved in developing effective behavioral therapies, but many questions remain about what works best, for whom and under what conditions.

In FY 1998, NIDA plans to spend $72.5 million on Prevention research.

Ms. Northup: What percentage of the $30 million increase that you have requested will go to prevention research?

Dr. Leshner: Fifteen to twenty percent of the $30 million increase that NIDA has requested will go to prevention research.

Ms. Northup: Most of your prevention research budget is focused on HIV and AIDS and how to prevent the spread of infectious diseases through needle sharing, etc. Why is this work being done by your Institute --- isn't this already being completed by the National Institute of Allergy and Infectious Diseases?

Dr. Leshner: The National Institute on Drug Abuse has supported research on the prevention of HIV infection among drug users, their sexual partners, and their offspring since the early 1980's. Given the large, and growing, proportion of HIV infections and AIDS cases related to drug use and abuse, one cannot adequately address the drug problem in this country without addressing the HIV/AIDS connection. Approximately one third of AIDS cases in adults are among injection drug users alone. Over half of pediatric AIDS cases occur in mothers who have been infected through their own drug use or have sexual partners who are injection drug users. NIDA has supported research on a variety of strategies to reduce the risk of HIV infection in these groups. These strategies primarily involve changing high risk drug using and related sexual behaviors through drug abuse treatment, education, and HIV counseling and education. The focus of the HIV prevention efforts at the National Institute of Allergy and Infectious Diseases (NIAID) has been on the development of biomedical approaches such as vaccines and topical microbicides. NIDA's program has, on the other hand, primarily focused on risk behavior change. NIDA has a long history of supporting research on risk factors for drug abuse and strategies to change behavior and reduce the consequences of drug use and addiction. These approaches are part of a continuum of prevention strategies that are being researched by several NIH Institutes, including the National Institute of Mental Health, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Child Health and Human Development, and the National Institute of Nursing Research, along with the NIAID and the NIDA.

TOBACCO

Ms. Northup: Has the FDA followed the recommendations by the Federal Advisory Board regarding bupropion?

Dr. Leshner: The FDA has not yet approved Bupropion for smoking cessation.

Ms. Northup: What other types of nicotine replacement are you working on?

Dr. Leshner: The National Institute on Drug Abuse (NIDA) has an ongoing program which supports research studies employing various methods to facilitate smoking cessation. Nicotine replacement therapy is currently widely used and has become central to most formal smoking cessation treatment programs, as well as now available over-the-counter. The majority of smoking cessation research at NIDA focusing on nicotine replacement utilizes polacrilex gum or transdermal patch. This research typically examines the optimum dose and schedule of nicotine. One small grant investigating nicotine delivery in the form of a nasal spray has been funded in the past and another study is currently examining the use of a nicotine inhaler. Behavioral strategies in some form are usually adjunct to most nicotine replacement protocols, since research has determined that effective treatment of nicotine addiction requires both pharmacological and behavioral treatment. NIDA also supports some studies which use the nicotine patch as a research tool. In these studies, nicotine is administered via the patch to experimental volunteers without using cigarettes. This allows the study of craving for nicotine or other smoking behavior by separating out the pharmacological from the behavioral factors.

SCHOOL BASED DRUG PREVENTION

Ms. Northup: Did your study on school based prevention programs include the DARE program? Would you care to comment on the recent reports that DARE is not effective, and relate this to your research on prevention programs?

Dr. Leshner: DARE was created in 1983 and continues to be an evolving program. There have been a number of evaluations that have been conducted on DARE since its inception. Several of the earlier evaluations have been critical of the effectiveness of DARE. NIDA's drug abuse prevention research program includes the study of several drug abuse prevention programs implemented by schools across the country, including DARE. Research from individual research studies sponsored by NIDA and a meta-analysis of multiple rigorous studies of DARE conducted over the past ten years that was sponsored by the Department of Justice and published by Dr. Susan Ennett and colleagues (American Journal of Public Health, 1994, 84, 1394-1401) indicates that DARE has not been effective in reducing adolescent drug abuse in comparison to controls. More recently, the Department of Education reported in their evaluation of school-based drug prevention programs (Feb., 1997) that school based programs that had the best prevention outcomes included: "prevention-related classroom instruction other than DARE, and special school-wide events that focused on prevention."

Given that DARE is in the majority of school districts in the United States, it is imperative that research sponsored by NIDA and other interested agencies continue to assess under controlled conditions the efficacy of DARE to prevent adolescent drug abuse. Toward this end, NIDA staff have been meeting with the senior staff of the national DARE organization to plan research and determine ways DARE might better reflect science-based principles. We are optimistic about the progress that is being made on this program.

Ms. Northup: News reports recently indicate that we have not won the war on drugs, and that the usefulness of parent-child talks about this subject varies according to the parent vs. the child. Does any of your research on prevention address this issue and if not, will you expand your research to include an investigation of relationship and discussion between parents and children?

Dr. Leshner: The National Institute on Drug Abuse has developed a program of research to study the efficacy and effectiveness of prevention interventions focused upon a broad spectrum of parent and child interactions to include child-parent discussions. For example, as part of a multi-level approach to family intervention for children at high risk for problem behaviors to include drug abuse, Dr. Thomas Dishion's research at the Oregon Social Learning Center suggests that an optimal strategy is to work with the entire family. This work could include brief, focused interventions on communications practices and competency skills or more intensive behavioral family therapy.

Another example is the Focus on Family project developed by Dr. Richard Catalano of the University of Washington which is a promising family approach to prevent drug abuse in children of parents who are in drug treatment. Parents are taught a variety of social competency or interactional skills to increase child involvement in problem-solving, provide opportunities for parental involvement in the daily activities of the child, set clear expectations for their children and to address conflict, and most importantly, parental techniques to effectively "monitor" the child's activities to include peer associations. In the study, the sample was divided into children ages 9 to 11 and children ages 12-14. The program consists of 32 parent training sessions which last for 1.5 hours each. Children attend 12 of the sessions to practice developmentally appropriate skills with their parents. The program offers drug relapse training for the parents. Preliminary analysis of the program indicates that it had a more positive effect on families with younger children. Researchers speculated that older children may have perceived changes in rule setting by the parents as too restricting and they had less positive perceptions of family involvement.

To address the many important prevention research questions posed by family-focused drug abuse prevention strategies, NIDA has developed a program of study and has published a research program announcement that targets this area of prevention research, entitled Drug Abuse Prevention Through Family Intervention. Areas of research include the study of developing and strengthening communications and interactional skills that are needed between parents and their children.

PREVENTION PROGRAMS FOR ELEMENTARY AND SECONDARY SCHOOL STUDENTS

Mr. Obey: Please summarize your findings on the effectiveness and importance of drug abuse prevention programs targeted at elementary and secondary school students.

Dr. Leshner: Currently, drug abuse is threatening the successful social and educational development of millions of our nation's youth. As a result, drug abuse prevention research has the highest priority at the National Institute on Drug Abuse (NIDA).

Drug abuse prevention research sponsored by NIDA indicates that science-based drug abuse prevention programs can be very effective in reducing the risk of adolescent drug abuse. Numerous well-controlled studies suggest that drug abuse prevention programs based upon improving social competencies, (such as drug resistance skills, interpersonal communications, and problem solving), and establishment of anti-drug abuse norms within schools and communities, (through effective media campaigns, parent education, community coalitions, and enactment of prevention policies) can significantly reduce the prevalence of adolescent use of marijuana, tobacco, alcohol, and illicit substances. Tragically however, health services research indicates that for the most part, science-based drug abuse prevention programs are NOT being implemented in schools across the country. Rather, schools are reporting the implementation of either untested drug abuse prevention curricula or the use of drug prevention programs that research suggests are not effective in preventing adolescent substance abuse.

AIDS/HIV AND DRUG ABUSE

Mr. Stokes: AIDS continues to take a devastating toll on people worldwide. In the United States, it is the leading cause of death among people in the 25 to 44-year-old age group. People in this age group are normally in the prime of life. These individuals are generally in their most productive years. What portion of the AIDS/HIV toll is attributed to drug abuse? What major research initiatives are underway in this area, and what is planned for FY 1998?

Dr. Leshner: Of total AIDS cases (cumulative) in the U.S. reported as of June 1996 by the Centers for Disease Control and Prevention in Atlanta, approximately 76% were among individuals between the ages of 25 and 44. Of the cumulative adult/adolescent AIDS cases (over age 13), over one-third (36%) were drug abuse-related, that is, among injection drug users (IDUs), or those who were infected through sexual contact with an IDU. These cases, by exposure categories, were distributed as follows: approximately 25% were among IDUs, 7% among men who have sex with men and are IDUs, and 4% were among sexual partners of an IDU.

Recent CDC data suggest that 50% of new HIV infections (and therefore future AIDS cases) are among IDUs, and in addition, a significant portion of the 25% of new HIV infections among heterosexuals are drug abuse-related in that they are from sexual contact with an IDU. (Holmberg, AJPH, 1996)

NIDA has a multiple disciplinary program of research which comprehensively addresses the AIDs and drug abuse problem. The focus of this program has been to develop improved strategies to reduce drug-abuse related HIV/AIDS risk behaviors and to reduce the transmission of HIV. These strategies include drug abuse treatment and outreach strategies to drug abusers not in treatment. In support of this effort, NIDA's program also includes epidemiologic studies of seroincidence, seroprevalence, and progression to disease among drug users (in and out of treatment), their sexual partners, and their children; and studies of the effects of drugs of abuse on the immune system.

In FY 1998, NIDA will continue to support research to improve existing treatment approaches and to develop new pharmacologic and behavioral therapies to improve drug abuse treatment as an AIDS prevention strategy. NIDA will also continue to conduct research to improve educational and behavioral strategies to reduce HIV transmission among drug abusers, and has begun new initiatives focussing on gender and cultural issues, drug-using networks, and pediatric AIDS.

Finally, NIDA plans to continue to develop and enhance effective methods for treating and preventing drug abuse-related risky behaviors. The continuation and strengthening of this research are central to the Nation's hopes for developing effective HIV/AIDS prevention strategies.

Mr. Stokes: With regard to drug abuse as a major risk factor for AIDS/HIV, to what extent does this account for the spread of AIDS across gender and across racial and ethnic groups who are at increased risk -- Please be specific?

Dr. Leshner: The AIDS epidemic has had and continues to have a disproportionate impact on African American and Hispanic populations in the United States. As of June 1996, African Americans (age 13 and older) represent 10.9% of the population, but 35% of all AIDS cases. Hispanics represent 8.4% of the population (age 13 and older), but 18% of cumulative AIDS cases. In addition, African Americans represent 52% of all HIV cases that are not AIDS. Significant differences also exist when AIDS cases are examined by exposure category. Among white males, injection drug users (IDUs) account for 16.6% of AIDS cases. Among black males, IDUs account for 43.8% of cases, and among Hispanic males, IDUs account for 44% of cases. Drug abuse is linked with AIDS in a much higher percentage of blacks and Hispanics than with whites.

Drug abuse is the single most significant risk factor for AIDS among women. Among females, 64% of AIDS cases are linked to drug abuse, either through injection drug use or sex with an IDU. IDUs accounted for 46% of the cumulative number of all women (13 years and older) diagnosed with AIDS (78,654). Of the cumulative female IDU AIDS cases, African American females accounted for 58%, Hispanics, 20%, and Whites, 22%. For the cumulative AIDS cases of women who had sex with an IDU, African Americans comprised 50%, Hispanics, 28%, and Whites, 22%.

Mr. Stokes: Have we had any new findings with regard to the relationship between AIDS/HIV and drug abuse, explain.

Dr. Leshner: Emerging data show that drug abuse is the single largest risk factor for new HIV infections. A recent CDC report suggests that a majority of new HIV infections (as contrasted to AIDS cases) are drug-abuse related. While approximately one third of the AIDS cases are related to drug abuse through injection drug use, sexual contact with an injection drug user (IDU), or perinatal transmission to the infant of a mother infected through her own drug use or through sexual contact with an IDU, this report suggests that half of the new HIV infections occur in IDUs, and that a significant proportion (up to another 25%) of cases transmitted heterosexually occur among IDUs and their sexual partners. Research has also shown a significant association of maternal drug use during pregnancy with an increased risk of perinatal HIV transmission. In one study, mothers who used drugs were more likely to transmit the HIV to their offspring than non-drug using mothers (27% vs. 16%).

Mr. Stokes: How much of your Institute's budget is invested in AIDS/HIV Drug Abuse research?

Dr. Leshner: Approximately 31% of our budget is directed to AIDS/HIV research.

Mr. Stokes: Are there outreach activities underway and/or planned by the institute in this area? What portion of the budget is allocated to this effort?

Dr. Leshner: **Outreach Activities Underway** -- Since 1987, NIDA has supported two large AIDS community-based outreach intervention research programs: "The National AIDS Demonstration Research" (NADR program), 1987 -1992, and the "Cooperative Agreement for AIDS Community-Based Outreach Intervention/Prevention Research Program" (1990 - ongoing). Together, these two research programs have reached more than 75,000 out-of-treatment injection drug users and crack/cocaine users in over 40 communities with a standardized intervention that combines outreach with HIV testing and counseling risk reductions. Fourteen communities have been involved in intervention research programs since 1987. Community-based outreach will continue in six of these communities through 1999.

The National AIDS Demonstration Research (NADR) Program was initiated in 1987 by the Community Research Branch (CRB) of the National Institute on Drug Abuse (NIDA). By 1988, a total of 41 projects were involved in NADR, operating in 47 communities within those cities. It was designed to limit the spread of AIDS among out-of-treatment injection drug users (IDUs), crack cocaine users, and others at demonstrated risk for initiating injection behavior. The NADR Project reached over 45,000 out-of-treatment IDUs and over 10,000 IDU sexual partners.

The Cooperative Agreement (CA) for AIDS Community-Based Outreach/Intervention Research Program was initiated in September 1990 by NIDA's CRB. By August 1994, the program had grown to 23 research sites -- 21 sites located in the United States and one each in Puerto Rico and Brazil. The Cooperative Agreement Database is the largest and most current database on out-of-treatment IDUs and crack users. As of January 31, 1997, the Cooperative Agreement Database included information on multi-ethnic/racial populations of male and female drug injectors and crack users at risk for HIV infection (N=25,777). Outreach programs will continue in six sites through 1999.

At the recent NIH Consensus Development Conference on "*Interventions to Prevent HIV Risk Behaviors,*" February 1997, a review and evaluation of 36 publications resulting from the National AIDS Demonstration Research Program and the Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research Program provided the following information.

Outreach-based interventions have resulted in significant:

- **reductions in drug risks (stopping injection, reducing frequency of injection), (reducing multiperson reuse of injection equipment and paraphernalia)**
- **increased safer behaviors (needle disinfection, entry into drug treatment, use of condoms).**
- **reductions in HIV incidence.**

Planned Outreach Activities: With the epidemic evolving and subgroups of at-risk populations emerging (e.g., new injectors, women, crack/cocaine users), the Institute will be encouraging researchers to implement community-based interventions to prevent the further spread of HIV in these risk groups. NIDA also has interest in continuing outreach in communities to assist IDUs who have changed their behaviors to sustain lower or no risk HIV behaviors.

Portion of the budget allocated to this effort: NIDA's total AIDS budget for fiscal year 1996 was $153.2 million. Of this amount, approximately $11.8 million supported outreach intervention research grant activities.

EXTENT OF THE PROBLEM

Mr. Stokes: What is the extent of the drug abuse problem in the United States and how does it compare with that of other countries?

Dr. Leshner: An estimated 12.8 million Americans, about 6 percent of the household population aged twelve and older, currently use (within the past 30 days) illegal drugs. This number of "past month" drug users has declined by almost 50 percent from the 1979 high of 25 million. In regard to how the U.S. drug problem compares to other countries, in the past, the United States has been cited as having the most serious substance abuse problem in the industrialized world. However, it is difficult to substantiate because little valid and reliable information on drug use is available for many--if not most--other countries. There are a number of countries that have followed the United States example and have conducted comprehensive surveys, including Sweden, the Netherlands, Greece, Italy and Spain. While limited, these data suggest that most countries of the world have substantial drug abuse problems ranging from inhalant use among street children to misuse of medical prescriptions among the elderly.

Mr. Stokes: What is the extent of the problem across racial and ethnic populations in the United States?

Dr. Leshner: The problem of drug use in our country cuts across demographic subgroups. The use of some substances, such as marijuana, is increasing for people of all race/ethnicities. Relationships between race/ethnicity and drug use are complex and vary considerably according to type of drug and intensity of use as well as by age and socioeconomic factors such as education, employment, and income.

Monitoring the Future Study data indicate that, between 1992 and 1996, past year marijuana use has increased dramatically among all three grades surveyed and in virtually all demographic and geographic subdomains. Among African-American 8th graders, past year use tripled (4.1% of 8th graders in 1992 to 14.0% in 1996). Marijuana use also tripled among 10th grade African Americans during this time period, rising from 7.6% in 1992 to 25.7% in 1996. For African American seniors, past year use of marijuana increased from 11.5% in 1992 to 30.2% in 1996. Among

Hispanic eighth graders, past year use of marijuana rose from 11.9% in 1992 to 20.8% in 1996. For Hispanic 10th graders, the proportion reporting past year use went from 18.9% to 34.6%. By comparison, the proportion of white 10th graders reporting past year use went from 17% to 32%.

Data from SAMHSA's 1995 National Household Survey on Drug Abuse (NHSDA) for persons 12 years of age and older, show that the rate of current (past month) illicit drug use for African Americans (7.9 percent) remained somewhat higher than that for whites (6.0 percent) and Hispanics (5.1 percent). However, among just youths the rates of use are about the same for the three groups. The rate of current illicit drug use for youths in "other" race/ethnicity groups increased from 2.7 percent to 11.2 percent between 1994 and 1995. This result should be viewed with caution, however, as the NHSDA sample size is small for this group. Most current illicit drug users were white. There were an estimated 9.6 million whites (75 percent of all users), 1.9 million African Americans (15 percent), and 1.0 million Hispanics (8 percent) who were current illicit drug users in 1995.

Data from the Drug Abuse Warning Network indicate that there were an estimated 531,800 drug-related hospital emergency department episodes in 1995, with 54 percent of these episodes occurring among whites, 27 percent among African Americans, and 9 percent among Hispanics; for the remaining 10 percent, race/ethnicity was unknown. Between 1994 and 1995, total drug-related episodes decreased by 10 percent for Hispanics (from 50,400 to 45,500). There was no change among whites or African Americans over this time period.

Mr. Stokes: Can you bring the committee up-to-date on targeted research and research training that is underway to further advance knowledge across racial and ethnic populations?

Dr. Leshner: We have been working intensely to ensure that the scientific knowledge base on drug abuse and addiction across racial and ethnic populations is inclusive and thorough so that effective policies and prevention and treatment protocols can be developed and implemented. In 1993, we created a Special Populations Office (SPO) in the NIH Office of the Director that has two primary goals: to ensure that racial and ethnic minority research (and research on other special population groups) is attended to and represented in the research we support, and to work to increase the number of individuals in underrepresented groups participating in drug abuse research. We have in place certain institutional practices and programs that we believe are making a difference in this regard. For example, the SPO reviews all proposed program announcements to ensure that issues of race and ethnicity are articulated, when appropriate. Therefore, the field is reminded of the need for research on racial and ethnic minorities each time a new program announcement is issued. The SPO and the Consortium on Minority Concerns, an institute-wide work group, have recently begun work to assess the status of minority research at NIDA, identifying areas of strength and need. In addition to these measures, there are some specific programs that target research and research training that are positively affecting our ability to stimulate

research and encourage more members of racial/ethnic populations to enter research. They include the following:

- Specific program announcements. We have two current program announcements that specifically call for research on racial and ethnic populations: PA-96-018, Drug Abuse Prevention/Intervention Research for Women and Minorities and PA 93-046, Drug Use and Abuse in Minority and Underserved Populations. We sponsored a technical assistance workshop, with support from the NIH Office of Research on Minority Health (ORMH), in 1996 for persons interested in applying for grants under PA 93-046. In addition, we have a joint announcement with NIAAA and NIMH titled Epidemiologic and Services Research on Mental Disorders that Co-Occur with Drug and/or Alcohol Disorders Among American Indians, Alaskan Natives, and Native Hawaiians.

We also support the Minority Institutions Research Development Program (MIRDP). Under this program support is provided to minority institutions (or institutions with a minority education emphasis) to conduct developmental or pilot work and provide research development experiences for faculty and students. We are re-issuing this announcement, possibly as a joint announcement with NIAAA.

Last year SBIR applications were solicited on developing guidelines or protocols to address the recruitment of racial and ethnic populations into drug abuse research. Applications received in response to that call were recently reviewed.

- Historically Black Colleges and Universities (HBCU) Initiative. This initiative supports two contracts, one to establish a research center on drug abuse and the other to provide technical assistance to 10 or more HBCUs on developing drug abuse research expertise at their schools. This initiative has stimulated research development in both the biomedical and behavioral fields. About seven applications were received for competitive review from these schools during the most recent submission date, with most of them focusing on issues pertaining to racial/ethnic populations. Furthermore, we started a collaborative project with our HBCU center and the Center for Substance Abuse Prevention's HBCU initiative which involved 7 other HBCUs. Their focus is on drug use and other health behaviors of young African American women on college campuses.

- Work Groups. We have two groups of scholars to provide guidance to us on matters pertaining to Hispanic and African-American populations. Each has identified gaps in the literature and recommendations for addressing drug abuse research needs in these communities. Some activities of the workgroups include: A conference on Drug Abuse in Hispanic Populations was held at the annual meeting of the College of Problems of Drug Dependence (CPDD) in June 1996 (proceedings to be published); a conference to involve community-based organizations in research was

sponsored by a grantee and a member of the African-American work group in July 1996; and a grantee and member of the African-American work group hosted a meeting on establishing ways to facilitate collaborative research between established and emerging (mostly minority) investigators and institutions.

- Hispanic Initiative. We have been working to increase our understanding of the many issues affecting this varied population group. The Hispanic work group has been involved with these efforts. With support from the ORMH, we will start a project this year to prepare various data sets for secondary data analysis and to train Hispanic and other investigators on conducting analyses and preparing grant applications.

- Native American Initiative. With support from the ORMH some of our grantees have been investigating over the last two years issues of recruitment and retention in Native American populations. Aspects of this work continue and publications are forthcoming. We hope this will provide guidance to other investigators interested in working with this population.

Mr. Stokes: What is planned for FY 1998 and how much is included in the FY 1998 budget request for this activity?

Dr. Leshner: In FY 1998, NIDA plans to maintain all of our current programs, as they are listed above. We hope to improve and, perhaps, expand some. Our plans for changes or new efforts include the following:

- Program announcements. We anticipate that the new MIRDP announcement will be approved and ready to receive applications. We have individuals waiting for the new announcement, and we hope that new awards can be made in FY 1998.

We also plan to develop program announcements for minority faculty and minority dissertation awards to stimulate participation in competitive research for racial and ethnic students and scholars.

- The contract for the HBCU research center will end in FY 1997; however, the HBCU technical assistance contract will be extended for a year.

NEEDLE EXCHANGE

Mr. Stokes: The debate continues on the pros and cons of "needle exchange" especially as it relates to controlling and preventing the spread of AIDS/HIV. Is it clear that needle-exchange programs help to reduce the spread of AIDS/HIV, please elaborate on your response for the record? As the Director of the National Institute on Drug Abuse, in your professional judgment, is there a need for needle-exchange programs, and if so, why, and if not, why not -- Please elaborate?

Dr. Leshner: The data available indicate that participants in needle exchange programs (NEPs) have changed their behaviors that place them at risk for acquiring and/or transmitting HIV and other blood-borne diseases and that NEPs have helped to reduce the spread of HIV/AIDS. Needle sharing is the major route of HIV transmission among injection drug users and the source of subsequent infections among their sexual partners and children. NEPs, through the exchange of used needles for new needles, remove infectious needles from circulation and/or reduce the time that syringes are available. There is significant evidence that increasing the availability of sterile injection equipment reduces the spread of blood-borne diseases. Research has also demonstrated that IDUs that use NEPs report reductions in needle sharing, increased disinfection of needles, and increased referrals to drug abuse treatment. This translates into a reduction in risk for HIV transmission. Further, in almost all communities in which there are NEP programs, other prevention activities are ongoing, and the combination provides the greatest potential for preventing the spread of HIV and other blood-borne diseases.

Mr. Stokes: To what extent are there needle exchange programs in the United States? Does the Institute have any major research underway in this area, and if so, would you elaborate on your findings thus far?

Dr. Leshner: Needle exchange programs (NEPs) were first introduced in the United States in the late 1980s. Many early exchanges operated illegally in those States requiring prescriptions for needles. In 1992, State/local governments began to create exemptions to existing prescription laws, sparing NEP participants from prosecution; or declaring local public health emergencies, allowing NEPs to operate. A non-government organization reports that there are now approximately 100 NEPs operating in the United States; over half of them operate legally.

Major research underway: In November 1993, NIDA announced support for research on NEP effects in PA 94-010, *Research on Needle Hygiene and Needle Exchange Programs*. A ban continues in effect on the use of Federal funds for needle exchange services. Between 1992, and the present, NIDA has funded 15 grants to evaluate the effectiveness of NEPs. Currently NIDA is supporting 13 research studies to evaluate the relative efficacy of existing NEPs in facilitating behavior change, averting HIV infection, and reducing drug use for a total funding for FY 1996 of $4,825,783.

NIDA's needle exchange evaluation research program studies are focusing on:

- assessing the effectiveness of NEPs in reducing risk behaviors and blood-borne diseases such as HIV, Hepatitis B virus (HBV), and Hepatitis C virus (HCV).

- evaluating needle exchange in combination with providing health services through mobile vans.

- o comparing the effectiveness of NEPs to an education and skill enhancement modality for IDUs in reducing targeted risk behaviors (e.g., reuse of previously used needles, needle sharing, needle lending, cooker sharing, and unprotected sex).

- o comparing the relative effectiveness of pharmacies and NEPs in affecting behaviors and serostatus.

Research underway: Research is also underway to examine the variability in the structure and functioning of the needle exchange process and their effects on behavior. For example, needle exchange varies greatly across the country in terms of type of location, hours and days of operation, number of needles/syringes allowed to be exchanged, and the number of other direct or referral services available such as referral to drug abuse treatment. Despite these variations, evaluation studies have shown that the needle exchange concept is effective in reducing sharing of needles/syringes and other injecting equipment, in engaging drug abusers in drug abuse treatment, and in some cases, in increasing the use of condoms. In several studies, the incidence rates of HBV infection have decreased.

Mr. Stokes: As a researcher and as the Director of the National Institute on Drug abuse, in your professional judgment, what should the nation be doing with regard to AIDS/HIV and needle exchange?

Dr. Leshner: Since no one single strategy is likely to be effective in reaching the at-risk population, communities should create multiple opportunities for IDUs to reduce their risk of HIV infection, with the goal of eliminating drug abuse through effective treatment for drug abuse. A number of strategies have been developed to reduce the risk behaviors of drug users, including drug abuse treatment and outreach-based strategies to out-of-treatment drug users, including HIV risk reduction education, HIV counseling and testing, and needle exchange. These strategies constitute a hierarchy of HIV risk reduction. The most effective way to eliminate risk of transmission of HIV is to eliminate the risk behavior. Several drug abuse treatment approaches have been shown to be effective in achieving and maintaining abstinence for significant numbers of drug dependent individuals. For those users unable or unwilling to stop, several other risk reduction strategies have been developed to help users reduce their drug use and particularly their HIV risk. For drug users who continue to use drugs, the risk reduction hierarchy consists of elimination of drug injection; for those who continue to inject, elimination of sharing of drug injection equipment; and for those who continue to share equipment, disinfection of drug injection equipment. NEPs provide risk reduction interventions targeting this hierarchy of risk reduction: providing syringe and other drug injection equipment, safer drug and safer sex information, and risk reduction materials such as bleach, other drug injection equipment, condoms, referrals to HIV testing and counseling, as well as referrals to drug treatment and medical services.

NIDA will continue to support research on the effectiveness of a spectrum of risk reduction strategies, including NEPs that are established by communities and other

public health approaches that respond to the changing epidemic.

Mr. Stokes: With regard to drug abusers who have been diagnosed as having AIDS/HIV, do we know which drugs they were abusing, and if the drug of choice made a difference in the degree of their disease?

Dr. Leshner: Data from studies indicate that polysubstance abuse is highly prevalent among drug users who are infected with HIV, both by self report and by toxicology. While data do not demonstrate significant differences in overall rates of HIV disease progression by primary drug of choice, studies have demonstrated that the presence and severity of certain HIV-associated diseases can be affected by drug use behaviors. One example of this is the increased occurrence of pneumonia in HIV-infected persons in association with smoking of illicit drugs.

MARIJUANA FOR MEDICAL PURPOSES

Mr. Stokes: As the debate continues to focus on marijuana especially as it relates to the use for medical purposes and the implications for contributing to increased drug abuse, what are your concerns regarding this matter? What are the primary medical benefits of this product and like any medication, what are the side effects? To what extent is the Institute conducting research in this area?

Dr. Leshner: The data on the possible medical benefits of marijuana were recently reviewed at an NIH conference held on February 19-20, 1997. An expert panel heard scientific and medical presentations on medical marijuana as well as marijuana users with medical conditions report on the benefits they ascribe to the use of marijuana. The experts, whose written conclusions will be sent to Dr. Varmus, NIH Director, hopefully by early April, were struck by the paucity of data in controlled clinical trials but suggested that such trials should be conducted. At the press briefing at the end of the conference, some panelists opined that trials should initially be conducted in diseases with objective endpoints; e.g., multiple sclerosis, glaucoma, vomiting associated with cancer chemotherapy. These diseases are within the mission of the various NIH institutes with expertise in those areas.

The side-effects of marijuana include acute effects that involve the brain (deficits in attention, learning, and memory mechanisms) and the heart and vascular system (increases in blood pressure while lying down; increase in cardiac output, with a decrease in peripheral resistance, increase in norepinephrine levels). Some of these effects may be dangerous in persons with coronary artery disease. In fact, one presenter at the marijuana conference stated that individuals over 30 may present a different risk for cardiovascular effects than their younger counterparts. There are also pulmonary effects in terms of decreased resistance to lung infections and pre-cancerous changes in the cells lining the lung. The former effects are of particular concern in individuals with compromised immune systems. It has been shown that smoking marijuana (or cigarettes or crack cocaine) can increase the risk of bacterial pneumonia in HIV-positive patients.

NIDA funds research evaluating the health risks associated with marijuana. We have funded research on the pulmonary and cardiovascular effects as well as the effects on the brain. NIDA is also funding basic science research evaluating the role of the endogenous cannabinoid system in brain. Marijuana use has risen in recent years as the perception of harm of marijuana has decreased. Whether use of "medical marijuana" would drive abuse up further in adolescents and young adults is an open question but certainly one that demands careful thought.

COLLABORATIVE EFFORT

Mr. Stokes: To what extent is there a collaborative effort underway between the Institute, the Substance Abuse and Mental Health Services Administration, the Department of Education, and the Department of Defense, can you elaborate on this?

Dr. Leshner: NIDA collaborates with many government agencies to fulfill its mission, especially the SAMHSA. In addition to some of the more formalized mechanisms that are set forth in the ADAMHA Reorganization Act of 1992, such as requiring that the newly established NIH agencies and SAMHSA collaborate in developing methods by which the research findings of the three research institutes are disseminated to service providers, health professionals, and the general public to improve the effectiveness of treatment and prevention services, NIDA has also developed informal collaborations with SAMHSA's senior and program staff. NIDA is currently teaming with SAMHSA's Center for Substance Abuse Treatment (CSAT) to support a project to be undertaken by the National Academy of Sciences Institute of Medicine to help in the dissemination of basic and treatment research. The project will work to achieve two major objectives. One is to determine mechanisms for effective transfer of basic and treatment research to the drug abuse treatment community and the other is to explore mechanisms by which the treatment community can participate in developing research agendas and participating in research projects. Another specific example of NIDA coordinating with SAMHSA to ensure that research is disseminated effectively to the field is the collaboration between the agencies to sponsor two recent major conferences: "The National Conference on Drug Abuse Prevention Research: Putting Research to Work for the Community" in September 1996, and the "National Conference on Marijuana Use: Prevention, Treatment, and Research" held in July 1995. NIDA will continue to collaborate with SAMHSA.to ensure the effective dissemination of research information.

NIDA is also funding a number of research grants in collaboration with the Department of Education. For instance, NIDA is working directly with the Department of Education's Safe and Drug Free Schools Program by participating in research conferences, sharing research findings and assessing the application of science-based principles to school-based programs. NIDA is also working collaboratively with the Department of Defense (DOD) through interagency agreements as well as with the DOD and other federal agencies in the Human Brain Project.

NIDA will continue to work closely with other federal agencies, private and

public organizations, community agencies, and others in its efforts to ensure that the most effective substance abuse treatment programs reach those suffering from addiction to drugs and to find the most useful prevention methods to teach our youth about the dangers of illegal drug use.

BIOLOGY OF THE BRAIN

Mr. Stokes: According to the budget submission, the "Biology of the Brain" is one of the NIH's major areas of research emphasis. One would expect that your Institute would have a major role in this initiative. Can you elaborate on what benefits would be achieved by major investments in "Biology of the Brain" as it relates to drug abuse and your Institute's research activities.

Dr. Leshner: The "Biology of Brain Disorders" is a major area of emphasis for NIH as a whole. NIDA considers this a pivotal area for its research endeavors as well. Two decades of research have clearly established that drug addiction is a disease of the brain. Research into the biology of the brain as it relates to addiction has identified brain areas, neural circuits and neurochemicals that are involved in the addiction process. Most recently, advanced technologies, such as brain imaging, are allowing us to study the functioning human brain, thus facilitating a greater understanding of the addiction process. These insights into the neurobiology of addiction are a critical component to the development of medications for treating drug addiction. For example, years of research into the actions of cocaine in the brain have provided the foundation from which it is now possible to develop an anti-cocaine medication.

While we now know a great deal about the neurobiology of addiction, there is still much that needs to be learned. Investments in the "Biology of the Brain Disorders" initiative will facilitate continued breakthroughs in our understanding of the brain's role in all aspects of addiction. These investments will allow researchers to gain greater insight into cocaine's actions in brain as well to clearly define the neurobiology of many other abused drugs that are less well understood. Investments in brain biology will also allow researchers to identify the long-term effects of drugs on the brain and the brain's role in other aspects of the addiction process, such as craving. Brain research is beginning to identify the circuitry and neurochemicals involved in craving. Continued research in this area should ultimately lead to an understanding of the precise brain mechanisms involved in craving. This in turn will allow for the development of an anti-craving medication that could dramatically reduce the rate of relapse among recovering drug addicts. These are but a few examples of how brain research plays an integral role in drug abuse research.

Mr. Stokes: One would think that this increased investment and research emphasis on the biology of the brain would yield significant knowledge about drug abuse and addiction, would you elaborate on this?

Dr. Leshner: As I noted earlier, research has clearly established that drug addiction is a disease of the brain. Studies into the brain's role in addiction have

provided us with tremendous insights into the process of addiction. They have also provided the foundation for the development of an anti-cocaine medication. Increased investments in the "Biology of the Brain Disorders" initiative would greatly facilitate our ability to determine the precise brain mechanisms underlying addiction and would ultimately facilitate the development of medications for the treatment of addiction.

Mr. Stokes: In total, how much is included in the NIH FY 1998 budget request for "Biology of the Brain" and how much and what percent of that total is allocated for your Institute? How does the FY 1998 allocation compare with the Institute's investment in this area of research in FY 1995, FY 1996, and FY 1997?

Dr. Leshner: In FY 1998, the NIH budget request included $2.2 billion for research on Biology of the Brain. Of that total 11% or $241 million is allocated to NIDA. In FY 1995 NIDA spent $196 million, FY 1996 spending was $207 million and the FY 1997 estimate is $221 million.

COST TO THE NATION

Mr. Stokes: Last year, the Institute indicated that drug abuse costs the nation an estimated $67 billion, and that new estimates were under development that would incorporate data reflecting each of the following major components -- drug related criminal justice expenditures, the crack-cocaine and the AIDS epidemics, the medical and social costs associated with the resurgence of TB and hepatitis, and prenatal exposure to drugs. What is the cost of drug abuse to the nation, and for the record could you provide the individual amount for each of the categories referenced?

Dr. Leshner: The ramifications of drug abuse extend far beyond the individual drug abuser. The health and social consequences of drug abuse such as HIV/AIDS, violence, TB, fetal effects, crime, disruptions in family and workplace and educational environments have devastating impacts on society and cost billions of dollars each year. We are currently working with the NIAAA and an external group to develop more current estimates of the cost of drug and alcohol abuse. We hope to complete and disseminate this new report within the year. Meanwhile, the number we are currently using to estimate the total annual economic costs to society of drug abuse is $67 billion [Rice, 1990]. This does not include the costs of buying the drugs themselves, estimated at perhaps $100 billion. The costs of nicotine addiction and smoking cigarettes add another $72 billion [Rice, 1990]. Costs related to AIDS continue to dramatically increase each year, with injection drug users and their sexual partners comprising the fastest growing segment of the HIV population. Recent CDC findings show that, as of June 1995, approximately 3 in 8 cases of AIDS were related to injection drug use. One report, "Pathways of Addiction: Opportunities in Drug Abuse Research" by the National Academy of Sciences Institute on Medicine estimates that the collective cost of drug, alcohol and nicotine use is approximately $257 billion. This exceeds their estimated annual cost of $117 billion incurred for heart disease and their estimated annual cost of $104 billion for cancer.

DRUG INTOXICATION

Mr. Stokes: As you know, last week, the CDC released data indicating that deaths from AIDS were decreasing in some but not all major risk groups. However, death rates are still increasing in women as a group and in both men and women who are exposed through heterosexual contact. I understand that there has been an extensive amount of research on the relationship between the use of drugs and the transmission of HIV and other communicable diseases. How much of this research has focused on needle-sharing as a high-risk behavior in and of itself? Will you please elaborate on the findings of this research?

Dr. Leshner: **Co-occurring epidemics and needle sharing**: Today, there are co-occurring epidemics of human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) among IDUs. These blood-borne diseases are spread through multiperson use of contaminated drug injection equipment such as needles.

Recent mortality data indicates that in 1994, there were an estimated 6,000 deaths attributable to chronic liver disease associated with Hepatitis B and an estimated 8,000 - 10,000 deaths associated with Hepatitis C. There were 22,000 AIDS deaths during the period of January - June 1996.

New injectors, HBV, HCV, and HIV: Recent data indicate an increasing incidence in heroin use by younger persons who began by snorting and/or smoking the drug. Preliminary data from a NIDA supported study following non-injecting heroin users (NIUs) indicate that 7% were HIV seropositive, 27% were hepatitis B seropositive, and 15% were hepatitis C seropositive. We will be following this cohort over time to help us better understand rates of change from non-injecting heroin to injecting the drug, and the relationship between drug user, risk behaviors, and blood-borne diseases.

In another study, data indicates that the risk of acquiring these infections, particularly HBV and HCV is extremely high in the first year after initiating injection drug use. For those who had been injecting for less than one year, 50% acquired HBV, 65% acquired HCV and 0.5% HIV. This research underscores the potential of a singular behavioral vector - multiperson reuse of drug injection equipment contributing to widespread transmission of blood-borne diseases among IDUs.

IMPACT OF DRUG ABUSE

Mr. Stokes: I understand that the Institute has supported an extensive amount of research on the development of children who are exposed to drugs. What are the most significant findings from that research?

Dr. Leshner: Researchers have made significant progress in studying developmental sequelae of exposure to illicit drugs during pregnancy, including improved assessment strategies and enhanced approaches for examining confounding

factors such as growing up in a drug-using environment. Physical status at birth (e.g., low birthweight, preterm delivery) has commonly been associated with prenatal drug exposure. Findings have begun to suggest that certain specific areas of function may be affected in some children (e.g., some aspects of attention and problem solving, arousal regulation). These findings have been reported for marijuana-exposed children who are in the school years and for some cocaine-exposed children ranging from the newborn period to the early school years. Given the possible implications (e.g., implications of early arousal and attention difficulties for information processing, learning, school performance, and later behaviors), these associations must be examined for replicability, and if replicable, for the mechanisms underlying the associations. In-progress NIDA-supported studies are examining multiple age groups of drug-exposed children, with a broad range and high specificity (subtlety) of function, increased measurement of the social environment, and increased examination of dose and timing of exposure.

Many of the children in the cocaine-focused NIDA studies are approaching the school-age years, a critical time for continued study. The nature of the complex mix of possible biological and environmental influences of prenatal drug exposure changes with the age and development of the child. New aspects of the complexity exist in the preschool and school-age years, when the child experiences an expanded environment and encounters the challenges presented by the demands of school. Educators and other child care providers continue to seek information on the preschool and school age groups in order to address needs appropriately. In addition, given that these children have been studied since birth, the studies offer unprecedented opportunity to examine factors in vulnerability to drug abuse as the children increase in age. Future NIDA research is planned for these areas.

PROGRESS

Mr. Stokes: What can you tell us this year that you could not tell us last year with regard to how close we are to having an effective treatment for any of the major drugs of abuse, like cocaine -- and equally important, treatments that do not themselves create another adverse dependency?

Dr. Leshner: NIDA is funding behavioral, pharmacological, and immunological approaches to the treatment of addiction. Behavioral approaches have shown that "contingency management" strategies which use positive reinforcement for abstaining from cocaine yield a greater percentage of subjects attaining abstinence in a clinical trial. NIDA continues to fund a multiplicity of pharmacotherapeutic approaches. New data suggesting that, independent of a drug's initial site of action, every drug--be it nicotine, heroin, cocaine, or amphetamine--appears to increase the levels of the neurotransmitter dopamine in the brain pathways that control pleasure, are leading us closer to the development of medication to treat addiction. During the past year, we have identified several compounds that show promise as long-acting cocaine treatment medications. One compound in particular, GBR 12909, works on the dopamine system and seems to reduce cocaine taking in monkeys. Of significance, this

compound suppresses the desire for cocaine, while not affecting other pleasurable activities controlled by the dopamine reward pathway, such as eating. To expedite the path from these types of new findings in basic research to actual changes in clinical practice, NIDA has funded the first three grants of its Strategic Program for Innovative Research on Cocaine Addiction Pharmacotherapy.

These grants strongly encourage collaborations between the basic and clinical sciences, collaborations that are needed to accomplish the very difficult goal of developing anti-addiction medications. It is our goal to identify compounds that can alleviate cocaine's impact, while leaving normal functioning intact. In regard to the second part of your question, if treatments are done properly, the adverse dependency risk is minimal.

In addition to our effort to develop pharmacotherapies for cocaine dependence, NIDA is also in the final stages of developing two closely-related products, buprenorphine and buprenorphine-naloxone for the treatment of opiate dependence. These products are being tested in an ongoing multicenter clinical trial which will terminate in one year. The New Drug Applications (NDAs) are scheduled to be filed this year for these products. NIDA is performing the work under a Cooperative Research and Development Agreement with Reckitt and Colman, the company sponsor of the NDAs.

Finally, barring unforseen delays, an immunological approach will be tested in human subjects in 1997. NIDA is supporting the development of a vaccine that stimulates the immune system to produce antibodies which will bind cocaine in the bloodstream and reduce its entry into the brain. This reduction in the concentration of cocaine has been shown in animal models to reduce its pharmacological effects. This translational research is moving ahead with all deliberate speed. The feasibility of the immunological approach will take a few years to test but we are optimistic of its anticipated efficacy.

We envision combining modalities for optimizing treatment. We will be testing the interactions between behavioral and pharmacological approaches initially. Should the immunological approach be deemed feasible for large scale clinical trials, we will evaluate combining different behavioral therapies with this vaccine.

BRAIN IMAGING

Mr. Stokes: I understand that cocaine craving studies have been conducted in two sites that use brain imaging techniques to determine which areas of the brain are activated during craving? Can you bring the committee up-to-date on the most recent findings of the Institute's brain imaging studies? How much is included in the budget for these studies, and how does it compare to the FY 1997 funding levels?

Dr. Leshner: NIDA has supported two extremely important studies establishing for the first time the neurobiological basis to drug craving, which points to the fact that

the intense drug hunger associated with craving is the result of particular areas of the brain being activated; these areas have long been associated with such cognitive functions as learning and memory. In addition to these very significant neuroimaging studies, NIDA's program in Human Neuroscience and Clinical Neurobiology is currently supporting neuroimaging research that is yielding many new and extremely exciting findings.

For example, the group at the Brookhaven National Laboratory, Dr. Nora Volkow and her colleagues, have used positron emission tomography (PET) neuroimaging techniques to compare the brains of chronic cocaine abusers to those of nondrug-using individuals. They observed distinct differences in the brains of cocaine abusers in terms of structure, physiology, and neurochemical function, and these cocaine-induced brain changes were found to be long-lasting. Specifically, results showed a marked reduction of glucose metabolism (a process necessary for brain cell life and function) in the frontal brain regions. The decreased levels of activity persisted after 3 to 4 months of abstinence and were correlated with the dose and the duration of cocaine use. Studying the effects of cocaine on brain dopamine (an extremely important brain neurotransmitter directly linked to psychoactive drugs' addicting properties), Volkow and colleagues found reductions in dopamine (D2) receptor availability in cocaine abusers compared to normal controls, and these reductions also persisted after 3 to 4 months of abstinence. These changes in the dopamine system were correlated with brain metabolism changes. The areas most affected are several regions of the frontal cortex, most markedly the orbitofrontal cortex, the prefrontal cortex, and the cingulate cortex – areas thought to be involved in impulse control. Alteration of dopamine function in these areas is thought to contribute to an overall lack of control and compulsive drug-seeking behavior.

In another related set of PET neuroimaging studies, this group has identified some of the unique properties of cocaine that account for the bingeing pattern of use exhibited by cocaine addicts. Their studies show that repeated and frequent activation of the dopaminergic system by cocaine results in an abnormal state in one of the brain's neural circuits. This altered brain circuit may be responsible for the dramatic difference in brain functioning that has been found to exist between the occasional drug user and the cocaine addict. Cocaine use is uniquely characterized by bingeing; this drug produces a rapid, yet short-lived "high," which results in users consuming the drug frequently and repeatedly. The results of this study provide a neurobiological mechanism that explains this type of drug-seeking behavior. Volkow *et al.* (1996) found that cocaine enters the brain very rapidly and also clears from the brain very rapidly. It may be the rapid uptake into the brain that gives rise to the initial pleasurable experience of cocaine, and, in turn, the extremely rapid clearing of cocaine that sets the stage for the bingeing behavior that is exhibited. These findings have significant implications for the development of treatments for cocaine addiction as they suggest that the actual physical properties of cocaine and its interaction within the body (that is, the pharmacokinetic properties) might explain why it is so addictive.

Using neuroimaging techniques to study chronic marijuana users, Volkow *et al.*

(1996) evaluated marijuana's effects on brain glucose metabolism. Findings revealed that marijuana users had disrupted metabolic activity in the brain region called the cerebellum. This brain structure is extremely rich in cannabinoid receptors (these brain receptors are the sites where marijuana's psychoactive component, delta-9-tetrahydrocannabinol, has its effects) and is important in movement. These changes were thought to reflect changes to these cannabinoid receptors. Also, they found that metabolic activity was increased in the prefrontal cortex, orbitofrontal cortex and basal ganglia. Alterations in metabolism in these areas were thought to explain the drive and compulsion to self-administer the drug in addicted individuals.

In two series of very recent studies by Fowler *et al.* (1996), new insights have been elucidated about the effects of cigarette smoke on the brain. They showed that two extremely important brain enzymes, monoamine oxidase A and monoamine oxidase B, responsible for the breakdown and metabolism of several neurotransmitters (dopamine, serotonin, and norepinephrine), are significantly reduced in the brains of chronic cigarette smokers. Decreases in these enzymes suggest that the ability to break down dopamine, a neurotransmitter responsible for the pleasurable aspects of addictive drugs, is compromised in smokers, perhaps contributing to the reinforcing/pleasurable properties of cigarette smoking, and thus making it even more difficult to quit.

Another NIDA researcher, Dr. George Ricaurte of Johns Hopkins University, is using neuroimaging techniques to study the neurotoxic effects of chronic methamphetamine and MDMA (Ecstasy) abuse in humans. Animal studies have clearly established that chronic exposure to these two drugs produces profound damage to brain cells (serotonin and dopamine cells). In a recent study, Ricaurte *et al.* (1995) found damage to serotonin neurons in brains of human MDMA users. The studies currently under way are focusing on understanding what the functional consequences (for example, effects on mood, aggression, movement, memory, sleep cycles, and impulse control) of these brain changes might be.

Neuroimaging techniques can also be used to provide insights into how AIDS affects the brain. Dr. Linda Chang at Harbor-UCLA is studying the effects of cocaine on the progression of the AIDS dementia complex, a loss of cognitive and physical ability caused by HIV infection of the brain.

Overall, neuroimaging studies are providing NIDA with critical new insights into the addictive process. Tremendous advances will continue to be made in the next few years on the neurobiology of addiction that will have direct impact on the development of new therapies, both pharmacological and behavioral, to treat drug abuse and addiction. In turn, increased success will be possible in the prevention of this brain disease. In FY 1997 we estimate that we will spend approximately $9 million for neuroimaging studies. In FY 1998 we estimate our level will increase to $10 million.

GENETIC AND ENVIRONMENTAL INFLUENCES

Mr. Stokes: Would you bring the committee up-to-date on the initiative to expand

research on human neuroscience, and explain, why this is a critical area of research for your Institute?

Dr. Leshner: Tremendous advances have been made over the last two decades in understanding the neurobiology of addiction. Much of this progress has been from basic studies utilizing animal models. Within the past decade, significant advances in human neurobiological techniques, especially technological advances of computer brain imaging, for the first time have allowed neuroscientists and clinical neurobiologists to investigate directly in humans the processes involved in normal brain function and those in disease. For NIDA, the ability to study various structural and functional processes of the human brain in the normal, awake and functioning human has opened the door to tremendous research possibilities, especially with respect to assessing brain alterations while correlating them with the behavioral or psychological state of the patient. These new human neuroscience techniques and methods now allow us to determine specifically and directly in humans how drugs of abuse act on the brain to alter normal function and to understand how drugs of abuse affect the brain reward pathway and transform normal behavior into compulsive drug-seeking behavior. Furthermore, we now, for the first time, can actually see how drugs might produce damage to the brain by generating maps of changed brain structure.

In a concerted effort to expand research on human neuroscience and to seize the opportunity offered by these new clinical research tools (such as positron emission tomography (PET); single photon emission computed tomography (SPECT); magnetic resonance imaging (MRI); magnetic resonance spectroscopy (MRS); and electroencephalography (EEG); as well as post mortem analysis of human brain tissue), a new branch -- the Etiology and Clinical Neurobiology Branch -- was established a little over two years ago within the Division of Clinical and Services Research. The major goal of this Branch is to promote a clinical research program focused on the neurobiology of human drug abuse disorders. This program targets questions of how abused drugs affect the structure, function, development and maturation of the human central nervous system, as well as the neurobiological factors that may predispose individuals to, or even protect them from, drug abuse and addiction through its stages (*e.g.*, initiation, escalation, dependence, addiction, withdrawal, craving, relapse). Another focus of this program is to assess the effects of treatment (both pharmacological or nonpharmacological) on altering the structure and/or function of the human brain. Investigations related to changes in the neurobiology of the human brain resulting from HIV/AIDS in substance abusers are also supported by this program.

With respect to the expansion of the human neuroscience initiative at NIDA, a Request for Application (*Human Basic and Clinical Neuroscience of Drug Addiction)* was issued during the past two years, as well as a program announcement (PA-95-089, *Clinical Neuroscience of Drug Abuse and Addiction*). The goal of this line of research is to provide a neurobiological basis for the development and improvement of behavioral and pharmacological treatments of drug-abusing patients. This year a Request for Application (RFA-97-001, *Neurobiological Substrates of Cognitive Functioning in Drug Abuse*) was issued on November 9, 1996 that solicits research

focusing on the neural substrates of the addictive process relating to cognitive brain functions. The results obtained from these studies should ultimately guide the development of improved drug abuse prevention and treatment strategies by identifying brain circuits and neurobiological mechanisms specifically affected in addiction.

NIDA has also established two major neuroimaging centers within the last year. The first is a PET neuroimaging center at our Division of Intramural Research (DIR) in Baltimore. This state-of-the-art facility was a joint NIDA-Office of National Drug Control Policy (ONDCP) project that will serve as a resource for both intramural and extramural researchers. The second neuroimaging center was more recently established through joint support from NIDA, the Department of Energy, and ONDCP. This center is a comprehensive regional neuroimaging center at the Brookhaven National Laboratory, which has PET, SPECT, and MRI capabilities. Both centers will also serve as regional resources to other scientists lacking the facilities to do neuroimaging studies. The purpose of these centers is to deepen the understanding of the mechanisms of addiction in humans, to develop and test new pharmacological treatments, and to create new imaging tools to advance the treatment of addiction.

Mr. Stokes: To what extent is there research underway and planned to delineate the interaction of genetic and environmental influences on drug abuse? How much of your budget would be invested in this segment of your portfolio in FY 1997 and FY 1998?

Dr. Leshner: Presently there are four NIDA studies that are designed to directly assess the genetic and environmental influences on drug abuse behavior. The most major effort is being carried out in the Minnesota Twin study, which has been ongoing for nearly a decade. The project was designed as a prospective study in which twin pairs were assessed at age 11 and reassessed twice more at 3-year intervals. Assessments include mental health variables, substance use and abuse history, psychophysiological measures, personality, interests, social adjustment scales, and environmental factors. The second study utilizes a large database of the Vietnam Era Twin Registry to compare monozygotic and dizygotic twin pairs discordant for drug use. Differences between these groups can inform a model that separates genetic from environmental, shared and unique, components and their contribution to drug use and abuse. The third study is conducted as part of the Colorado Adoption Project, a program project that includes animal components as well as human. Behaviors, drug use, family factors and environment are assessed and entered into predictor models that determine relative contribution of genetic, shared and unique environmental components. Finally, a FIRST Award has specific aims to estimate marital assortment for the liability to substance abuse and determine how risk liabilities due to both genetic and exogenous factors are transmitted by parents to their offspring.

In addition to these studies, NIDA is supporting several molecular genetic studies that assess large numbers of subjects and collect environmental data as well as medical, substance use and abuse, behavioral, and physiological measures against which to compare prevalence of allelic variations of candidate genes. In our Intramural program,

we are analyzing monozygotic and dizygotic twin data to fit models of heritability or environmental contribution to drug use and abuse.

Additional family, adoption, and twin studies are also being supported by NIDA. One of the larger of these, at Yale, utilizes data that have been collected over the years on drug use and abuse, assessing psychopathological factors in the probands and relatives, and family interaction and vulnerability patterns to determine the relative contributions of these to drug abuse. Another large long-term study in Iowa studies probands that have been adopted away from their biological parents at an early age. Comparison of the adoptees' environment, drug use, and psychopathology between the biological and adoptive home provides relative contribution of these variables to drug abuse.

NIDA is projecting spending $4.8 million for this area in FY 1997 and $5.1 million in FY 1998.

OUTREACH

Mr. Stokes: Last year, the Institute indicated that it had initiated a series of town meetings to bring the results of research to the community. Can you update the committee on this initiative?

Dr. Leshner: One of NIDA's most important goals is to expand our efforts to translate research findings, especially those about the actions of drugs on the brain, to help the public better understand the nature of addiction and the most effective strategies for its prevention. The Institute carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. For example, NIDA holds Town Meetings at various locations across the country to present the latest scientific information available to prevent and treat drug abuse and addiction. Scientists discuss with parents, teachers, concerned citizens and civic leaders what science has taught us about drug abuse and addiction and ways to reduce their impact. In turn, NIDA also learns from community members what kinds of scientific information they believe are needed to better deal with these problems.

Another important mechanism for information dissemination is NIDA's Science Education Program which funds projects of interest to children to increase science knowledge about drug abuse and addiction and to interest them in pursuing careers in science. The program presents scientific topics in ways that encourage children and adults to make good choices about drug use and other health matters.

IMPROVING THE HEALTH OF MINORITIES

Mr. Stokes: African Americans and other minorities continue to suffer disproportionally from a tremendous number of diseases and disorders -- from cancer to cardiovascular diseases to AIDS to diabetes. It is thought that fuller participation of minorities in the biomedical research enterprise, -- from the conduct of research to

research training to research decision making on the front-end, would help to dramatically close this long standing gap in health status. What is the Institute doing to increase minority representation in basic research and research training?

Dr. Leshner: Our institute has a number of activities to increase the representation of minorities in drug abuse research. Our Special Populations Office, as do all our divisional program staff, actively seeks opportunities to inform students, faculty and organizations about drug abuse research and the career paths available for racial and ethnic minority scholars. This involves presentations at various meetings, talking informally with persons (e.g., on the phone, E-mail, correspondence), and organizing special awareness events. For example, a staff person delivered the keynote address for a MARC-type program at Temple University (program participants were high school and undergraduate students; audience members were students, parents, nonparticipating students, and Temple faculty). In November 1996, we sponsored a minorities in neuroscience forum at the annual convention of the Society of Neuroscience. Some of our minority supplement recipients presented posters, we provided information packets, and training directors were there to discuss their programs. A large number of minority students from local high schools, colleges, youth groups, and Upward Bound attended with faculty and parents. They were assigned staff mentors who viewed the posters with them and talked with them about careers in biomedical and behavioral research. At the upcoming Annual Conference on Psychopathology, Psychopharmacology, Substance Abuse and Culture, we are supporting an effort to involve MARC and other students in the meeting with some special programming for students. Last year, through our Seminar Series, we worked with community college students (large numbers of minority students are in community colleges) through the American Psychological Association. We have heard from one of the sponsors that already several students have continued to a 4-year university with the expressed intent of pursuing a doctoral degree with hopes of entering research. We will continue our involvement with this group. Each year we support and make a presentation at the National Association for Equal Opportunity in Higher Education (NAFEO) conference. We intend to continue our support of these opportunities.

In terms of formal, ongoing programs, our most active current ones are the Underrepresented Minority Supplement Program, the Seminar Series, the MRTP, and the HBCU Initiative. We anticipate increased use again of the MARC and MIRDP programs. The newly expanded Hispanic Initiative will provide opportunities for training in Hispanic-related issues for Hispanic and other investigators.

CLINICAL RESEARCH

Mr. Stokes: Clinical research is a critical component of the research continuum, as its findings are one of the most important means of determining what constitutes appropriate medical care or treatment. What portion of the Institute's budget is invested in clinical research and how does this compare with the basic research investment?

Dr. Leshner: In FY 1998, NIDA plans to invest 42 percent of its budget in clinical research and 58 percent in basic research.

Mr. Stokes: Obviously, the relevance of clinical research findings are greatly enhanced when the study group is representative of the nation's population as a whole. What is the Institute doing to ensure minority representation in its clinical research programs?

Dr. Leshner: The National Institute on Drug Abuse promotes clinical research that addresses the unique needs of ethnic and racial minorities.

- It is the policy of NIDA, NIH, that members of minority groups must be included in clinical trials unless a clear and compelling rationale and justification is provided that inclusion is inappropriate to the health of the subjects or the purpose of the research. This language is included in all NIDA Program Announcements and RFAs.

- The appropriate representation of minority groups in clinical trials is both a consideration at the time of peer review of grant applications and at the time of award.

- All NIDA PAs and RFAs are reviewed to include research priorities related to ethnic and racial minorities.

- NIDA has recently developed an Action Plan for the DHHS Hispanic Agenda to ensure that Hispanic populations are appropriately represented in clinical research studies funded by NIDA and to increase the number of minority investigators participating in drug abuse research.

- Through its Minority Recruitment and Training Program (MRTP) at the Division of Intramural Research, NIDA offers minority students in the health and social science field an opportunity to be exposed to drug addiction research. Through the MRTP a number of meetings have been conducted at Historically Black Colleges to learn more about the needs of minority researchers. In addition, minority students have been engaged in summer student fellowships.

- NIDA also encourages minority supplements to existing clinical research studies to increase the number of minority investigators participating in drug abuse treatment research.

- Recently NIDA established the "Minority and Gender Bar Working Group," chaired by the Deputy Director of NIDA. This working group is addressing issues and procedures related to minority representation in research.

KNOWLEDGE "BOTTLENECK"

Mr. Stokes: The Director of NIEHS, Dr. Olden, spoke about a "bottleneck" when referring to the problems of identifying environmental hazards that contribute to human disease and illness. With regard to the diseases and disorders under the purview of your Institute, what are the most significant "bottlenecks in the Institute's knowledge base," and what are the health implications?

Dr. Leshner: When dealing with a complex disorder such as drug addiction, it is impossible to pinpoint a single bottleneck in the institute's knowledge base that when opened up will cure addiction. However, I will highlight two examples of bottlenecks, which if opened up I feel will have a dramatic impact on the treatment of addiction. One is in the area of behavioral therapies. As many of you are aware, there are a number of drug abuse programs that for some individuals seem to work very well. However, we do not know which specific components of these programs are indeed therapeutic and which are not. In fact, there is very little scientific data out there that we can cite to say with any certainty why some of these programs seem to work. To address these questions, we are launching a major treatment initiative to build the scientific data base on behavioral therapies and to disseminate this information to treatment providers so that more effective as well as efficient programs can be designed to help individuals afflicted with this disease. Another major bottleneck is in the development of an effective anti-cocaine medication. Cocaine addiction is a complex problem which will have no simple solutions. As we begin to understand the phenomena of initiation of drug use, craving and relapse, we will be able to design medications that can effectively attenuate these problems. I am confident that with advancing scientific technology, we can develop specific, efficacious medications to curb cocaine craving for example, but that is just part of the story. We need to continue to encourage interest from pharmaceutical companies to help us in this effort.

Mr. Stokes: To what extent will the FY 1997 Appropriations allow the Institute to address the "knowledge bottleneck" problem, and how much is included in the FY 1998 budget request for such? In your professional judgment, is the proposed funding level adequate to address the "knowledge bottleneck," Explain?

Dr. Leshner: NIDA's FY 1998 budget requests $15 million for new research in the area of an anti-cocaine medication as well as $5 million in the area of behavioral therapies.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists cloning of adult sheep, and Oregon researchers cloning monkeys. These articles expressed excitement with regard to opportunities for advances in medical treatments, and concern with regard to misuse of the technology and the possibility of human cloning. This is another area where we must now be certain to examine and address the ethical, legal, and social issues of research on the front-end. As a leading researcher and as an Institute Director, what is your professional opinion of this technology and what are your most serious concerns?

Dr. Leshner: I think this technology could have important uses medically, but it also raises a number of ethical concerns which need to be addressed in a forthright and public manner. President Clinton has asked the National Bioethics Advisory Commission to review the issues and to prepare a report on the matter. I think this was a very good decision on his part.

Mr. Stokes: With regard to the diseases and disorders studies by your institute, what are the most significant benefits that the cloning technology would yield?

Dr. Leshner: I can envision some new approaches to drug abuse and addiction that would be made possible by this new technology. However, I think we need much more public debate and a resolution on the ethical issues involved in advances of moving any of these ideas to the laboratory.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are currently underway, and what are the expected benefits to be achieved from this investment?

Dr. Leshner: NIDA has recently developed and expanded the extensive clinical trials infrastructure that is necessary to facilitate medication discovery and development. In addition to this improved infrastructure, we have had dramatic advances in our understanding of the neurobiology underlying addiction, such that we now have several specific targets at which to aim our medications development efforts.

NIDA is conducting two multicenter trials of buprenorphine tablets and buprenorphine-naloxone tablets and pharmacokinetics studies of these dosage forms necessary for approval of buprenorphine as a maintenance treatment for opiate dependence. These products should offer advantages (safer against overdose and less withdrawal) to both patients and physicians at a time when heroin use may be rising. Once buprenorphine is approved for this use, physicians treating opiate dependence will have a third choice for management of patients with this disorder. Additionally, our grantees and Intramural Research Program are exploring the potential utility of buprenorphine as a treatment for dual dependence on opiates and cocaine. Other studies are exploring the feasibility of administering buprenorphine on an every other day or every third day basis.

NIDA recently funded several investigators taking novel approaches to developing treatments for cocaine or methamphetamine dependence. Some trials of interest include the evaluation of kappa opioids (which are thought to be non-addicting) on the effects of cocaine. Preclinical studies suggest a powerful blocking effect of these potential medications on the actions of cocaine; e.g., reduction of cocaine self-administration and blockade of sensitization in the rat. Clinical concept testing will evaluate the translation of this finding to human subjects and the viability of using kappa opioids as a treatment for cocaine dependence.

A second approach involves the assessment of an adrenaline antagonist, propranolol, as a possible treatment for cocaine dependence. Studies have shown that the significance of an event and its retention in memory are influenced by adrenaline release. An area of the brain known as the amygdala is involved in the development, and possibly the maintenance, of this process. Evidence suggests this brain region imparts the emotional quality of memories, including memories of previous drug taking. Hence, this region influences ongoing decisions regarding drug-seeking behavior. By blocking the adrenaline component of this process, drug craving or drug-seeking may be reduced or extinguished. A Phase II clinical trial is underway in cocaine dependent subjects.

A third novel approach will assess the effect of glucocorticoid antagonists on the effects of cocaine. Glucocorticoids are adrenal gland hormones released in response to stress and cocaine. A current hypothesis is that these hormones affect the response to cocaine and the desire to take cocaine through disinhibition of frontal lobe circuitry.

Other trials will evaluate a combined behavioral and pharmacological approach to cocaine dependence. Of significance is that fact that none of these potential approaches involves a medication that would be considered addicting.

We are also funding new approaches, some of which combine behavioral and pharmacological therapies, for the investigational treatment of methamphetamine dependence. Methamphetamine dependence is a newly emerging, rapidly growing problem, particularly in the western United States.

In addition, NIDA also supports clinical trials that are testing behavioral approaches. There is a cooperative agreement currently under way that compares efficacy of four behavioral therapies for cocaine dependence. These treatments are: Group Treatment (12 step) alone, Individual Drug Counseling (12 step) plus group, Cognitive Therapy (behavioral) plus group, and Supportive-Expressive Therapy (psychodynamic) plus group. This study has a large sample (480 subjects) of cocaine-dependent individuals in four sites plus a coordinating center. This clinical trial will help to inform us about the best ways to treat cocaine addiction, and to determine the value of psychotherapy vs. counseling in cocaine addicted individuals who have other psychiatric problems. It will also shed light upon the relative value of individual vs. group treatment.

Investigators at Johns Hopkins are currently conducting a clinical trial contrasting several medications for the treatment of heroin addiction including LAAM three times per week, daily methadone at two different dosage levels and buprenorphine three times per week. This comparison study will provide important scientific data for developing policy decisions regarding the optimal dosing for these drugs, and for making rational choices among agonist medications available for opioid addiction treatment and for matching patients with a specific medication.

Dr. Kelly Avants at the Connecticut Mental Health Center is currently

conducting a clinical trial, "Reducing High Risk Behavior in HIV-Positive Drug Abusers," evaluating an intensive behavior therapy targeting HIV-infected drug abusers. The study will determine the efficacy of a specialized Risk Reduction Therapy for reducing high risk behaviors and increasing compliance with medical regimens in HIV-seropositive injection drug users. This is a promising approach for individuals who engage in more high risk behaviors and have higher rates of cognitive impairment and psychological distress than HIV-negative drug abusers. The public health impact of this project will be enormous if it can demonstrate significant reduction of high risk behaviors among seropositive drug abusers who are the primary vector of the spread of HIV infection within the drug abusing community.

Another controlled trial currently under way is investigating the efficacy of a structured behavioral intervention using a contingency management approach in treating antisocial opioid addicts in methadone maintenance treatment. The experimental intervention involves a 9-step approach using both positive and negative reinforcement for reducing drug use. Each step rapidly conveys greater or lesser control to patients over major aspects of their treatment (e.g., number of counseling sessions, methadone dose levels) based on urine results from the prior two weeks. This study is providing valuable information about the treatment of heroin addicts with antisocial personality disorders, one of the most difficult, treatment resistant subpopulations of heroin addicts. Efforts to improve treatment outcome in this subgroup are critical, especially given the increased risk of HIV transmission by the antisocial heroin addict.

Mr. Stokes: What major clinical trials that are ready to be implemented will the FY 1998 budget request allow the Institute to pursue, and what are the expected benefits to be achieved?

Dr. Leshner: We will continue the work described in the answer to the previous question for cocaine and methamphetamine dependence. The work often takes two-three years to complete; continuation is necessary for study completions. In addition, NIDA recently awarded three cooperative agreements for the evaluation of new therapies for cocaine dependence. Some clinical work could begin in FY 1998.

NIDA also plans to test three new potential medications that are currently undergoing the necessary preclinical evaluations to support human studies. Each of these compounds works on the dopamine system to reduce the effects of cocaine.

NIDA also plans to perform several multicenter trials in cocaine dependent subjects. For example, methylphenidate will be evaluated in cocaine dependent subjects with a diagnosis of Attention Deficit Disorder. We are also going to test the new anti-depressant Nefazodone in a depressed cocaine dependent population.

The major benefit of this research is to perform clinical concept testing of hypotheses and potential medications that have been suggested from preclinical

findings. NIDA is pursuing a strategic approach to developing medications for cocaine dependence that relies heavily on neurobiological findings from preclinical and clinical pharmacology. We believe this will lead to more rapid follow up of promising leads and more rapid dismissal of unpromising compounds. NIDA is also testing whether subpopulations will respond differently to medications. As many cocaine dependent patients have concomitant psychiatric disorders, this therapeutic approach may prove valuable for these patient subgroups.

The FY 1998 budget request will allow NIDA to continue testing various forms of behavioral/psychosocial therapy in clinical trials. Stage III behavioral therapy trials for drug use disorders are ready for implementation. Stage III research investigates the transportability to the community of behavioral therapies that have been shown to be efficacious in Stage II clinical trials. Numerous behavioral therapies have been developed and tested for efficacy, and now need to be researched in community settings. It is not enough to show that a therapy is efficacious under highly controlled circumstances and when administered by highly trained and rigorously monitored research personnel. Stage III research will tell us which therapies remain doable, useful and effective when administered by practitioners outside of traditional research/academic settings. Family therapy with polydrug-using adolescents and cognitive therapy for cocaine-dependent adults are both ready to be tested in such studies.

MINORITY AND WOMEN'S HEALTH

Mr. Stokes: Doctor, as it relates to areas under the purview of your Institute, in your professional opinion, what is the overall status of minority and women's health in this country?

Dr. Leshner: The rate of drug use, while an important indicator for targeting prevention and treatment efforts, is not the only indicator of the overall status of health for minorities in this country. The consequences or impact of drug use may be more critical. Poverty is more likely to be experienced by members of racial and ethnic populations. That and other factors associated with minority status may limit the group's ability to access good, effective treatment services, to escape the dissolution of family units often caused by a family member's addiction (e.g., child welfare agencies report a high correlation between substance abuse and substantiated child abuse and neglect and subsequent removal or abandonment of children), to avoid the serious health consequences of drug use (e.g., HIV/AIDS), or to provide a community that is free from drug trade and crime. Issues like this pose a great threat to the overall health of members of minority populations.

We have brought together experts from various ethnic populations to help us better understand and address the issue of drug abuse in racial and ethnic populations. In particular, the Hispanic and African-American work groups are comprised of some of our minority grantees as well as of minority individuals who are practitioners or work in various capacities, including church-based programs, social groups, and state

offices. We also held meetings to discuss issues pertaining to Native American and Asian American populations. We have an internal group, the Consortium on Minority Concerns, that seeks to lay out what the research issues are for ethnic populations. They all agree that the following items are needed: more epidemiologic and etiologic data; smaller, local area surveys to reach some ethnic minority populations that may not be reached by larger surveys if we are to truly understand the drug use practices of some groups (e.g., migrant workers, many Asian subgroups, rural ethnic populations); better research recruitment and retention strategies; research on etiology and treatment that fits the particular group needs to be pursued; and examination of issues like social policy, racism and criminal justice. And, they all think that the impact of drugs on ethnic communities is devastating and needs more resources and attention from everyone.

We believe that the use of licit and illicit drugs is correlated with negative conditions and behaviors in communities. Evidence strongly suggests that there is a relationship between drugs and crimes, drugs and violence, drugs and morbidity, drugs and community safety, and drugs and death. Many argue that these effects are felt first and most intensely by minority communities, and that minority communities have fewer resources to respond to the threats posed by drugs.

Regarding the status of women's health at it relates to the problems of drug abuse, the 1994 National Household Survey on Drug Abuse indicated that females comprise 45.4% of those who reported ever using illicit drug in their lifetime and 37.2% of individuals reporting use in the prior month. The survey also found that more women than men reported having taken prescription drugs for nonmedical purposes during the past month. The National Comorbidity Survey, conducted between 1990 and 1992, estimated that six percent of all women ages 15 to 54 years of age have met the criteria for lifetime drug dependence.

An aspect of drug abuse by women that is of particular concern is the use of drugs during pregnancy. Pregnant drug users are at increased risk for miscarriage, ectopic (tubal) pregnancy, stillbirth, low weight gain, anemia, thrombocytopenia, hypertension and other medical problems. Their newborns may have lower birth weight and smaller head size than babies born to nondrug-using mothers. The National Pregnancy & Health Survey was conducted by NIDA for the purpose of providing a national estimate of the number of women who use licit and illicit drugs during pregnancy. Based on a sample of 2,612 women who delivered in 52 hospitals from October 1992 through August 1993, it was estimated that of the approximately 4 million women who deliver live-born children annually in the United States, 5.5% or 221,000 women are projected to have used some illicit drug during pregnancy.

Cocaine is the primary drug problem of the majority of women of childbearing age admitted to treatment in the past decade. Women dependent upon cocaine are also more likely to drink alcohol, smoke tobacco, and use other illicit drugs. At admission to treatment, drug-dependent women tend to present with multiple problems including low educational levels and a higher likelihood of co-occurring mental disorders,

especially depression, and are often at risk for HIV infection.

Research has found that there are effective treatment programs for addicted women, pregnant addicts and their children. Components of treatment found to be important in attracting and retaining women in treatment are the availability of female-sensitive services: non-punitive and non-coercive treatment that incorporates supportive behavioral change approaches; and treatment for a wide range of medical problems, mental disorders, and psychosocial problems. Data indicate that women remain in treatment longer if their children live with them than if they are separated from their children while in treatment. Data also indicate that treatment for women is more likely to be successful if provided in a supportive, female-sensitive therapeutic environment that addresses: psychopathology; interpersonal relationships; and a woman's role as mother, including parenting education.

For women in need of treatment, there are many social, legal, and practical barriers to obtaining it. The fear of legal sanctions and of losing custody of children deters many women from seeking treatment. It may also discourage them from seeking prenatal care for fear that a drug screening test could lead to their incarceration or loss of custody of their children. Drug-dependent women are often the sole support for their families, but their jobs may provide limited job security, little or no health insurance, low wages, and little flexibility for scheduling drug abuse treatment. Child-care and transportation to treatment may be unavailable or too costly. Additionally, the use of drugs by family and associates may interfere with an abstinent lifestyle.

Ultimately, interventions are needed to significantly reduce or prevent drug use in women. In order to reach this goal, studies that examine the pathways and progression of drug abuse are essential. Research indicates that they are not the same for men and women. For example, among women in treatment, 50% to 90% reported a history of childhood sexual abuse. This is not so for men. Therefore, a broad-based research program that investigates gender differences in the pathways and determinants of initiation, progression and maintenance of drug use must be maintained in order to advance the field of prevention and treatment.

THE SEARCH FOR A CURE

Mr. Stokes: I understand that one of the Institute's priorities is to develop an effective medication to treat cocaine addiction. Do you envision such a medication as a cure, or a palliative remedy similar to methadone in the treatment of heroin addiction? How would the Institute use other forums of treatment, such as behavioral and psychological counseling, in connection with such a medication, and what is the evidence that such counseling works?

Dr. Leshner: Indeed, one of the top priorities of the National Institute on Drug Abuse is the development of an effective anti-cocaine medication. However, we never expect to have a "magic bullet" that will make any drug addiction go away. Drug addiction is a complex problem that requires complex solutions. Our current efforts are

focussed on developing an anti-cocaine medication. We currently have several compounds proposed for clinical trials with promising preclinical data.

Since we do not yet have the first approved cocaine treatment medication, it is difficult to state the level of its effectiveness or whether it would have any potential for misuse (as many psychoactive drugs such as tranquilizers, stimulants, or methadone do). With the exception of antibiotics, nearly all medicines are palliative, be they for epilepsy, migraine headaches, glaucoma, heart disease, high blood pressure, high cholesterol, or virtually any other chronic condition. The medical community speaks in terms of disease management for most conditions that are successfully treated. I think we all agree that Americans live better today with the current pharmacopeia that even a few short years ago. Therefore, it is vitally important to have both more and better medications to treat addiction.

We envision medications to be given within a treatment program. Medications can treat a damaged brain but successful treatment requires treating the whole patient. Cocaine dependence often produces problems in other areas of an individual's life. These issues must be addressed through various forms of counseling and, often, development of new skills. NIDA's research program is systematically addressing the efficacy of various forms of behavioral/psychosocial treatment modalities and the interactions of behavioral/psychosocial treatments with medications.

The evidence that counseling or other forms of therapy work has been provided by NIDA researchers who have evaluated different forms of behavioral/psychotherapy. One form of behavioral therapy, contingency contracting, has produced impressive results in sustaining abstinence from cocaine in several studies. Future studies will vary the contingencies to evaluate "dose" effects of such contingencies.

As I mentioned earlier, we have recently launched a major treatment initiative to stimulate research aimed at identifying the therapeutic aspects of behavioral therapies and disseminating this information to treatment providers. A major focus of our research efforts has been on developing new medications to restore a degree of normalcy to patient function so that other rehabilitative measures, such as counseling and psychotherapy, can be more effective. Although behavioral and pharmacologic treatments can be extremely useful when employed alone, integrating both treatments, in ways specific to an individual's needs, is likely the best way to treat addictive disorders.

OUR NATION'S YOUTH

Mr. Stokes: Recent survey results point to an increase in drug use among our youth. According to the Institute, prevention research is a top priority, would you describe your research activities in this area, and are we finding that prevention research works, please elaborate?

Dr. Leshner: NIDA's drug abuse prevention research program is comprehensive

in nature. Scientific results from NIDA's prevention research identify promising clinical and educational practices that prevent the onset of drug use, interrupt progression to drug abuse, dependency and addiction, reduce the likelihood of relapse or recurrence, and ameliorate drug-related morbidity and related adverse health and social consequences. NIDA's Prevention Research Branch supports scientific studies that test under controlled conditions the efficacy and effectiveness of theory-based Universal, Selective, and Indicated drug abuse prevention interventions. Special emphasis is given to assessing culturally appropriate prevention interventions and those that are salient to the needs of sub-groups at-risk to drug abuse.

NIDA-sponsored prevention research indicates that drug prevention programs do work to prevent drug use onset and progression to abuse and dependency. For example, controlled research indicates that comprehensive, multiple component prevention interventions can significantly reduce the use of nicotine, alcohol, and marijuana for youth in the program in comparison to controls. Research also indicates that drug education programs based upon social learning theory that impart social competency skills and that promote/reinforce anti-drug abuse norms can prevent adolescent drug abuse. In general, prevention intervention research indicates that focusing only upon the individual may be insufficient given the vital role played by family, peers, friends, teachers, and others in the social environment who encourage and reinforce positive health behavior changes. Finally, prevention research suggests that successful outcomes require high-quality implementation of multiple combinations of prevention strategies that focus upon individual health behaviors, families, the schools, mass media, the workplace, the neighborhood, social networks to include peers, and health policies. Collectively these preventive strategies help shape, mold, and reinforce anti-drug abuse societal norms and promote the reduction of drug-related health behaviors for the general populations and at-risk groups. The emerging science of drug abuse prevention indicates that theory-based programs can prevent adolescent drug abuse.

However, health services research indicates that, despite the existence of positive drug abuse prevention research findings, many drug abuse prevention activities implemented in schools and in communities consist of untested prevention strategies or prevention programs that have been tested under controlled conditions but shown to be ineffective. One of the greatest challenges facing drug abuse prevention today is the adoption and effective implementation of science-based drug abuse prevention strategies nationwide.

INFORMATION DISSEMINATION

Mr. Stokes: In the last Congress, the Institute was urged to disseminate basic research findings so that they could be put to practical use. Do you have significant examples of research results that have been used, or are ready for use in real life settings?

Dr. Leshner: We at NIDA recognize that doing great science is not enough if the results are not shared with those who could directly benefit from our country's

investment in research. One example of NIDA's dissemination efforts is the sponsoring of the National Conference on Drug Abuse Prevention Research this past September to share our prevention research findings with community members from across the country. We have just produced and begun disseminating the first research-based guide to drug abuse prevention to schools and communities. This user-friendly guide provides science-based prevention principles and practical guidance on how these principles can be applied by the community to address local drug abuse problems.

Another example of how NIDA is bringing research findings to practical real life settings is seen in the development of effective behavioral therapies. To begin answering many of the questions about what works best, for whom and under what conditions, NIDA has established a program to test promising behavioral therapies in a controlled process similar to the clinical trials approaches used to evaluate new medications. Some of the approaches under study include interpersonal psychotherapy, contingency management and other behavior therapies, cognitive therapy, skills training, counseling and other rehabilitative therapies. Treatments that work in research clinics will be examined for their potential use in community settings. NIDA will then support the development of manuals to provide systematic guidance on how to implement the particular therapies, and promote widespread application by practitioners. Another example of NIDA's research dissemination efforts can be seen in our hosting of Town Meetings across the country.

BRAIN DEVELOPMENT IN ADOLESCENT DRUG USERS

Ms. DeLauro: What types of research is NIDA conducting on brain development in adolescents who use drugs and their ability to learn?

Dr. Leshner: Several studies have been conducted on brain development and the ability to learn. The most recent observations of Pope and Yurgelum-Todd (1996), Slowij et al, (1995), and Block and Ghoneim (1993) in humans show that chronic marijuana use is associated with impairment of cognition, particularly, affecting short term memory and executive functioning, and this impairment does not recover even after abstaining from marijuana use for at least 24 hours (Pope and Yurgelum-Todd, 1995), or six weeks (Slowij, 1995). Many other older studies also have reported that marijuana use is associated with impairment of short-term memory and not 'old' memory. Similar effects on cognitive development are also seen in young school age children born to mothers who smoked marijuana during pregnancy.

At present, NIDA has no neuroimaging studies focussed specifically on the effects of drugs on brain development in adolescents, especially with respect to learning. Clearly, the effects of drug use on learning or other aspects of cognitive development is critical and now neuroimaging technology allows for the direct assessment of brain structure and function in clinical populations such as adolescent drug users.

We are presently discussing the possibility of supporting a study in Chile to assess the effects of cocaine on the brain using state-of-the-art neuroimaging techniques. A population of adolescents has been identified in this country that abuses large amounts of cocaine exclusively. Results from this type of study could show very important brain effects following drug abuse in adolescents.

In addition, the area targeting the effects of drug abuse on brain structure and function in adolescents has been identified as a gap area in our portfolio, and consequently, research studies are being strongly encouraged. We do support studies that assess the risk factors (genetic, environmental, behavioral) that may predispose adolescents to abuse drugs. Also, NIDA maintains a portfolio of grants assessing developmental effects on infants prenatally exposed to drugs of abuse. Assessments of cognitive, perceptual, and motivational development are being conducted. The Institute does maintain a fairly sizeable portfolio of grants using animal models to examine the effects of drugs of abuse on neural development.

The following describe summaries of present, ongoing studies related to the question above:

Contribution of ADHD Symptoms to Substance Problems and Delinquency in Conduct-Disordered Adolescents: Researchers examined adolescents with conduct disorder (CD) and substance abuse problems to determine if those with attention deficit hyperactivity disorder (ADHD) symptomatology had more severe delinquency and substance involvement. The study sample consisted of 171 adolescent boys, 13-17

years of age, enrolled in a residential program for substance abusers with behavioral problems. Results showed that boys with either self-or multi-source ADHD had more conduct disorder symptoms, earlier age of conduct disorder onset, more substance dependence diagnoses, and more co-morbid depression and anxiety. (LL Thompson, PD Riggs, SK Mikulich, and TJ Crowley, Journal of Abnormal Child Psychology, 24(3):325-347, 1996).

An Open Trial of Pemoline in Drug-Dependent Delinquents with Attention-Deficit Hyperactivity Disorder: Research shows that adolescents with conduct disorder and substance use disorders have high rates of co-morbid attention disorder hyperactivity disorder (ADHD). Further, ADHD may contribute to the severity and persistence of substance use disorders and antisocial behaviors. A study was conducted to examine if adolescents with ADHD and substance use disorders could be successfully treated. The study sample consisted of 13 male adolescents with CD, substance use disorder, and ADHD, in a residential program. Patients were treated with Pemoline, schedule IV stimulant medication but with a known low abuse potential, at a standard daily dose of 37.5 mg, that was increased over the subsequent 3 weeks to a total of 112.5 to 185.5 mg (=1.2-3.3 mg/kg maximal dosing). Results showed that hyperactivity and motility declined significantly by 13.9% and 7%, respectively, with pemoline treatment. However, the continuous performance scores did not change. These data indicate that pemoline may be a useful treatment for ADHD in substance-dependent delinquents. (PD Riggs, LL Thompson, SK Mikulich, EA Whitmore, and TJ Crowley, Journal of American Academy of Child Adolescent Psychiatry, 35(8):1015-1024, August 1996).

Frontal P300 Decrements, Childhood Conduct Disorder, Family History, and the Prediction of Relapse Among Abstinent Cocaine Abusers: Antisocial personality disorder is a frequent co-morbid diagnosis in cocaine dependent patients. A study was conducted in 49 cocaine dependent patients, abstinent for 1-5 months, to examine the following: (i) the neurophysiological effects of pre-morbid antisocial personality symptoms (ASPD; e.g., conduct disorder) occurring before age 15 versus co-morbid or post-morbid ASP symptoms occurring after age 15, (ii) comparison of ASPD in patients with a family history of alcoholism and in cocaine dependent patients, (iii) to examine the usefulness of P300 in predicting relapse, and (iv) examine the time course of P300 decrements in cocaine abusers, with or without ASPD. Patients were assigned according to the presence/absence of a DSM-IIIR diagnosis of ASPD. Analysis of P300 recorded during a visual selective attention task revealed reduced amplitudes at frontal electrode sites among patients with ASPD, relative to the ASPD negative patient and control groups. The frontal P300 decrement was significantly correlated with the number of childhood conduct disorder symptoms, but not with the presence/absence of a family history of alcoholism. Further, discriminant function analysis revealed that P300 amplitude alone accurately identified 71% of the patients who later relapsed, and 53% of the patients who did not. (Bauer, LO, Drug and Alcohol Dependence, in press, 1996.)

EFFECT OF WELFARE REFORM ON ADDICTS

Ms. DeLauro: Recent welfare reform measures have eliminated SSI payments for people addicted to drugs and alcohol. Individuals who received SSI under this law were required to seek treatment. Now many of these individuals will be disconnected from the treatment community. How does your institute address research on hard to target populations?

Dr. Leshner: NIDA's program of health services research is broad-ranging. A principal focus is on treatment access, utilization, and outcomes for hard to target populations, including women, women with children, adolescents, patients with dual drug abuse and psychiatric diagnoses, the homeless, and ethnic minorities. Our research indicates that drug addicts often lead a precarious existence. Of those who come into publicly funded drug abuse treatment, a high proportion have serious medical and psychiatric problems at entry to treatment (Flynn et al., 1996), and many are homeless. Under its health services research program, NIDA will encourage research on the short- and long-term impact of SSI and other welfare reform changes. For example, does the elimination of SSI disrupt the process of recovery for treatment patients previously receiving SSI? What is the impact of eliminating SSI on access to drug abuse treatment?

Addicts are less likely than non-drug users to have private health insurance. In DATOS, a major study of individuals entering treatment in 1991-1993, the percentage with private health insurance ranged from less than 6 percent of those entering long-term residential, 11 percent in methadone, 15 percent in outpatient treatment, and 40 percent for those entering hospital inpatient programs (Hubbard et al., forthcoming). In many states, private health care coverage for drug addiction has been reduced, and there is now less coverage for hospital-based treatment.

In DATOS, the percentage receiving public assistance (including SSI, AFDC, food stamps, housing assistance, etc.) also varied by modality. More than one-third of methadone patients reported that public assistance was a major source of income, compared to 16 percent of long-term residential clients, 17 percent of hospital inpatients, and 25 percent of outpatients.

Research (Chitwood et al., forthcoming) indicates that chronic drug users, especially those without health insurance, underutilize all types of health care, including emergency medical care, compared to non-drug users. From a public health standpoint, the consequences of this may be that infectious diseases (e.g., tuberculosis, HIV) are more likely to be spread among this population, and that health problems that could be treated less expensively at earlier stages of progression will require intensive and costly later interventions.

Ms. DeLauro: According to the Social Security Administration, some of this disenfranchised SSI population will qualify for benefits because the secondary symptoms of their drug abuse are so disabling. How does your institute address

research on the secondary health effects of drug abuse?

Dr. Leshner: NIDA supports clinical and health services research concerning secondary health effects of drug abuse. Issues include medical conditions, mental disorders, and health care access, utilization, and retention in medical treatment. Major areas of emphasis are the prevention and treatment, among drug users, of hepatitis B and C and other blood-borne infections, including HIV infection and its progression to AIDS; other sexually transmitted diseases; and tuberculosis.

To this end, NIDA funds several grants for studies which seek to increase linkage between primary health care and drug abuse treatment. Included are studies of primary care and drug abuse treatment delivered via a mobile van-based clinic and health care delivery within a needle exchange program. The development of an interactive computerized system for substance abuse screening in the primary care setting is being funded under Phase II of Small Business Innovation Research (SBIR) grants. NIDA plans to study medical care and health care access issues among the rural poor, women, adolescents and children, and individuals under the jurisdiction of the criminal justice system.

NIDA-SAMHSA COORDINATION

Ms. DeLauro: As a sister organization to SAMHSA, how do your two agencies coordinate to ensure that the research done at NIDA is applied to the field through SAMHSA?

Dr. Leshner: One of the outcomes intended by the 102nd Congress in enacting the ADAMHA Reorganization Act of 1992 (P.L. 102-321) was to eliminate competition between the 3 research institutes (NIDA, NIAAA, and NIMH) and the newly-established Substance Abuse and Mental Health Services Administration (SAMHSA) and to create a more collaborative atmosphere between research and service-related functions. In addition to some of the more formalized mechanisms that are set forth in the Act, such as requiring that these agencies collaborate in developing methods by which the research findings of the three research institutes are disseminated to service providers, health professionals, and the general public to improve the effectiveness of treatment and prevention services, NIDA has also developed informal collaborations with SAMHSA's senior and program staff. Two specific examples of NIDA coordinating with SAMHSA to ensure that research is disseminated effectively to the field is demonstrated by the collaboration between the agencies to sponsor two recent major conferences: "The National Conference on Drug Abuse Prevention Research: Putting Research to Work for the Community" in September 1996, and the "National Conference on Marijuana Use: Prevention, Treatment, and Research" held in July 1995. NIDA will continue to collaborate with SAMHSA to ensure the effective dissemination of research information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

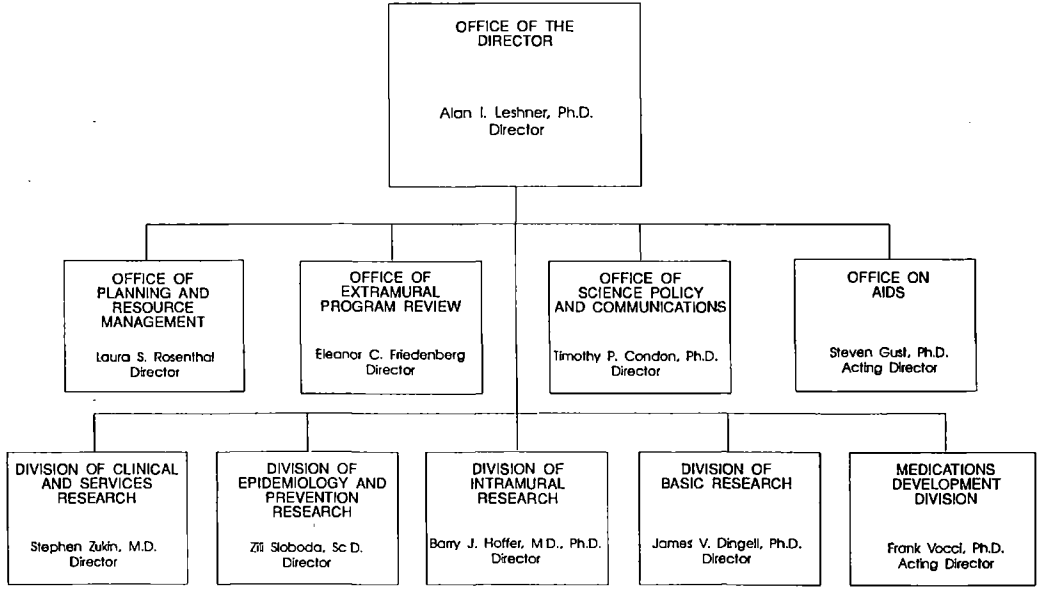
National Institute on Drug Abuse

FY 1998 Budget	Page No.
Organization chart	2
Appropriation language	3
Amounts available for obligation	4
Justification narrative	5
Budget mechanism table	24
Budget activity table	25
Summary of changes	26
Budget authority by object	28
Administrative costs	29
Significant items in House and Senate Appropriations Committee reports	30
Authorizing legislation	34
Appropriation history	35
Detail of full-time equivalent employment (FTE)	36
Detail of positions	37

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

For carrying out section 301 and title IV of the Public Health Service Act with respect to drug abuse, [$489,375,000] *$358,475,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations and the Department of Interior, 1997, P.L. 104-208.)

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$458,441,000	$489,375,000	$358,475,000
Rescission in accordance with P.L. 104-134	(263,000)	---	---
Reduction in accordance with P.L. 104-208	---	(215,000)	---
Subtotal, Adjusted Appropriation	458,178,000	489,160,000	358,475,000
Real transfer from: Other NIH Institutes through the NIH Director's one percent transfer authority	176,000	---	---
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	(153,299,000)	(160,832,000)	---
Comparative transfer to: OD, NIH for EEO Activities	(42,000)	(42,000)	---
Subtotal, adjusted budget authority	305,013,000	328,286,000	358,475,000
Unobligated balance, lapsing	(57,000)	---	---
Total obligations	304,956,000	328,286,000	358,475,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1996 - $2,181,000; FY 1997 - $2,030,000; FY 1998 - $2,030,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research:
FY 1998 - $163,440,000

Note: Excludes $91,600 in FY 1996 and $91,600 in FY 1997 for royalties.

JUSTIFICATION

NATIONAL INSTITUTE ON DRUG ABUSE

Authorizing Legislation: Sections 301 and Title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
363	$305,013,000	363	$328,286,000	363	$358,475,000	--	+$30,189,000

This document provides justification for the FY 1998 Non-AIDS activities of the National Institute on Drug Abuse (NIDA). Justification of NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

Recent scientific advances have revolutionized our understanding of drug abuse and addiction. The majority of these advances, which have dramatic implications for how to best prevent and treat addiction, have been supported by the National Institute on Drug Abuse (NIDA) at the National Institutes of Health (NIH). NIDA supports over 85 percent of the world's research on the health aspects of drug abuse and addiction. NIDA-supported science addresses the most fundamental and essential questions about drug abuse, which range from the molecule to managed care and from DNA to community outreach research. NIDA is not only seizing upon unprecedented opportunities and technologies to further their understanding of how drugs of abuse affect the brain and behavior, but NIDA also is working to ensure the rapid and effective transfer of scientific data to policy makers, drug abuse practitioners, other health care practitioners and the general public. The scientific knowledge that is generated through NIDA research is a critical element to improving the overall health of the Nation.

As we approach the new millennium, we are equipped with a formidable foundation of knowledge to confront today's issues and to respond to tomorrow's challenges. The Administration has made drug research a high priority program for FY 1998 and is requesting a $30 million increase for NIDA. The increased funding will further the development of a medication for the treatment of cocaine addiction. Over the past two decades research has firmly established that drug abuse is a preventable behavior and that drug addiction is, fundamentally, a chronic, relapsing disease of the brain. We also now have the research to show in exquisite detail what drugs are actually doing to, and in, the brain. Scientists have identified and cloned receptors in the brain for every major drug of abuse. Researchers have discovered not only the specific brain circuits involved in drug experiences, but are starting to uncover the changes in activity patterns in these brain circuits

over time, during the processes of addiction and during drug withdrawal. Research also shows that addiction occurs as a result of the prolonged effects of abusable drugs on the brain, and that addiction is characterized by important changes in brain structure and function.

Drug abuse affects every segment of American society, but nowhere is it more of a problem than among our nation's youth. NIDA research has shown that parental involvement in all aspects of a child's life, coupled with other research-based intervention approaches, can significantly reduce drug use among young people. Ever-changing drug use patterns, such as the increasing drug use by our Nation's youth, underscores the importance of research in finding new and better ways to alleviate the pain and devastation of addiction. NIDA will sustain its rich portfolio of research, while vigorously pursuing the development of an anti-cocaine medication, the prevention of drug use among our Nation's youth, the systematic testing of the efficacy of behavioral treatments, and the expansion of developmental and advanced instrumentation in the forthcoming year. The expansion of NIDA's research portfolio will continue to hold the best hope for solving the Nation's drug problems.

As stated in a recent Institute of Medicine report: "In the final analysis, the value of the Nation's investment in NIDA and our drug abuse research is measured in lives saved and reclaimed, in the success of each young person who stays in school and joins the work force, and in the happiness of each child nurtured by his or her parents rather than abused or abandoned by them."

STORIES OF DISCOVERY

Progress in Understanding the Brain through Drug Abuse Research

At the time of NIDA's establishment, twenty years ago, NIDA-supported researchers began aggressively studying the neurobiological mechanisms for drug abuse, understanding that drug's effects on behavior must be mediated by the drug's effects on the brain. These studies rapidly led to the development of an animal model of drug self-administration and the discovery that animals will self-administer most drugs that people do. This model, as well as research on the brain-stimulation reward system, moved drug abuse research into the neuroscience laboratory and sparked the search for the brain's opioid receptors and their natural ligands. With the landmark discoveries of endogenous opiate receptors by NIDA-funded researchers and the subsequent isolation and characterization of endogenous opiates, the fields of neuroscience and drug abuse research became inextricably linked.

As drug abuse/neuroscience research continued to elucidate the sites and mechanisms of action of drugs of abuse, our understanding of the function and structure of the brain was propelled dramatically forward. In subsequent years, neuroscience researchers identified multiple receptors for opiates, as well as receptors for nicotine, cocaine, THC, the major active component of marijuana, LSD, and amphetamines. In the last few years, as part of NIDA's marijuana research endeavors, NIDA-funded investigators have identified the anandamides, the endogenous substances in the body that bind to the THC receptor. This discovery has opened up an entirely new avenue of research into the physiological role of these endogenous compounds and is leading to a better understanding of the consequences of marijuana abuse. Molecular neurobiology has

also contributed heavily to drug abuse research. We have now identified and cloned the genes for the receptor sites for virtually every drug of abuse. This achievement sets the stage for using rational drug design to develop new addiction medications.

Neuroimaging has also helped to revolutionize drug abuse research. For the first time drug abuse researchers are able to actually visualize in real time where drugs like cocaine are binding in the brain, areas of the brain involved when an addict experiences "craving" and "withdrawal" and the sites of long term changes in the brain that result from chronic drug use. Most recently, scientists have not only been able to visualize where drugs bind, but they have been able to actually visualize changes in the brain that are caused by drugs or triggered by drug-associated traits such as craving. Through the use of neuroimaging, scientists are also beginning to identify specific neurochemical systems that are involved in craving. These studies are proving invaluable in the quest to understand the neurobiological mechanisms of addiction and they will undoubtedly serve as a cornerstone in our efforts to develop effective treatments for addiction.

It has long been thought that drugs designed to act in the brain must contain a nitrogen atom. However, while searching for an anti-cocaine medication, scientists have recently discovered that compounds in which the nitrogen molecule has been replaced by an oxygen molecule can not only bind to the same sites as the nitrogen containing compounds, but that these new compounds produce similar biological activity. This discovery sets the stage for the development of an entirely new class of therapeutic compounds. Furthermore, it suggests the possibility of yet undiscovered brain chemicals that do not contain a nitrogen molecule.

It is clear that not only has neuroscience research revolutionized our thinking about drug abuse and addiction, but over the past twenty years drug abuse research has significantly impacted the evolution of contemporary neuroscience research.

Progress in Developing Medications for the Treatment of Cocaine Addiction

With over 1.5 million people in our Nation currently using cocaine, and significant increases in the prevalence rates of current cocaine use among younger people, an effective medication for the treatment of cocaine addiction continues to be one of our nation's greatest needs. In contrast to substances like heroin, where NIDA's research has lead to the development of effective medications, such as naloxone for overdose and methadone for addiction treatment, there are no medications currently available for treating any aspect of cocaine addiction. Recent attention and emphasis on the development of an anti-cocaine medication have resulted in a series of basic scientific discoveries at the cellular and molecular levels that are cause for great optimism that an anti-cocaine medication is actually within reach.

Scientists have identified and genetically cloned receptors for every major drug of abuse including the cellular sites where drugs like cocaine exert their addictive properties. Recent scientific advances have led us to the recognition of the dopamine reuptake transporter as the major site for the behavioral and biochemical action of cocaine. In addition, researchers have found that there are multiple dopamine receptors that have been shown to respond differently to various compounds. In general, activation in the brain of one type of dopamine receptor, the D1,

suppresses drug seeking behavior and relapse, whereas activation of another, the D2, triggers drug-seeking behavior. This suggests that D1-receptor agonists may diminish episodes of intense craving for cocaine in humans, and ultimately prevent relapse in people who have stopped using the drug. This important piece of information identifies the D1 dopamine-receptor system as a potential target for medications to treat cocaine addiction.

Building upon this knowledge, NIDA-supported researchers have used state-of-the-art genetic engineering technology to develop "knockout" mice which lack two of the major neurobiological sites for addiction, the dopamine reuptake transporter and the dopamine D1 receptor. These mice give researchers the tools to better understand the neurobiological processes underlying cocaine addiction. These types of studies can ultimately identify new candidate targets for the development of the country's much needed anti-cocaine medications. Similar approaches in the study of opiates have recently produced "knockout" mice lacking the mu opiate receptor subtype. One result of these studies is that the mu opiate receptor subtype has been found to be the critical site of action for one of the most commonly used opiates, morphine.

Our knowledge of cocaine addiction has also been greatly enhanced by the development and screening of a number of compounds that can bind to the transporter and block cocaine from entering the brain cell without actually blocking the normal function and activities of the transporter. A recent NIDA supported study suggests that we may have made a significant stride in this direction. A study published in November 1996 demonstrates that GBR 12909, a long-acting form of the dopamine reuptake inhibitor, substantially reduces cocaine self-administration in monkeys but does not affect food intake, another pleasure sensation associated with dopamine. Previous studies in this area have been unable to separate the rewarding effects of drugs of abuse from other pleasure invoking stimuli such as food. The GBR compound maintained its effects for 30 days after only a single dose without affecting behaviors associated with food. Another benefit of the compound is its slow onset of action, which greatly reduces its abuse potential. Although further studies are needed to verify these effects in humans, this study may pave the way to the development of an effective long-acting medication that can be used for the treatment of cocaine addiction The duration of action may make this compound particularly useful for treating poorly compliant cocaine-dependent patients.

The tremendous strides that have been made in basic research have given investigators unprecedented opportunities to explore these findings in clinical studies Utilizing the most advanced and sophisticated equipment available, such as positron emission tomography (PET), scientists have been able to actually identify brain regions that are particularly responsive to cocaine-associated stimuli. As animal studies have predicted, these responsive areas of the human brain are the ones that are particularly rich in dopamine neurotransmitters. These PET scans have also enabled researchers to see not only cocaine working in the brain, but also enable them to view the regions in the brain that are particularly active during cocaine craving.

A hallmark of addiction is the phenomenon of relapse. Even for successfully treated addicts, mere exposure to cues associated with drug use can trigger tremendous craving and relapse to drug use, even after long periods of abstinence. In fact, clinical research has actually "captured" drug craving or the "memory of drugs" in PET scans of addicts while they are craving drugs. Since

drug craving is one of the major factors that can precipitate relapse, these images provide unprecedented opportunities to determine the neurobiological mechanisms of craving, which can lead to the development of treatments that might prevent or reduce craving. Basic pharmacological testing will be increased through new efforts aimed at developing "relapse models" of cocaine-taking behavior.

Building on this knowledge, NIDA now has the unparalleled opportunity to be able to develop a rational and systematic process based on both basic and clinical research in which to design and screen potential anti-cocaine medications. Scientific advances already have brought us a long way in our understanding of and approaches to cocaine addiction, and there is great cause for hope that we will continue to make progress in dealing with drug abuse and addiction, the most complex and compelling issue facing modern day society.

Drug Abuse Outreach and Treatment Can Change Risk Behaviors Known to Spread Infectious Diseases

Drug addiction and the spread of infectious diseases, such as HIV (human immunodeficiency virus) infection, hepatitis and tuberculosis are inextricably linked public health problems that confront our Nation. Drug abuse is currently the fastest growing vector for the spread of HIV in the United States. All drug users place themselves at great risk for infectious disease transmission when engaging in unsafe sexual behavior while under the influence of drugs. Injection drug users (IDU), in particular, are at high risk for exposure and transmittal of HIV/AIDS, as well as to other drug-health related problems ranging from blood borne infections such as hepatitis B and C, and tuberculosis, to physical deterioration and death.

Approximately 30 percent of AIDS cases reported through June 1996 were related to injection of illegal drugs through three major mechanisms: the sharing of contaminated injection equipment, heterosexual contact with an injection drug user (IDU), or maternal injection of illegal drugs[1]. Maternal-infant transmission of HIV is often an indirect health consequence of injection drug use. Of the 7, 296 cases of AIDS among children younger than 13 reported to the Centers for Disease Control and Prevention (CDCP) through June 1996, 90% were attributable to perinatal HIV transmission with 55% being drug-related (mother is an IDU or through sexual contact with an IDU).

Transmission of infectious diseases, such as HIV, through injection drug use is not limited to IDUs and their sexual partners; young smokers of crack cocaine, particularly women who trade sexual relations for money or drugs, are also at great risk for HIV transmission. Although nearly one third of the more than 500,000 adult and adolescent AIDS cases in the United States are drug related, progress is being made to promote and develop research to reduce HIV transmission among drug abusers, their sexual partners and offspring.

Since the discovery of the connection between the injection of drugs and the transmission of HIV,

[1]"HIV/AIDS Surveillance Report Through June 1996" Vol.8 No. 1(Atlanta, Georgia: Centers for Disease Control and Prevention, June 1996)

NIDA has been conducting research to better understand this association, and to disseminate our research findings to ensure that effective prevention and treatment programs are developed. NIDA research has shown that drug addiction treatment, prevention and outreach programs can change behaviors, which in turn can save lives and enormous costs to society.

NIDA's years of experience in developing and implementing drug abuse treatment, prevention and outreach programs have enabled the Institute to identify, study, and modify drug-use behaviors that increase HIV transmission risks among people who are in- and out-of-treatment. NIDA-supported studies have shown repeatedly that people still using drugs intravenously are responsive to behavior change strategies. A recent four-year study at one of the first NIDA-funded National AIDS Demonstration Research (NADR) projects in Chicago, used ex-addicts to deliver HIV-prevention services. It targeted IDU social networks in community settings, in a street-based outreach intervention program to lower Seroincidence among IDUS. The study found that Seroconversion was significantly correlated with injection risk behaviors, but not with sexual risk behaviors. This study provides a model for effective outreach strategies to prevent the spread of the AIDS virus.

Additional NIDA-supported studies have reinforced these findings. A study conducted in New York City demonstrated that multi-faceted risk reduction programs can produce large and significant and sustained decreases in HIV risk behavior among IDUs, even among those who continue their drug abuse. Among actively injecting addicts admitted for detoxification, the use of potentially contaminated syringes has declined from 51 percent of injections in 1984 to only 7 percent of injections in 1992. Further declines in unsafe injection practices were seen in addicts who participated in syringe exchange programs

University of Pennsylvania researchers studying heroin addicts in Philadelphia found that out-of-treatment subjects were injecting drugs, sharing needles, visiting shooting galleries, and practicing unsafe sex at significantly higher rates than in-treatment subjects. The study found that the addicts who did not receive treatment had a conversion rate to HIV-positive status that was six times higher than the rate among in-treatment injecting drug users who had been regularly exposed to risk-reduction education, counseling, and other strategies. Although drug treatment remains the preeminent means of reducing HIV risk among drug abusers, it has now been shown that much can be accomplished with addicts not yet able or willing to enter treatment.

NIDA will continue supporting research that tests the effectiveness of outreach and treatment programs that change risk behaviors known to spread infectious diseases.

Progress Toward Reduction of Nicotine Addiction

Research has shown without question that tobacco use causes lung cancer and in fact is responsible for 30 percent of all cancer deaths (NCI, 1996). In addition to the health risks associated with tobacco, there are numerous economic and societal costs. The estimated costs of medical, illness, deaths, and special conditions due to smoking were 72 billion dollars in 1990. Tobacco also contributes to other cancers and a host of chronic debilitating and fatal heart and lung diseases. Today, more than 45 million Americans smoke, with more than 3,000 American

children beginning smoking every day. In a NIDA-funded study, the University of Michigan reported that in 1996, cigarette smoking continued to rise among eighth and tenth graders and remained at high levels among twelfth graders.

During the past 25 years, research has demonstrated that nicotine, the main reinforcing agent in tobacco delivery systems, is an addictive substance which acts on the peripheral nervous system, stimulating the ganglia, the central nervous system, the cardiovascular system, the gastrointestinal tract, and the exocrine glands. Nicotine is readily absorbed by numerous sites in or on the body and exhibits both stimulant and depressive phases of action. Withdrawal and craving symptoms often occur upon cessation of smoking. Treatment of nicotine addiction has had mixed results, despite the fact that most smokers report a desire to quit. Two forms of nicotine replacement systems, nicotine gum and the transdermal patch, are available to the U.S. market which act to produce gradual and better tolerated withdrawal. The first non-nicotine prescription drug, bupropion, may be approved for use as an aid for smoking cessation. In December 1996, a Federal advisory committee recommended that the Food and Drug Administration (FDA) approve bupropion, an anti-depressant drug available in the United States, to become the first drug to help people quit smoking that could be taken in pill form, and the first not to contain nicotine.

The 1970s saw the coalescence of a directed research effort on nicotine addiction. The research focus deepened in the 1980s and by 1983, NIDA supported researchers had created the prototype of the nicotine transdermal patch as well as demonstrated that nicotine met the criteria for a drug of abuse. The FDA approval of nicotine gum in 1984 marked the availability (by prescription) of the first nicotine replacement therapy on the U.S. market. Unfortunately, nicotine gum often has side effects such as nausea and jaw irritation, and many smokers are reluctant to use it and physicians reluctant to prescribe it. Dissatisfaction with nicotine gum prompted increased research into other areas of nicotine replacement therapy as well as a recognition that treatment of nicotine addiction must be accompanied by behavioral adjuncts, such as developing self-monitoring and coping skills. In 1991, the FDA approved the transdermal nicotine patch. The introduction of the patch was a major contribution in that it provides an improved nicotine replacement treatment in the U.S.

Since the introduction of nicotine gum and the transdermal patch, estimates based on Food and Drug Administration and pharmaceutical industry data indicate that more than one million individuals have been successfully treated for nicotine addiction. Building on this success, the testing of additional forms of nicotine replacement systems and the pending approval of non-nicotine prescription drugs, are being sought as potential treatments for additional smokers.

OTHER SCIENCE ADVANCES THAT HIGHLIGHT THE BENEFITS AND IMPACT OF RESEARCH

Identification of a Potential Long-Acting Medication for the Treatment of Cocaine Abuse (New Avenues for Development of Therapies): A recent study has demonstrated that a dopamine reuptake inhibitor that has been reformulated to be long-acting substantially reduces cocaine self-administration but does not affect food intake. The compound, a long-acting form of the dopamine reuptake inhibitor, GBR 12909 maintained its effects for 30 days after only a single

dose without affecting behaviors associated with food. Importantly, the compound had a slow onset of action, thereby greatly reducing its abuse potential. Because dopamine plays a role in many behaviors, most dopamine reuptake inhibitors not only impact cocaine self-administration, but they also interfere with food intake and feelings of pleasure associated with certain other activities. The ability of this compound to selectively reduce cocaine self-administration suggests that it may be a very useful anti-cocaine medication. Importantly, the compound also has a slow onset of action, thereby greatly reducing its abuse potential. Although further studies are needed to verify these effects in humans, this study may pave the way to the development of an effective long-acting medication that can be used for the treatment of cocaine addiction. The duration of action may make this compound particularly useful for treating poorly compliant cocaine-dependent patients. (Glowa JR, Fantegrossi WE, Lewis DB, Matecka D, Rice KC, and Rothman RB, Sustained Decrease in Cocaine-Maintained Responding in Rhesus Monkeys with 1-[2-[Bis(4-flourophenyl)methoxy]ethyl]-4-(3-hydryoxy-3-phenylpropyl)piperazinyl Decanoate, a Long-Acting Ester Derivative of GBR 12909, *Journal of Medicinal Chemistry,* 39(24):4689-4691.)

Chronic Morphine Use Produces Structural Changes in Brain Cells (Biology of Brain Disorders): Researchers have recently demonstrated that chronic morphine can cause marked structural changes in the dopamine neurons in the brain's ventral tegmental area (VTA). Dopamine neurons in the VTA are known to be involved in addiction. Chronic morphine treatment resulted in a dramatic decrease in the size of the dopamine neurons and a change in the shape of the neurons and their processes. These changes were only observed in neurons that contain dopamine. The results of this study suggest that effective treatments for drug addiction should include treatments to reverse biological structural changes in the brain. (Sklair-Tavron L, Shi, WX, Lane SB, Harris HW, Bunney BSS and Nestler EJ 1996, Chronic morphine induces visible changes in the morphology of mesolimbic dopamine neurons, *Proceedings of the National Academy of Science*, 93:11202-11207)

Changes in Brain Metabolism in Chronic Marijuana Users (Biology of Brain Disorders): NIDA-supported researchers have recently demonstrated that chronic marijuana users have significantly lower metabolic activity in the cerebellum of the brain than nonmarijuana users. When exposed to tetrahydrocannabinol (THC), the active ingredient in marijuana, the chronic marijuana users showed an increase in metabolism in the cerebellum, prefrontal cortex, orbitofrontal cortex, and basal ganglia. In contrast, normal subjects showed an increase only in the cerebellum in response to THC. Metabolism in the other brain areas either showed no change or decreased. This research suggests that the lower baseline cerebellar metabolic activity in chronic marijuana abusers could reflect changes in cannabinoid receptors in the cerebellum. Also, the THC-induced activation of the orbitofrontal cortex and basal ganglia in abusers could be one of the underlying neural mechanisms leading to the drive and compulsion to self-administer the drug in addicted individuals. (Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A and Hollister L (1996), Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication, *Psychiatry Research*, 67:29-38)

Cognitive Deficits Associated with Drug Use in Adolescents (Biology of Brain Disorders): NIDA researchers have demonstrated that drug use by adolescents can result in long-lasting cognitive deficits. Using longitudinal data to model the relationships between several cognitive

skills and drug use over time, a significant association was found between drug use and weak cognitive and affective self-management strategies in early adolescence. This relationship became stronger over time. The exacerbation of these cognitive weaknesses with increased drug use may contribute to impaired social, emotional and psychological growth in late adolescence. As the authors note in their comment on a study of cognitive effects of heavy marijuana use, deficits in cognitive efficacy may actually precede and perhaps predispose to problematic drug use. Weaknesses in cognitive skills and learning disabilities may be undetected factors which underlie recognized risk factors such as low self-esteem, academic failure and school dropout; as such, further longitudinal studies and modeling, and perhaps early identification and intervention, are needed. (Scheier LM and Botvin GJ (1996), Effects of early adolescent drug use on cognitive efficacy in early-late adolescence: A developmental structural model, *Journal of Substance Abuse*, 7(4):379; Scheier LM and Botvin GJ, Cognitive effects of marijuana (ltr), *Journal of the American Medical Association*, 275(20):1547)

Opiates and Pain Fibers (Biology of Brain Disorders): Pain is carried to the brain by two classes of fibers: A-delta and C fibers. A-delta fibers generally mediate acute sharp pain, whereas chronic aching pain is mediated by C fibers. NIDA-funded research has recently established a noninvasive method for exclusively activating either fiber class in rats. These researchers have found that pain produced by C-fiber activation is mediated by receptors for the neurochemicals substance P or NMDA. Conversely, pain produced by A-delta fibers is mediated by the release of excitatory amino acids. Despite its pharmacological difference, both types of fibers could be inhibited by endogenously released opioids. This research has important significance to pain control. Whereas opioids are effective on both acute and chronic pain, there are significant drawbacks of chronic opioid administration. The methods established in this study will be valuable in the study of the pharmacological differences between acute and chronic pains, and perhaps will lead to improved treatments for chronic pain. (Yeomans, et al., *Pain*, In press)

Effectiveness of School-Based Drug Prevention Programs (New Preventive Strategies Against Disease): The effectiveness of different drug prevention programs was examined in a meta-analysis of 120 school-based programs in grades 5 through 12 that evaluated success on self-reported drug use measures. Two major types of programs were identified: Interactive and Noninteractive. Six other factors related to program effectiveness (sample size, targeted drug, type of control group, special populations, type of leader, and attrition) were included as covariates. The Interactive programs achieved significant changes on knowledge, attitudes and drug use, whereas the Noninteractive programs affected only knowledge. The larger Interactive programs were less effective although still significantly superior to the Noninteractive programs which suggested implementation failures. The clinically significant superiority of Interactive programs was observed for all adolescents, including various minority populations, and was equal for tobacco, alcohol, marijuana and illicit drugs. The problem of drug abuse among youth has received unprecedented attention in recent years. Data from the 1995 Monitoring the Future Study and other research-based studies have found that drug use among youth continues at unacceptable levels. The results of this study will help develop more effective school-based drug prevention programs. (Tobler, NS and Stratton, H, Effectiveness of school-based drug prevention programs: A meta-analysis of the research, *Journal of Primary Prevention*, In press)

Discovery of Potential New Class of Therapeutic Drugs (Biology of Brain Disorders): Scientists have recently discovered a novel class of compounds that may pave the way for the development of new therapeutic drugs for the treatment of a variety of brain disorders. It has long been thought that drugs designed to act in the brain must contain a nitrogen atom, because nearly all brain neurochemicals contain this element. While searching for a compound that could block cocaine's effects in the brain, however, researchers have discovered that compounds in which the nitrogen molecule was replaced by an oxygen molecule, can bind to the same brain areas and produce similar biological activity as compounds with the nitrogen molecule. Researchers tested these non-nitrogen containing compounds for their ability to block the transporter molecules that recycle the neurotransmitters, serotonin, norepinephrine and dopamine. In some cases, the non-nitrogen containing compounds were even more potent than the traditional nitrogen containing compounds in blocking reuptake of the neurotransmitters by the transporters. This discovery is highly significant. The transporter molecules studied are involved in depression, Attention Deficit Hyperactivity Disorder and cocaine abuse. Furthermore, for decades drug design has been guided by the premise that nitrogen is essential for biological activity. These results suggest that this premise must be expanded and that scientists now have available to them a new class of compounds from which to draw upon in their efforts to develop pharmacotherapies. These results also open up exciting new avenues of neurobiology research that may lead to an increased understanding of how brain neurochemicals are able to elicit their complex effects. (Madras BK, Pristupa ZB, Niznik HB, Liang AY, Blundell P, Gonzalez MD and Meltzer PC (1996). Nitrogen-based drugs are not essential for blockade of monamine transporter, *Synpase*, 24:340-348)

Advances in Understanding the Neurobiology of Drug Craving (Biology of Brain Disorders): Drug craving is a major factor in relapse to drug use. Using PET, scientists are beginning to determine the neurobiological mechanisms of craving. Recently, NIDA researchers have, for the first time, visualized changes in the brain triggered by drug craving. Specific areas of the brain showed increased activity in response to environmental cues that are associated with past experiences of using drugs and that lead to drug craving, even when no drug is available. (Grant S, London ED, Newlin DB, Villemagne VL, Lieu X, Contoreggi C, Phillips RL, Kimes AS, and Margolin A (1996). Activation of memory circuits during cue-elicited cocaine craving, *Proceedings of the National Academy of Science, 93*:12040-12045.) In another PET study, NIDA researchers determined that mu opioid receptor binding is associated with cocaine craving. Mu opioid receptor binding was found to be increased in several brain regions of cocaine addicts, as compared to controls, both 1 - 4 days after their last use of cocaine and after four weeks of monitored abstinence. In certain brain regions, the extent of this increase in mu receptor binding was correlated with the severity of craving. These results demonstrate for the first time an involvement of the brain's endogenous opioid system in craving and cocaine dependence. This study, in combination with the above PET study, provides important clues to the neurobiological mechanisms of craving. By understanding the neurobiological mechanisms of craving, it may eventually be possible to develop pharmacotherapies that will interfere with craving and subsequently reduce the rate of relapse among recovering drug addicts. (Zubieta JK, Gorelick DA, Stauffer R, Hayden TR, Dannals RF and Frost JJ (1996). Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving, *Nature Medicine, 2*(11):1225-1229.)

Maternal Drug Use and Mother-to-Infant HIV Transmission (New Preventive Strategies Against Disease): Multivariate analyses in a recent report from the Women and Infants Transmission Study (WITS) indicate an almost three-fold increase (Odds Ratio 2.77) in the risk of mother-to-infant HIV transmission associated with prenatal drug use (i.e., a measure combining use of cocaine, heroin/opiates, methadone, and/or injecting drug use), for women with duration of membrane rupture greater than four hours. The increased risk observed in this subsample was greater than that seen in univariate analysis for the total sample of 530 HIV-infected women and their infants (Odds Ratio 1.89). These results not only document a prenatal drug use-perinatal transmission relationship, but also provide a basis for further hypotheses as to the timing (intrapartum, intrauterine) and mechanisms of transmission. WITS is an ongoing study of HIV-infected pregnant women and their infants conducted at pediatric and obstetric settings in Illinois, Massachusetts, New York, Puerto Rico, and Texas. NIDA collaborates with the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development in supporting WITS. (Rodriguez EM, et al., Association of Maternal Drug Use During Pregnancy with Maternal HIV Culture Positivity and Perinatal HIV Transmission. *AIDS*, 10:273-282, 1996.)

Brain Imaging Studies Reveal Possible Mechanism for Cocaine Binging (Biology of Brain Disorders): Using PET, scientists compared the properties of cocaine and methylphenidate (another drug that inhibits the activity of the dopamine transporter), in an effort to determine why cocaine is more addictive. It was determined that while both cocaine and methylphenidate have rapid uptake rates and bind to the dopamine transporter similarly, cocaine is cleared from the brain much more rapidly than methylphenidate. This rapid clearance may be responsible for the binging behaviors seen with cocaine. Methylphenidate continues to occupy the dopamine transporter long after the high has diminished, making a second dose less effective in eliciting a high and therefore not reinforcing. In contrast, because cocaine is rapidly released from the transporter, frequent doses continue to have reinforcing effects. Both drugs are thought to mediate their responses through activation of a particular circuit in the brain (orbitofrontal-thalamo-striatal). In the case of methylphenidate, continued occupation of the dopamine transporter prevents reactivation of the circuit, thus allowing it to deactivate. Cocaine's rapid clearance from the transporter, however, allows for continued activation of the circuit that may trigger a continuous state of hyperactivity that is perceived as an intense desire for the drug, loss of control and an inability to discontinue using the drug. This study provides important clues into the neurobiological mechanisms of craving and may eventually contribute to the development of treatments for craving. (Volkow ND, Ding YS, Fowler JS, Wang GJ, Cocaine Addiction: Hypothesis Derived From Imaging Studies with PET. *Journal of Addictive Diseases*, in press, 1996.)

GOALS TO BE ACCOMPLISHED AND THE PRIORITY SETTING PROCESS

NIDA does not set its research agenda in isolation. NIDA staff continuously engages in ongoing discussions with the public health community, including scientists, policy makers and the general public. The National Advisory Council on Drug Abuse, a council of eminent scientists and public members of the community, serves as a barometer and resource to keep NIDA abreast of emerging research needs and opportunities and is a primary consultant to NIDA in setting its

research priorities. NIDA also consults with: (1) grantees, researchers and other scientists from within and outside of the drug abuse field; (2) members of Congress; (3) clinicians, practitioners and other health care providers; (4) NIDA work groups and other NIH sources; (5) other federal agencies; and (6) representatives of the Administration. NIDA also uses other mechanisms in seeking the public health concerns that contribute to establishing research priorities, such as monitoring national drug abuse trends through research-based surveys such as NIDA's Monitoring the Future Study and its Community Epidemiology Work Group. All of these participants have helped NIDA identify the development of an anti-cocaine medication, prevention of drug use among our nation's youth, behavioral treatment initiatives, and the expansion of advanced technology as critical areas of research for our nation.

DEVELOPMENT OF AN ANTI-COCAINE AGENT (Biology of Brain Disorders): There is widespread agreement that the single most important need in this nation's battle against drug abuse and addiction is an effective anti-cocaine medication -- what some have called a "cocaine blocker." Not only do we now have no way to treat cocaine overdose, resulting in a large number of lost lives, but we also have no medications with which to treat any aspect of cocaine addiction. It results in violence, family disruption and excess health care costs.

We are now on the threshold of being able to provide this country with just such a medication. The last several years have seen tremendous advances in understanding how cocaine affects the brain at the cellular and molecular levels. NIDA/NIH supported scientists have identified and genetically specified the major receptor site where cocaine works on the brain, and have discovered many of the mechanisms of action both at the receptor and the molecular levels. Building on this knowledge about the specific receptors and sites in the brain where cocaine acts, NIDA now has the unprecedented opportunity to systematically explore methods to interrupt, modify, attenuate or extinguish this process through a rational process of medication design and testing

Among the critical elements of medication development is the identification of candidate compounds. NIDA is in the process of obtaining promising existing compounds from several sources, including the academic community and chemical supply houses, and from chemical libraries of pharmaceutical companies. NIDA is proposing to take a proactive role in compound screening and contract with three pharmaceutical companies to gain access to their entire chemical libraries for the purpose of screening compounds. Such an effort would be more efficient and effective than our current method of compound screening, since many of the compounds have already been screened for psycho-active attributes. Never has the opportunity to utilize the fruits of years of basic research in a systematically-applied fashion to deal with a major public health problem been greater.

PREVENTION OF DRUG USE AMONG CHILDREN AND ADOLESCENTS (New Preventive Strategies Against Disease): The problem of drug abuse among youth has received unprecedented attention in recent years. Data from the 1996 Monitoring the Future Survey and other research-based monitoring tools show drug use among youth continues at unacceptable levels. The relationship between drug use and transmission of HIV and perinatal transmission of HIV increase the urgency of the development of solutions to this public health

problem.

NIDA proposes to use the basic science of development to identify the determinants of drug taking behaviors among children and adolescents, and apply these findings to implement effective prevention and treatment approaches. This would encompass studies of:

- risk and protective factors for initiation of drug use and progression to abuse and ultimately addiction, such as prior history of parental drug use, co-existing mental disorder; genetic predisposition; and gender differences. Environmental factors, such as poverty, violence, inadequate nurturing, drug exposure, and stress will also be examined in regard to their effects on drug use among children and youth;
- the effects of the children's own drug use on their development and behavior;
- the effects of in utero exposure to drugs on fetal development and outcomes as well as subsequent developmental outcomes;
- using current research about risk and protective factors to improve existing prevention approaches and to developing new ones;
- developing targeted treatment approaches sensitive to the unique needs of youth; including improvements to current approaches for identifying troubled adolescents, improving screening instruments and diagnostic procedures, development of treatment matching criteria for adolescents, and improvements to existing treatment approaches;
- using molecular biological techniques to develop medications for addicted pregnant women which do not affect the fetus, including: development of ligands for specific opioid receptors which are present in the adult but not expressed during early fetal development, designing medications which do not pass the placenta; and designing bipolar antibodies which interact with both a placental antigen and a drug of abuse to prevent or reduce fetal exposure.

BEHAVIORAL TREATMENT INITIATIVES (New Avenues for Development of Therapies): Behavioral therapies often remain the only available effective treatment approaches to many drug problems, including cocaine addiction, where there are no viable medications yet. Behavioral interventions are needed, even when pharmacological treatments are being used. An explosion of knowledge in the basic behavioral science field is ready to be translated into new behavioral therapies and NIDA will encourage research: (1) to develop and establish the efficacy of promising behavioral therapies for the treatment of drug addiction and abuse; (2) to determine how and why a particular behavioral intervention is effective; (3) to develop and test behavioral interventions to reduce AIDS risk behaviors in drug treatment populations; and (4) to disseminate efficacious behavioral interventions to practitioners in the field.

NIDA proposes to use those four general areas as an outline for more specific research initiatives, specifically:

- research on therapies for adolescent drug abuse. Targeted will be the early treatment of adolescents and pre-adolescents who abuse drugs but do not yet have serious drug difficulties, the treatment of adolescents with multiple problems, such as delinquency and comorbid mental disorders, nonfamily interventions as alternative to family therapy for the treatment of adolescents and special treatment needs and barriers for adolescents as a special population.

- research addressing drug addiction treatment and HIV risk reduction. NIDA proposes to build its research program on HIV sexual risk reduction, drug abuse treatment as HIV prevention, and the development of novel interventions to reduce HIV risk behavior.
- Research to determine the transportability of these empirically-supported therapies to the community. NIDA proposes studies to test the transportability of behavioral therapies and AIDS risk-reduction interventions to the community, to determine whether an intervention shown to be efficacious in a highly controlled setting, such as cognitive-behavioral therapy, operant behavioral therapy and family therapy are among those therapies potentially ready for such testing.

EXPANSION OF BRAIN IMAGING TECHNOLOGY AND PET INSTRUMENTATION FACILITIES (Computers and Advanced Instrumentation/Biology of Brain Disorders): In the past decade, technological advances in the field of functional brain imaging have presented an opportunity to bridge the gap between basic neuroscience and clinical research. Positron-emission tomography (PET), single-photon emission computed tomography (SPECT), and more recently, functional magnetic resonance imaging (fMRI) are being used in studies of the mechanisms of action of abusable drugs and of the metabolic and neurochemical changes in the brain associated with addiction. There is no doubt that studies of the neurochemical state of the brains of neuropsychiatric patients made possible by PET and SPECT imaging will one day provide novel and essential information on neuropsychiatric disorders. Additional brain imaging methodologies, notably magnetic resonance spectroscopy (MRS), also promise to provide anatomic and neurochemical information that has until very recently been completely inaccessible in neuropsychiatric patients.

A major accomplishment of the NIDA Intramural Research Program over the past several years has been the establishment of a PET facility devoted to drug abuse research. PET is an imaging technique that measures the concentration of positron-emitter labeled compounds in the living brain noninvasively. The short-lived positron emitters used with PET, such as carbon-11, can be used to label organic compounds without affecting their pharmacological properties. Thus, PET can be used to assess neurochemistry and pharmacology of the human brain. This year, efforts using PET resulted in a discovery that provides a major advance of our understanding of the brain mechanisms involved in cocaine craving

Another technology of particular promise includes fMRI because of its exceptional sensitivity and MRS because of its ability to estimate directly the concentration of many chemical components of brain tissue. Magnetic resonance also offers the ability to image brain vasculature (magnetic resonance angiography (MRA) and fluid motion (diffusion-weighted imaging (DWI). Since most drugs of abuse are vasoactive and some of the clinical sequelae associated with drug abuse may be associated with brain perfusion abnormalities, both MRA and DWI might also play important roles in understanding the mechanisms and consequences of drug abuse.

Ultimately, brain imaging technology has a singular purpose: to better understand drug dependence and other neuropsychiatric disorders so that more effective treatments can be developed. It has resulted in major advancements in the understanding of the brain mechanisms involved in cocaine craving and will play a large part in NIDA's discovery of an anti-cocaine

agent.

OTHER AREAS OF INTEREST

Response to Congressional Initiatives

Methamphetamine: The Senate Appropriations Committee expressed concern about evidence of the growing popularity of methamphetamine, and encouraged NIDA to continue research in this critical area.

NIDA's Community Epidemiology Work Group and other monitoring mechanisms have indicated that there have been significant increases in methamphetamine use in specific areas of the country. We know from research that methamphetamine is a powerfully addictive stimulant associated with serious health consequences, including brain damage, memory loss, psychosis, heart damage, hepatitis and HIV transmission. As methamphetamine abuse escalates, NIDA will continue to monitor its use, stimulate new research to understand methamphetamine abuse, ameliorate its health consequences, and develop effective intervention strategies. To this end, in December 1996, NIDA held a two-day conference in San Francisco on methamphetamine abuse, which brought together scientists, civic leaders, policy makers, public officials and drug abuse treatment and prevention professionals to improve the state and local response to methamphetamine abuse.

Neuroscience and Advanced Instrumentation: Both the House and Senate Appropriation Committee Reports commended NIDA for recent breakthroughs in neuroscience research and encouraged NIDA to continue its research efforts in this area. Conferees specifically emphasized the promise that magnetic resonance imaging may hold in understanding and treating drug abuse

A variety of new technologies have finally enabled the study of brain function in awake, behaving individuals. As one example, using PET scientists have, for the first time, visualized changes in the brain triggered by drug craving. A new Regional Brain Imaging Center was established in December 1996 at NIDA's Intramural Research Program on the Johns Hopkins University Bayview Campus in Baltimore, Maryland, in part, with financial support from the Office of National Drug Control Policy (ONDCP). NIDA also established a Regional Imaging Center at Brookhaven National Laboratories in collaboration with ONDCP and the Department of Energy. The new Centers will enable NIDA to accelerate efforts to identify compounds that neutralize the effects of illegal drugs on the brain and develop treatments for drug addiction.

Information dissemination: The House Appropriations Committee stated that they believe disseminating research findings in a timely manner is an important component of the NIH mission.

NIDA supports over 85 percent of the world's drug abuse research - research that has totally revolutionized our understanding of addiction. One of NIDA's most important goals is to expand our efforts to translate research findings, especially those about the actions of drugs on the brain, to help the public better understand the nature of addiction and the most effective strategies for its prevention.

The Institute carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. For example, NIDA holds Town Meetings at various locations across the country to present the latest scientific information available to prevent and treat drug abuse and addiction. Scientists discuss with parents, teachers, concerned citizens and civic leaders what science has taught us about drug abuse and addiction and ways to reduce their impact. In turn, NIDA also learns from community members what kinds of scientific information they believe are needed to better deal with these problems.

Another important mechanism for information dissemination is NIDA's Science Education Program which funds projects of interest to children to increase science knowledge about drug abuse and addiction and to interest them in pursuing careers in science. The program presents scientific topics in ways that encourage children and adults to make good choices about drug use and other health matters.

Medications Development: Both the House and Senate Appropriation Committee Reports emphasized medications development as an area having great promise and encouraged NIDA to continue work toward discovery and development of anti-addiction medications, particularly for cocaine addiction. The development of effective medications for treatment of addiction remains a top priority for NIDA, especially the development of an anti-addiction medication for cocaine. NIDA researchers have made tremendous progress in this endeavor, including having recently shown that activation in the brain of one type of dopamine receptor, the D1, suppresses drug seeking behavior and relapse, while activation of another, the D2, triggers drug-seeking behavior. Another NIDA-supported study, which is causing great optimism in the addiction research community, recently demonstrated that a long-acting form of the dopamine reuptake inhibitor (GBR 12909) substantially reduces cocaine self-administration in monkeys but does not affect food intake, another pleasure sensation associated with dopamine. The GBR compound maintained its effects for 30 days after only a single dose without affecting behaviors associated with food. Studies such as these are bringing us closer than ever before to discovery and development of anti-cocaine medications.

Ongoing and Planned Major Research Collaborations

A large number of recent basic scientific advances, particularly in the neurosciences, have also provided NIDA with the opportunity to work with other institutes within NIH, other government agencies and other research facilities. NIDA plans to collaborate with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Dental Research to increase its efforts in the area of pain. NIDA will also be collaborating with NINDS, the National Institute of Mental Health, the National Institute of Child Health and Development and the National Institute on Aging in such diverse areas as genetic medicine, development of the nervous system, and new treatments. NIDA's research program is working on spinal cord injury issues, and will be accelerating the research with NINDS.

As an example of interagency cooperation, a NIDA Regional Neuroimaging Center devoted to drug abuse research has just been established at Brookhaven National Laboratory through an interagency agreement with the Department of Energy. NIDA also teamed with the Office of

National Drug Control Policy to establish a new regional brain imaging center at NIDA's Intramural Research Program in Baltimore, Maryland.

Example of "High Risk" Research

There is an urgent need to develop effective multifaceted approaches to treat cocaine addiction. As reported in the 1995 Institute of Medicine Study there is a reluctance on the part of the pharmaceutical industry to enter the field of anti-addiction products, especially vaccine development, creating a "high risk" research area for NIDA, since it can not be certain that the scientific advances that are being made to treat addiction will be further pursued and marketed by the pharmaceutical companies. Despite the lack of interest by the private sector to pursue these endeavors, NIDA continues to invest in this "high risk" research of developing a vaccine for cocaine addiction. Recent examples of advances that enlist the body's natural defenses to combat cocaine were simultaneously reported by NIDA grantees at the Scripps Research Institute and through a Small Business Innovation Research (SBIR) grant by the Immunologic Pharmaceutical Corporation in the past year.

Both research teams have found that certain compounds, in animal studies, appear to lock the effects of cocaine without interfering with normal brain functions. The antibodies developed in these animals appear to be long-lasting and have kept up to 70% of administered cocaine out of the brain where it produces its addicting effects. The vaccines will eventually be tested in clinical trials and most likely used in combination with treatments such as behavioral therapy.

Research Training Efforts

The future of drug abuse research is dependent not only on a pool of qualified scientists to pursue research careers in the areas of drug abuse, but also upon the ability to attract and retain bright young investigators to the field. The recent Institute of Medicine report concludes, "The field has suffered from difficulties in recruiting and retaining young researchers and clinicians ... Society's capacity to contain and manage drug abuse depends upon a stable, long-term investment in research." This shortage of well-trained scientists impedes progress in all facets of drug abuse research, particularly in the area of clinical research, where researchers are needed to develop, test, and evaluate new drug abuse treatments. NIDA is committed to expanding its research training efforts. In FY 1994, NIDA's training budget, which is critical to the flow of young investigators into the field, was about 2 percent of its extramural budget. In FY 1996, it was increased to about 2.7 percent, a number that is still below the NIH-wide average of about 4 percent.

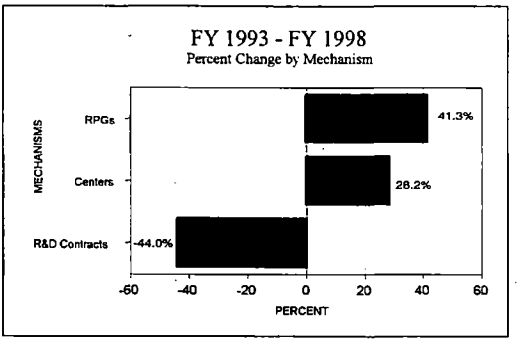
Administrative and Management Innovations

During this past year, NIDA has instituted a number of changes to redirect its use of both research and administrative resources to better enable the Institute to support research of the highest quality and priority. During this process, the Institute has sought input from outside scientists, health professionals, and the lay public, as well as from inhouse workgroups.

NIDA has already restructured the organization of its extramural program. Perhaps most importantly, the reorganization has resulted in enhanced program effectiveness and has allowed the Institute to more easily address changing scientific priorities. By design, it has resulted in a more effective infusion of neuroscience throughout the Institute, broadened the base for behavioral research, built a stronger clinical etiology and treatment program, enhanced services research, and focused the Institute's epidemiological efforts.

NIDA is also now taking a hard look at the organization and structure of its intramural research program, using the newly-established NIH review framework to bring in a blue-ribbon panel of extramural scientists that will review the operations of the intramural program, its human capital, and its facilities, and make recommendations on what changes might be made to facilitate even further the high quality and productivity of the current program.

Administratively, NIDA has aggressively participated in the new NIH program by which more consolidated service centers, run by Institutes, can provide services to other Institutes, often allowing for the reduction of administrative expenses and redirection of resources. In addition, NIDA has undertaken reviews of the management of its research programs per se, to ensure that the current mechanisms of support are the most effective for meeting particular research and program objectives. One result of this assessment process by NIDA has been the decision to reduce sharply NIDA's use of its research and development contracts mechanism as a vehicle for supporting research projects. The exception to this is the medications development program, which by necessity must conduct a substantial portion of its research activities as contracts. Although the contracts mechanism as a whole is a necessary option to have available and is the most effective vehicle for accomplishing certain program objectives, it was determined that many projects previously supported through the contracts mechanism could more effectively and appropriately be supported and performed as research grants. Limiting the funds available for the support of contracts has also meant the enhanced availability of funds for the competitive grant mechanisms. As can be seen from the chart below, on a comparable basis, since FY 1993 NIDA has decreased funding for non-medication development contracts by 44%.



NIDA BUDGET POLICY

NIDA is requesting $358,475,000, an increase of 9.2% over the FY 1997 level. Funding for the National Institute on Drug Abuse Non-AIDS activities during the last five years has been as follows:

	Amount	FTEs
FY 1993	$277,136,000	424
FY 1994	281,625,000	386
FY 1995	289,581,000	363
FY 1996	305,013,000	363
FY 1997	328,286,000	363

The FY 1998 Estimate for NIDA totals $358,475,000 excluding AIDS, and reflects an increase of $30,189,000 or 9.2% over the comprable level of $328,286,000.

NIH policy links RPG average cost increases to total program budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for research project grants (RPGs). In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs will increase by up to two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP). These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 293 competing RPGs, an increase of 58 competing RPGs over FY 1997, and 850 total RPGs (excluding SBIR/STTR), an increase of 83 total RPGs over FY 1997.

In FY 1998, NIDA will be receiving a total of $17 million for the NIH investment emphasis areas of biology of brain disorders, new preventive strategies against disease, developmental and advanced instrumentation, and therapeutics/drug development.

National Institute on Drug Abuse

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	527	138,235,000	532	134,518,000	557	145,063,000
Administrative supplementals	(14)	587,000	(9)	380,000	(9)	388,000
Competing:						
Renewal	62	17,767,000	80	27,210,000	100	25,600,000
New	134	27,411,000	155	33,044,000	193	46,247,000
Supplemental	2	222,000	0	0	0	0
Subtotal, competing	196	45,178,000	235	60,254,000	293	71,847,000
SBIR/STTR	22	3,627,000	33	5,779,000	33	6,431,000
Subtotal, RPGs	745	187,627,000	800	200,931,000	883	223,729,000
Research Centers						
Specialized/comprehensive	19	24,737,000	21	27,340,000	23	30,287,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research centers in minority institutions	0	0	0	0	0	0
Subtotal, Centers	19	24,737,000	21	27,340,000	23	30,287,000
Other Research						
Research careers	113	12,169,000	114	12,954,000	114	13,213,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	2	1,051,000	2	1,160,000	2	1,183,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	0	0	0	0	0
Other	10	2,911,000	13	3,410,000	13	3,478,000
Subtotal, Other Research	125	16,131,000	129	17,524,000	129	17,874,000
Total, Research Grants	889	228,495,000	950	245,795,000	1,035	271,890,000
Training	FTTPs		FTTPs		FTTPs	
Individual	93	2,006,000	97	2,230,000	99	2,317,000
Institutional	235	6,754,000	241	7,325,000	255	7,918,000
Total, Training	328	8,760,000	338	9,555,000	354	10,235,000
Research & development contracts	73	25,476,000	77	28,879,000	93	30,800,000
(SBIR/STTR)	(8)	(1,466,000)	(9)	(1,590,000)	(9)	(1,590,000)
	FTEs		FTEs		FTEs	
Intramural research	112	19,691,000	110	21,469,000	110	22,962,000
Research management and support	251	22,591,000	253	22,588,000	253	22,588,000
Cancer prevention & control		0		0		0
Construction		0		0		0
Total, NIDA	363	305,013,000	363	328,286,000	363	358,475,000
(Clinical Trials)		(30,950,000)		(33,100,000)		(35,100,000)

Note. Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Drug Abuse and Addiction		262,705		284,229		312,925		28,696
Subtotal, Extramural research		262,705		284,229		312,925		28,696
Intramural research	112	19,690	110	21,469	110	22,962	0	1,493
Research management and support	251	22,561	253	22,588	253	22,588	0	0
Total obligations	363	304,956	363	328,286	363	358,475	0	30,189
Unobligated balance lapsing		57		0		0		0
Total, budget authority	363	305,013	363	328,286	363	358,475	0	30,189

Note. Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Summary of Changes

1997 Estimated budget authority				$328,286,000
1998 Estimated budget authority				358,475,000
Net change				30,189,000
	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$7,793,000		87,000
b. Annualization of January 1997 pay increase		7,793,000		64,000
c. January 1998 pay increase		7,793,000		164,000
d. Legislative proposal, 1.51% increase in the CSRS rate		7,793,000		35,000
e. Service and supply fund		7,739,000		16,000
f. Increased cost of laboratory supplies, materials, and other expenses		5,948,000		329,000
Subtotal				695,000
2. Research Management and Support:				
a. Within grade increase		16,289,000		237,000
b. Annualization of January 1997 pay increase		16,289,000		134,000
c. January 1998 pay increase		16,289,000		342,000
d. Legislative proposal, 1.51% increase in the CSRS rate		16,289,000		72,000
e. Service and supply fund		2,112,000		21,000
f. Increased cost of laboratory supplies, materials, and other expenses		3,618,000		105,000
Subtotal				911,000
Subtotal, Built-in				1,606,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse
Summary of Changes--continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	532	134,898,000	25	10,553,000
b. Competing	235	60,254,000	58	11,593,000
c. SBIR/STTR	33	5,779,000	0	652,000
Total	800	200,931,000	83	22,798,000
2. Centers	21	27,340,000	2	2,947,000
3. Other research	129	17,524,000	0	350,000
4. Research training	338	9,555,000	16	680,000
5. Research and development contracts	77	28,879,000	16	1,921,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes	110	21,469,000	0	798,000
b. Special emphasis areas	0	0	0	0
Subtotal, intramural	110	21,469,000	0	798,000
7. Research management and support	253	22,588,000	0	(911,000)
Subtotal, program		328,286,000		28,583,000
Total changes				30,189,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Budget Authority by Object

	FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	363	363	---
Full-time equivalent of overtime and holiday hours			
Average ES salary	$125,203	$128,709	$3,506
Average GM/GS grade	11	11	
Average GM/GS salary	$48,167	$49,516	$1,349
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$52,981	$54,465	$1,483
Average salary of ungraded positions	$44,971	$46,230	$1,259

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	15,983,000	16,656,000	$673,000
11.3	Other than Full-Time Permanent	1,986,000	2,033,000	47,000
11.5	Other Personnel Compensation	373,000	383,000	10,000
11.8	Special Personnel Services Payments	1,616,000	1,704,000	88,000
11.9	**Total Personnel Compensation**	**19,958,000**	**20,776,000**	**818,000**
12.0	Personnel Benefits	4,124,000	4,290,000	166,000
13.0	Benefits for Former Personnel	0	0	0
	Subtotal, Pay Costs	**24,082,000**	**25,066,000**	**984,000**
21.0	Travel & Transportation of Persons	510,000	519,000	9,000
22 0	Transportation of Things	78,000	81,000	3,000
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	295,000	298,000	3,000
23 3	Communications, Utilities & Miscellaneous Charges	1,042,000	1,060,000	18,000
24.0	Printing & Reproduction	379,000	379,000	0
25 1	Consulting Services	300,000	297,000	(3,000)
25.2	Other Services	8,072,000	8,494,000	422,000
25.3	Purchase of Goods & Services from Government Accounts	13,471,000	14,242,000	771,000
25 4	Operation & Maintenance of Facilities	0	0	0
25.5	Research & Development Contracts	22,118,000	23,224,000	1,106,000
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	0	0	0
25 8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**43,961,000**	**46,257,000**	**2,296,000**
26 0	Supplies & Materials	2,015,000	2,093,000	78,000
31.0	Equipment	2,015,000	2,020,000	5,000
32 0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	253,909,000	280,702,000	26,793,000
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	0	0	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**304,204,000**	**333,409,000**	**29,205,000**
				0
	Total Budget Authority By Object	**328,286,000**	**358,475,000**	**30,189,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are in the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$15,983,000	$16,656,000	$673,000
Other Than Full-Time Permanent (11.3)	1,986,000	2,033,000	47,000
Other Personnel Compensation (11.5)	373,000	383,000	10,000
Special Personnel Services Payments (11.8)	1,616,000	1,704,000	88,000
Total Personnel Compensation (11.9)	**19,958,000**	**20,776,000**	**818,000**
Civilian Personnel Benefits (12.0)	4,124,000	4,290,000	166,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**24,082,000**	**25,066,000**	**984,000**
Travel (21.0)	510,000	519,000	9,000
Transportation of Things (22.0)	78,000	81,000	3,000
Rental Payments to Others (23.2)	295,000	298,000	3,000
Communications, Utilities and Miscellaneous Charges (23.3)	1,042,000	1,060,000	18,000
Printing and Reproduction (24.0)	379,000	379,000	0
Other Contractual Services:			
Advisory and Assistance Services (25.1)	300,000	297,000	(3,000)
Other Services (25.2)	8,072,000	8,494,000	422,000
Purchases from Govt. Accounts (25.3)	5,269,000	5,243,000	(26,000)
Operation & Maintenance of Facilities (25.4)	0	0	0
Operation & Maintenance of Equipment (25.7)	0	0	0
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**13,641,000**	**14,034,000**	**393,000**
Supplies and Materials (26.0)	1,985,000	2,043,000	58,000
Subtotal, Non-Pay Costs	17,930,000	18,414,000	484,000
Total, Administrative Costs	**42,012,000**	**43,480,000**	**1,468,000**

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND
CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

1997 House Appropriations Committee Report Language

Item

Neuroscience - The Committee recognizes that neuroscience research has fundamentally changed our understanding of addiction and that this understanding provides the foundation for new kinds of treatments. NIDA has made progress in identifying the neurobiological bases of addiction, including craving, which is one of the major factors that can precipitate relapse. NIDA-supported researchers have also made substantial progress in identifying potential anti-cocaine medications. NIDA-supported researchers have made great strides in understanding the brain's opiate system and its role- in addiction. The Committee considers neuroscience research a top priority and encourages NIDA to continue its research efforts in this area.

Action Taken or to be Taken

In the past decade, technological advances in the field of functional brain imaging have presented an opportunity to bridge the gap between basic neuroscience and clinical research. Positron-emission tomography (PET), single-photon emission computed tomography (SPECT), and more recently, functional magnetic resonance imaging (fMRI) are being used in studies of the mechanisms of action of abusable drugs and of the metabolic and neurochemical changes in the brain associated with addiction. There is no doubt that studies of the neurochemical state of the brains of neuropsychiatric patients made possible by PET and SPECT imaging will one day provide novel and essential information on neuropsychiatric disorders. Additional brain imaging methodologies, notably magnetic resonance spectroscopy (MRS), also promise to provide anatomic and neurochemical information that has until very recently been completely inaccessible in neuropsychiatric patients.

Ultimately, brain imaging technology has a singular purpose: to better understand drug addiction and other neuropsychiatric disorders so that more effective treatments can be developed. It has resulted in major advancements in the understanding of the brain mechanisms involved in cocaine craving and will play a large part in NIDA's discovery of an anti-cocaine agent.

Item

Medication Development - The Committee is pleased that NIDA has issued a program announcement to encourage expedited transition of ground-breaking research from advanced preclinical findings to applied clinical applications. The Committee recognizes this is a valuable tool in advancing the discovery and development of medications for cocaine addiction.

40-478 97 - 35

Action Taken or to be Taken

The development of effective medications for treatment of addiction remains a top priority for NIDA, especially the development of an anti-addiction medication for cocaine. NIDA researchers have made tremendous progress in this endeavor, including having recently shown that activation in the brain of one type of dopamine receptor, the D1, suppresses drug seeking behavior and relapse, while activation of another, the D2, triggers drug-seeking behavior. Another NIDA-supported study, which is causing great optimism in the addiction research community, recently demonstrated that a long-acting form of the dopamine reuptake inhibitor (GBR 12909) substantially reduces cocaine self-administration in monkeys but does not affect food intake, another pleasure sensation associated with dopamine. The GBR compound maintained its effects for 30 days after only a single dose without affecting behaviors associated with food. Studies such as these are bringing us closer than ever before to discovery and development of anti-cocaine medications. To expedite the transition of ground-breaking research such as this from advanced preclinical findings to applied clinical applications, NIDA has established the Strategic Program for Innovative Research on Cocaine Addiction Pharmacotherapy (SPIRCAP). This program will support innovative, integrated and interrelated preclinical and clinical research to validate clinical pharmacotherapeutic concepts for the treatment of cocaine addiction.

1997 Senate Appropriations Committee Report Language

Item

Methamphetamine - Methamphetamine represents the most commonly used synthetic drug in the United States. The Committee is concerned that there is mounting evidence of a growing methamphetamine epidemic, which bears the potential of becoming a truly national epidemic. The Committee recognizes NIDA's strong history of funding research on amphetamines and methamphetamine; however, there is an urgent need at present for attention to treatments of human populations, particularly those in the Western United States, including rural populations, and those who have been infected with HIV. A most pressing priority is the development of effective pharmacological treatments for methamphetamine abusers, in conjunction with behavioral treatments and prevention efforts. The Committee encourages NIDA to continue this critical research area as well as develop new mechanisms to expedite research on methamphetamine.

Action Taken or to be Taken

NIDA's Community Epidemiology Work Group and other monitoring mechanisms have indicated that there have been significant increases in methamphetamine use in specific areas of the country. We know from research that methamphetamine is a powerfully addictive stimulant associated with serious health consequences, including brain damage, memory loss, psychosis, heart damage, hepatitis and HIV transmission. As methamphetamine abuse escalates, NIDA will continue to monitor its use, stimulate new research to understand methamphetamine abuse, to ameliorate its health consequences, and to develop effective intervention strategies. To this end, in December 1996, NIDA held a two-day conference in San Francisco on methamphetamine abuse, which brought together scientists, civic leaders, policy makers, public officials and drug abuse treatment and prevention professionals to improve the state and local response to methamphetamine abuse.

Item

Research Centers - The Committee commends NIDA for encouraging applications for comprehensive research center grants to support research training, continuing education for health care professionals, dissemination of information to the public, and conduct of both basic and clinical research. The Committee notes that in fiscal year 1996, NIDA supported two new research centers and looks forward to NIDA's continuing commitment to this approach.

Action Taken or to be Taken

Beginning with issuance of its Research Center Program Guidelines in December 1995, NIDA alerted the field of its interest in receiving proposals using the full range of available center grant mechanisms. NIDA is particularly interested in supporting comprehensive center grants. These grants must demonstrate thematic integration, a multi-disciplinary perspective, synergy in research approach, and each individual research project must be inherently tied with the other projects and the core. The additional features that distinguish comprehensive centers from other centers are research training, continuing education for health care professionals, dissemination of information to the public, and, ideally, the conduct of both basic and clinical research. NIDA looks forward to receiving and being able to fund high-quality comprehensive center grant applications.

Item

Services to underserved populations - The Committee strongly encourages NIDA to support multidisciplinary comprehensive approaches to underserved populations including minorities, rural populations, children, women, and those already infected with HIV and at an elevated risk for HIV. The Committee hopes that such centers will be representative of the varying regional epidemiological profiles of drug problems in the United States, including consideration of methamphetamine abuse in at least some of the centers.

Action Taken or to be Taken

Drug abuse continues to be a major health problem among women and minorities in the United States. Since aspects of drug abuse and addiction vary among minority groups, the development of effective interventions for drug abuse must take into account the cultural and psychosocial differences among ethnic groups. NIDA's programs are creating a better understanding of how drug abuse and addiction affect underserved programs and are resulting in more culturally sensitive and effective prevention and treatment programs. NIDA will continue to recruit and develop a more culturally diverse research workforce to focus on drug abuse among ethnic and cultural minorities and among women.

Item

HIV prevention - The Committee understands that NIDA is in the process of expanding innovative community-based epidemiological and ethnographic research in relation to HIV transmission and prevention. The Committee encourages NIDA to continue to place high priority

in this area of research, particularly with regard to documentation of the growing methamphetamine epidemic in the West, Midwest, and South.

Action Taken or to be Taken

It now appears that injection drug use is the leading risk factor for new human immunodeficiency virus (HIV) infections in the United States. HIV/AIDS remains a central issue in drug abuse treatment research, and additional research addressing simultaneous drug addiction treatment and HIV risk reduction must be stimulated. NIDA researchers in 23 sites have developed and are evaluating interventions directed to injection drug users, now major transmitters of HIV/AIDS through the sharing of drug paraphernalia and through high-risk sexual behavior. These interventions have reduced the frequency of drug injection, needle sharing, and sexual encounters with injection drug abusers. NIDA plans to expand its research program on: HIV sexual risk reduction, HIV prevention tied to drug abuse treatment, and the development of novel interventions to reduce HIV risk behavior.

Item

Social work Services - The Committee commends NIDA's support for research on families and drug abuse, behavioral and psychological treatment research, and health services. The Committee also applauds NIDA for its initial effort to increase the number of social work researchers conducting drug abuse research, and encourages NIDA to expand these efforts in fiscal year 1997.

Action Taken or to be Taken

Results from longitudinal studies of children, particularly those children most at risk for problems, indicate that families can protect children and youth against drug use and abuse through effective family management practices that impart skills young people can use in resisting social pressures to use drugs. NIDA is developing programs that focus on drug abuse and families. NIDA is making sure it has the best possible team of experts to address this area as well as its remaining portfolio, including social workers. One example of NIDA's efforts to train social workers and other potential researchers in drug abuse and addiction is the National Research Service Award (NRSA). The NRSA supports research training leading to the Ph.D., or similar research doctorate degree in specified areas of behavioral, biomedical or social science to ensure that highly trained scientists will be available in adequate numbers and in the appropriate research areas and fields to meet the Nation's drug abuse research needs.

The future of drug abuse research is dependent not only on a pool of qualified scientists to pursue research careers in the areas of drug abuse, but also upon the ability to attract and retain bright young investigators to the field. NIDA is committed to expanding its research training efforts. In FY 1994, NIDA's training budget, which is critical to the flow of young investigators into the field, was about 2 percent of its extramural budget. In FY 1996, it was increased to about 2.6 percent.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Institute on Drug Abuse	Section 464L (d)	42§285o(d)	a/	$318,731,000	b/	$348,240,000
Medication Development	Section 464P(e)	42§285o-4(e)	a/		b/	
National Research Service Awards	Section 487(d)	42§288(d)	a/	9,555,000	b/	10,235,000
Total, Budget Authority				328,286,000		358,475,000

a/ Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208)
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	N/A	N/A	$410,502,000	$403,806,000 2/
1994	$407,098,000	$425,201,000	425,201,000	425,201,000
1995 3/	291,963,000	290,280,000	290,280,000	289,581,000 4/
1995 Rescission				-212,000
1996	298,736,000 3/	458,441,000	294,705,000 3/	458,441,000
1996 Rescission				-329,000
1997	312,014,000 3/	487,341,000	317,936,000 3/	489,160,000 5/
1998	358,475,000 3/			

N/A = Not Applicable

1/ Reflects enacted supplementals, rescissions, and reappropriations. Prior to the FY 1993 Senate Allowance, NIDA was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of $5,176,000.

3/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

4/ Excludes enacted administrative reductions of $39,000.

5/ Excludes enacted administrative reductions of $215,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	16	16	16
Office on AIDS	4	4	4
Office of Extramural Program Review	26	26	26
Office of Planning & Resource Management	54	52	52
Office of Science Policy & Communications	25	25	25
Division of Basic Research	25	26	26
Division of Clinical & Services Research	34	35	35
Division of Epidemiology & Prevention	31	31	31
Medications Development Division	36	38	38
Division of Intramural Research	112	110	110
Total, NIDA	363	363	363
	Average GS/GM Grade		
1993	10.9		
1994	10.9		
1995	11.1		
1996	11.2		
1997	11.2		
1998	11.2		

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute on Drug Abuse
Program Administration

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	2	2	2
ES-5	2	3	3
ES-4	1	1	1
ES-3	0	0	0
ES-2	1	0	0
ES-1	0	1	1
Subtotal	6	7	7
Total - ES Salary	$729,337	$850,893	$1,031,400
GS/GM-15	42	42	42
GS/GM-14	70	70	70
GS/GM-13	47	47	47
GS-12	37	37	37
GS-11	16	16	16
GS-10	0	0	0
GS-9	9	9	9
GS-8	18	18	18
GS-7	29	29	29
GS-6	15	15	15
GS-5	9	9	9
GS-4	12	12	12
GS-3	2	2	2
GS-2	3	3	3
GS-1	0	0	0
Subtotal	309	309	309
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	17	17	17
Senior Grade	4	4	4
Full Grade	4	4	4
Senior Assistant Grade	1	1	1
Subtotal	26	26	26
Ungraded	37	37	37
Total permanent positions	321	321	321
Total positions, end of year	378	379	379
Total full-time equivalent (FTE) employment,end of year	363	363	363
Average ES level	4.0	4.0	4.0
Average ES salary	$121,556	$125,203	$128,709
Average GS/GM grade	11.2	11.2	11.2
Average GS/GM salary	$46,764	$48,167	$49,516

TUESDAY, MARCH 4, 1997.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

WITNESSES

DR. ENOCH GORDIS, DIRECTOR
DR. MARY DUFOUR, DEPUTY DIRECTOR
MARTIN K. TRUSTY, EXECUTIVE OFFICER
STEPHEN LONG, DIRECTOR, OFFICE OF POLICY ANALYSIS
CARMEN M. RICHARDSON, BUDGET OFFICER
DR. HAROLD VARMUS, DIRECTOR, NIH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. PORTER. The subcommittee will come to order.

The subcommittee is now pleased to welcome Dr. Enoch Gordis, the Director of the National Institute on Alcohol Abuse and Alcoholism. Dr. Gordis, it's nice to see you. We appreciate your patience, we're running a little behind schedule. But we intend to give you a full hearing on your budget.

Please proceed with your statement after introducing the people at the table with you.

INTRODUCTION OF WITNESSES

Dr. GORDIS. At my left, your right, is Mr. Steve Long, who's our Director of the Office of Policy Analysis; Mr. Martin Trusty is our Executive Officer; Ms. Carmen Richardson is our Budget Officer. To my right, is Dr. Mary Dufour, who's the Deputy Director of the Institute. I think the other two gentlemen you know very well.

Mr. PORTER. I do.

OPENING STATEMENT

Dr. GORDIS. With your permission, I will not simply read the formal statement. I just want to comment on some of the issues in it. And I think this will open up the questions in an effective way.

As you know, the Institute is charged with providing the scientific basis for improved prevention and treatment of alcohol problems, and as such, we support about 90 percent of the alcohol research in this country. Alcohol problems cost the country a lot. The last estimate is about $98 billion to $100 billion a year. Somewhere between 10 and 50 percent of all hospital admissions are due to the complications of alcohol in many different organ systems.

VULNERABILITY TO ALCOHOLISM

This has been a really good year for NIAAA in the sense that many of the investments which Congress has seen fit to put into our scientific enterprise are beginning to show fruit in very impor-

tant ways. And I'm going to touch on some of them. The first is the issue of the vulnerability to alcoholism, which we know from fifteen years of studies on twins and adoption studies, indicate that a significant portion of the vulnerability to becoming alcoholic upon exposure to alcohol is inherited.

Based on these important population studies, seven years ago, we embarked on a collaborative study on the genetics of alcoholism, which is now taking place in six centers across the country. The first two years were devoted to creating assessment instruments to clearly define who had the condition and who didn't. Important surveys for doing that were defined, written up and have been translated and used internationally.

And over the course of the years, many thousands of people were interviewed extensively. And what has been culled are 300 so-called informative families in which there is multi-generational alcoholism, that is, some people have it and some don't. From them, we have obtained blood samples of various biological markers for DNA and have preserved and stored cell lines, which are held in two repositories.

We are pleased to inform the committee that during the past year, several striking findings are beginning to emerge in the genetic study. I should preface this by saying that over the course of the last few years, some important spinoff studies have occurred. But I will emphasize the findings related to genetics in this discussion.

The first is that several chromosomal hot spots, that is, areas of the genome where the genes related to alcoholism are likely to be found, have been identified on chromosome numbers 1, 4, 8 and 16. The next task, of course, will be to work on these zones for the next few years to find those genes which are related to the vulnerability to alcoholism.

I should point out that unlike many of the disorders in which there have been genetic triumphs, like cystic fibrosis, Huntington's, sickle cell and a very long list, complex disorders like alcoholism are due to the effects of a mix of genes. And therefore, the task of finding them, not one of which singly is responsible for the whole condition, is immeasurably more difficult. But with modern technologies, which are improving, even during the course of this study, that is being accomplished.

The resources of this study, both the data as well as the blood samples and the DNA, will become a scientific resource for the general scientific community in 1999. And at that point, other investigators, in addition to the current ones, if they are qualified, will have access to it, too, because it's a very important national resource.

ANIMAL MODELS

The other area where our field is distinguished is in the use of animal models for studying the genetics of alcoholism. Many of the behaviors related to alcohol can be mimicked in animal models. And for that reason, we are pleased to inform you that during the last couple of years, several of these loci on the animal genome, particularly the mouse, have been found relating to alcohol pref-

erence and to other aspects of alcohol related behavior. If the committee is interested, I'll be pleased to enlarge on the details later.

And finally, we are using the contemporary techniques of knockouts, where a single gene theorized to have an effect on the condition is knocked out so it does not get expressed in the adult animal. And it turns out we've had two very interesting successes here in which knockout genes have shed light on what possible circuits in the brain are related to alcohol misuse.

APPLICATION OF RESEARCH ADVANCES

Not stated in the written testimony I think is something important. And that is, what is the payoff for all this kind of work. Because there is a major payoff. I think they're in three real areas that are important. Once we find the genes which code for certain proteins, and we know what the functions of those proteins are, it's going to give us a clue to the physiology of this disorder and permit us to develop even more medications than we have now, although there's been progress on that front, as I'll tell you in a minute.

The second thing we're going to be able to do is more targeted prevention efforts. There aren't human or financial resources adequate to do all the prevention we'd like to do. And by focusing on those most likely to get into trouble, we can make that route more efficient.

And finally, by the more precise delineation of genetic influences, we will better understand the role of the environment. Because no one is saying that alcoholism is solely a genetic disease. Many environmental factors, beginning in the uterus and going through early development in the home and then all the environment around us, contribute as well.

Another area where we've had major advances is in the area of neuroscience, which is influenced by genetics but really a separate discipline in some ways. The main task with alcohol is somewhat different than with illegal drugs. Alcohol does not act on a specific receptor like cocaine and heroin do. It seems to act on a multiplicity of receptors. Alcohol kicks up some activities and inhibits others. And the delineation of that activity has been a very important aspect of our work.

Important advances have been made in understanding, on the one hand, the reward system which is more complex than dopamine in the case of alcohol. This is a positive feeling that makes people want to drink. And the other side of this, which is coming into the fore again, is interest in understanding the withdrawal state, or the dysphoria or the discomfort of not having alcohol once you are dependent upon it. Alcohol withdrawal seems to involve different neurotransmitters and different circuits. And both of these processes, of course, are candidates for understanding and for future medication development.

The imaging which Dr. Leshner addressed is very effectively used in our field as well. In the interest of time, I will not touch upon it, except to say that the issue of different cravings is very important here, too.

On a theoretical basis, although it sounds rather remote, our new understanding of how alcohol acts on cell membranes is leading to a total revision of how we understand alcohol's effect on the nerv-

ous system. We are learning in toxicology how alcohol damages the brain, the liver and the fetus, which I know is of great concern to the committee. And I'll be glad to enlarge upon that as well during the questions.

TREATMENT RESEARCH

I want to take the last couple of minutes on treatment and prevention. There are two kinds of treatment research which the Institute does. As you know, much of alcoholism treatment develops outside the mainstream of medicine. And therefore, many of the things which have been done by tradition and by convention did not develop with the usual rigorously controlled trials which are typical of other branches of health care.

One aspect of our treatment research is to apply contemporary clinical approaches in research, blind design, randomization and so on, to therapies that have been used traditionally without testing. One example of that is the Project MATCH, which examined in a large-scale, 6-year study in 1,700 patients randomized to three arms of behavioral therapy: 12-step facilitation, cognitive behavioral therapy, and motivational enhancement, to see whether by typing the patients precisely it would be possible to define a patient treatment match that would yield better treatment outcome.

Despite smaller studies in the literature and the hope from the Institute of Medicine that that would pan out, it turned out that by and large, no major matches were found. It turned out that all the patients did quite well. Except for psychiatric severity, where the patients with low psychiatric severity did somewhat better in the 12-step facilitation, the patients did equally well and no matches were found in the 10 that were explored.

The other side of treatment research is the development of new medications, and we've also been doing very well on this. During the last two years, we've told you about the FDA approval of naltrexone for the treatment of alcoholism after withdrawal. Nalmefene and other opioid antagonists have likewise been shown effective.

And a drug which has shown promise in Europe, which works by a different route called acamprosate, has been finally given an IND—investigational new drug—approval by the FDA. NIAAA has been helping the company design a treatment trial which will be conducted in this country during the next year and a half or two.

PREVENTION

I know there's been interest in the last discussion on prevention. This is a very important part of our portfolio. The part I'd like to emphasize is somewhat parallel to what Alan Leshner mentioned in the previous testimony. It's very easy to think of interventions which have a surface plausibility, which are expensive and which don't work. The experience of science, and I'm glad to say it's happening, is that the same techniques of rigorous analysis of what works for medications development are the same as those which work in prevention. It's a more difficult field because we cannot account for everything that's going on in the world around us.

But I'm happy to say that by virtue of rigorous studies of what is going on, several important trials have yielded important results,

which hold promise for prevention of alcohol problems in the young, especially. Community trials are going on in several paired communities in California and South Carolina. A very interesting study by Dr. Cheryl Perry called the Northland study, in 20 communities, 10 which used the interventions and 10 which didn't, among kids between the 6th and 8th grade years, showed 25 percent reduction in the initiation of drinking and several other positive outcomes.

[CLERK'S NOTE.—Later corrected to "28."]

RESEARCH DISSEMINATION

I'd like to conclude by talking about the importance of research dissemination. We have major publications which have come out, some of which have been prize winning, on a variety of topics, including prevention, including genetics, including imaging. We have a booklet called *Primary Care Recognition and Intervention* which has just come out. It's been distributed to about 200,000 people, including primary care doctors.

We have had help in this distribution from General McCaffrey's Office of National Drug Control Policy to the tune of about 60,000 copies. Dupont Pharma, which makes naltrexone, has distributed yet another 100,000. And this has been very widely received. The publications are here on the table, and during the course of this discussion, if you're interested in my discussing any elements, I'll be happy to do so.

The budget request for NIAAA for 1998 is $208,112,000, exclusive of AIDS. I'll be happy to answer any questions.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute on Alcohol Abuse and Alcoholism

I am pleased to be here with you today to discuss the many scientific advances and research opportunities at the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The NIAAA is the foremost Federal agency supporting biomedical and behavioral research directed towards improving the prevention and treatment of alcohol abuse and alcoholism and reducing associated health, economic, and social consequences. NIAAA funds 90 percent of all alcohol research in the United States and provides leadership in the country's effort to combat these problems by developing new knowledge that will decrease the incidence and prevalence of alcohol abuse and alcoholism, and its associated morbidity and mortality.

Alcoholism research has the potential to impact on the lives of approximately 14 million alcoholics, alcohol abusers and their families--an estimated 98 million Americans. Although a dollar figure cannot adequately reflect the social and human devastation caused by these illnesses, it is estimated that the economic and health care costs to society from alcoholism and alcohol abuse approach $100 billion annually[1]. Research findings that improve the prevention or treatment of alcohol abuse and alcoholism have tremendous potential for affecting the quality of life of nearly every American and can influence thinking in other areas of medicine.

Among the areas where alcoholism research has made significant strides is the demonstration that a significant amount of the vulnerability to alcoholism is inherited. Previous twin and adoption studies laid the foundation for current genetics work, much by individual NIAAA intramural scientists but most extensively in the Collaborative Study on the Genetics of Alcoholism (COGA) supported by NIAAA. COGA is a multi-site collaborative, tightly controlled study of large families who have alcoholism multiply represented among their members. COGA involves six extramural research study centers in which investigators are searching the entire human genome for genetic markers linked with alcoholism.

COGA scientists developed accurate, valid, reliable, and specific comprehensive interviewing tools, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) and its companion version for children (C-SSAGA-C) and adolescents (C-SSAGA-A). These new interviewing tools represent a major advance in currently available interviewing techniques, and are in use internationally. Resources subsequently developed by COGA include diagnostic and pedigree data on 3000

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[1]Rice, Dorothy P. The Economic Cost of Alcohol Abuse and Alcohol Dependence: 1990. *Alcohol Health and Research World* 17(1): 10-11, 1993.

individuals belonging to about 300 families with alcoholism, along with corresponding biochemical, genetic, and neurophysiological data. Also developed is a collection of DNA samples and immortalized cell lines derived from these individuals and maintained in a Cell Repository. COGA resources will thus provide a wealth of data available to the scientific community for further investigation.

We are very pleased to report that initial COGA findings have identified promising chromosomal locations relating to alcoholism, and colloquially referred to as hot spots. Distinct from this research is the finding of chromosomal locations for a specific brain wave pattern, P3, found in persons at high risk for alcoholism. Each chromosomal location contains many genes and the next task is to identify the precise genes. The payoff for this research is the development of new medications, targeted prevention programs, and a precise understanding of both the genetic and environmental influences on the development of alcoholism.

Another area where alcohol research has advanced is in the use of animal models for studying complex behavior, such as, alcohol consumption. Molecular biology techniques are being used to identify quantitative trait loci (QTL) which give investigators the ability to define the contribution of single genes, any of which together create the quantitative trait. We are pleased to report that an NIAAA-sponsored investigator has located two sex-specific genes influencing alcohol consumption in mice. One QTL (Alcp1) is active only in males; the other (Alcp2) is active only in females, and only when inherited through the maternal lineage. Because of similarities between the mouse and human genes, this work promises to accelerate locating human genes that contribute to alcoholism.

Earlier work led to the conclusion that the neurotransmitter, serotonin, is involved in alcohol consumption. Recently, a study identified one precise serotonin receptor subtype, 5-HT_{1B}, that is involved in regulating the consumption of alcohol in mice. This was accomplished by genetically removing the serotonin receptor, 5-HT_{1B}, and observing increases in alcohol consumption. Stimulation of the 5-HT_{1A} serotonin receptor subtype, however, reduces consumption. Other investigators showed that clinically realistic doses of alcohol affect several neurotransmitters including, NMDA subtype of glutamate receptor, the $GABA_A$ receptor, and other serotonin receptors. The effect of alcohol on these receptors varies among brain locations in single animals and between strains raised to demonstrate major differences in alcohol related behaviors.

Advances are also being made in understanding the mechanism of alcohol-induced tissue damage (toxicology). These findings include: the fact that alcohol can influence the expression of cytokine-regulated genes in the liver; that clinical management of alcohol-induced liver injury might be improved by reducing the number of gram-negative bacteria producing endotoxin in the intestine; and that the pathogenesis of fibrosis in alcoholic liver damage may involve the direct deposition of collagen induced by acetaldehyde, the first product of alcohol metabolism.

Advances are also beginning to unravel the mechanisms of alcohol's effects on human fetal development leading to the manifestations of fetal alcohol syndrome (FAS). Two findings suggest reasonable mechanisms for alcohol's effects on the fetus. One finding is that alcohol induces excessive cell death through the formation of free radicals in pre-migratory neural crest cells resulting in subsequent malformation. The addition of a free-radical scavenger can ameliorate alcohol-induced cell death. The second finding is that at clinically relevant levels, alcohol completely inhibits the activity of the L1 cell adhesion molecule which helps guide newly forming neural cells to their proper location.

Research on effective medications is built upon findings such as those previously mentioned. Naltrexone, nalmefene, and acamprosate are among the most promising medications. The use of naltrexone which was recently approved by the FDA for the treatment of alcoholism is based on clinical and basic science observations. NIAAA-sponsored clinical trials are now determining which groups of patients are most responsive to this medication and the benefits and side effects of long-term use. Nalmefene, another opioid antagonist, also appears promising and has several potential advantages over naltrexone including a longer half-life, enhanced bioavailability, less liver toxicity, and more complete blockage of opioid receptors. Acamprosate, now under an FDA investigational new drug protocol, has been tested in clinical studies throughout Europe with promising results. It appears to act on NMDA and GABA receptors. NIAAA is providing consultation on methodology and trial design to pharmaceutical companies planning clinical trials on acamprosate.

In addition to medications development, other aspects of treatment research are also advancing rapidly. We are ready to begin advanced clinical trials built upon data obtained from both medication studies and from the recently completed multi-site treatment trial, called Project MATCH. This study compared the effects of different treatment types when matched to specific patient characteristics and was the largest, most complex randomized clinical trial ever undertaken in alcoholism treatment. A number of alternative treatments for alcohol problems are available. They range from brief, motivational interventions to broad spectrum treatments, such as social skills training, and the 12-step Minnesota model. Frequently two or more treatment types are combined in one therapeutic approach.

Based upon the literature and previous small studies, the hypothesis was advanced that matching patient characteristics to specific treatment modalities would be the most efficacious. Patients were randomly assigned to well-specified treatment strategies. Subsequently the relationship between treatment outcome, patient characteristics, and treatment type were assessed. A total of 1728 patients were recruited from nine states, with ample representation of women (25 percent) and minorities (20 percent). Three specific, well-defined, and well-controlled treatment approaches were tested. The findings from MATCH, however, did not confirm this expectation.

Instead, the three treatments achieved comparable outcomes and the data indicate that each treatment type resulted in substantial reductions in drinking. Furthermore,

this reduction in drinking was generally sustained for 12 months. With the exception of patients with serious psychiatric problems, it appears that matching patient characteristics to a specific treatment type did not improve outcome. This study demonstrates that well-designed treatments, in combination with good training of therapists, contribute to excellent retention rates in treatment. Furthermore, these findings run counter to the belief that treatment gains are inconsequential and short-lived.

The next major step is to build upon the findings from Project MATCH and the randomized trials for medication, such as those previously reported for naltrexone. The major goal is to combine MATCH with new insights gained from medications research. Follow-up clinical trials will include new pharmacotherapies, such as naltrexone, nalmefene, and acamprosate, combined with standardized behavioral strategies. In sum, we expect findings from genetics research, neuroscience, and medications development to inform the development of increasingly improved treatment strategies.

Prevention research is also a priority at NIAAA, the goal of which is to obtain scientifically objective and measurable effects attributable to specific interventions. To ensure the acquisition of meaningful results, these studies employ rigorously defined scientific methodologies including random selection and control communities. One excellent example is a recent study nearing completion which may provide a model alcohol use prevention program that can be implemented in communities around the country. The Northland study used a multi-component, multi-year, community trial to delay, prevent, and reduce the prevalence of alcohol use and alcohol-related problems among a group of adolescents from 22 school districts in northeastern Minnesota. The project targets the Class of 1998 and has been ongoing for five years, beginning with students in the sixth grade and following them through grade 10. Interim results look quite hopeful. At the end of three years of program (grade 8) the rates of alcohol use were significantly lower among students in the program school districts compared to the reference districts. When compared to reference districts, 19 percent fewer students who received the program used alcohol in the past month, and past week use was 29 percent lower. Of great significance is the fact that overall fewer students initiated alcohol use. For instance, past month alcohol use by 8th graders who did not drink in grade 6 was 28 percent lower in program communities than in reference communities.

In addition, NIAAA is taking a leading role in educating the public and physicians about alcoholism. Our Alcohol, Health and Research World is an award winning journal and information about nearly all of NIAAA's activities are available on our web site, including grant and funding information. This past year we published and disseminated 75,000 copies of The Physicians' Guide to Helping Patients with Alcohol Problems. At the request of the Office of National Drug Control Policy (ONDCP), an additional 165,000 copies were printed for distribution by ONDCP. DuPont Pharma is also significantly aiding in this effort at their own expense by printing and distributing through their field representatives an additional 60,000 copies to primary care physicians nationwide.

In conclusion, alcohol research is progressing rapidly and the scientific advances and opportunities in our field are very encouraging. Mr. Chairman, the FY 1998 President's budget request for the National Institute on Alcohol Abuse and Alcoholism is $208,112,000. Thank you. I will be happy to answer any questions the committee may have.

TRENDS IN ADOLESCENT CONSUMPTION

Mr. PORTER. Dr. Gordis, thank you for that very good statement.

I was struck by the statistic in your budget justification that alcohol is used by more Americans than any other drug, including tobacco. We're all concerned about the increase in drug use among teenagers. What are the recent trends in alcohol use among teens?

Dr. GORDIS. There have been some minor decreases, fractions of a percent, in high school kids, for example, Mr. Porter. But it is still distressing that by the time kids reach their senior year of high school, a little under 80 percent of them have used alcohol, and about a third of them have had five drinks on one occasion during the previous two weeks.

So there is a welcome trend in the slight decline, but I think we still have a major issue of alcohol use among adolescents.

Mr. PORTER. In 1994, U.S. per capita consumption of alcohol sank to the lowest level in 32 years. How is the pattern of consumption distributed? What share of the population doesn't drink at all, and what share are heavy drinkers?

Dr. GORDIS. About one-third of the adult population does not drink. Among heavy drinkers, if we define it by people who are drinking, say, five drinks a day or more for men and four for women, then we're in the range of 10 to 15 percent. And the rest are drinking less, but not zero.

Mr. PORTER. Alcohol-related traffic deaths rose in 1995, reversing a 10-year decline. How does that data fit with the declining per capita consumption?

Dr. GORDIS. I can't explain this one-year change in the direction, Mr. Porter. There has been a decline over the last 10 years, and whether this represents a new trend or not, I think we're going to have to see in the next couple of years. It's very difficult for the change in one year to be accounted for.

RIGOROUS DESIGN AND FINDINGS OF PROJECT MATCH

Mr. PORTER. You described your Project MATCH, which to the surprise of many found that matching different patient characteristics to different therapeutic approaches does not substantially alter outcomes. This has been heralded as good news by those who point out that inexpensive treatments seem to work as well as expensive ones.

But what does the study tell us about the ultimate question? How well do any treatments work? What is the retention rate in treatment for patients, and what is the relapse rate after one year of treatment?

Dr. GORDIS. This is a very important and complex issue. However, I'll do my best to summarize it.

I think Project MATCH delivered contemporary treatment about as efficiently as can be done. The treatments were all standardized, that is, there were manuals of therapy which defined exactly what transpired during these verbal encounters between patient and therapist. This was not a trial of medication.

And as you know, it is easy in the course of a conversation, even in a therapeutic one, for the quality of the therapeutic encounter to be degraded by informal conversation and so on. In order to en-

sure that that didn't happen, the treatments were standardized, that is, there were three separate books, which defined the treatments precisely. And in fact, they've been in wide demand outside this research protocol, about 30,000 copies have been printed and circulated throughout the country.

The second way to ensure the quality is that many of these sessions were videotaped, so an outside observer could guarantee that the treatments were discriminable by somebody who didn't know which arm of the therapy was given. The therapists were all very well trained people. The reason I'm saying this preface is because it's important to understand that under the conditions of this study, I think we are maximizing the effects that current behavioral approaches can have, independent of the matching issue.

Now, how well do the patients do? Aside from the fact that the three groups did more or less the same, the absolute sobriety rates for the year ranged between 25 and 40 percent, depending on whether the patients had had a period of inpatient treatment or not. This abstinence rate, which is quite good, is probably a little bit better than most current programs achieve.

It's important to understand that alcoholism and other addictions are chronic relapsing disorders. So the way we would look at a condition, for example, arthritis, is not whether we can cure it absolutely, although that's the hope, but rather how many days free of symptoms and pain can we afford the patient by the best treatments that are available.

We hope to cure alcoholism in our lifetime. We hope to get total abstinence or no problems from alcohol as a goal of all of our research. What we can say now is that somewhere between 25 and 35 percent of patients are likely to remain abstinent for at least a year. And as we know from long-term longitudinal studies like those of Dr. George Vaillant, the longer you stay in the abstinent state, the longer you are likely to stay in it. And the biggest dropoff tends to be in the first few months.

Most treatment programs, and I think this is a precise answer to your question, will lose the majority of their patients, I believe, to relapse. Many of them will come back, but sometime during the first three or four months they will stop treatment. That's the most dangerous time for relapse.

So in summary, I would say that a minority of patients remained permanently abstinent. A good chunk of the patient population will have intermittent abstinence, which is far better than drinking continually, both in human, financial and medical terms. And a fraction of the patients, which is not inconsiderable, will not do well at all.

Mr. PORTER. Dr. Gordis, some of the popular press coverage of the trials' findings gave the impression that the Federal Government spent $27 million on a study, and now we don't have any better idea than we did before on what works in alcoholism treatment. How have you responded to that characterization?

Dr. GORDIS. Well, the only accurate part of that statement is the cost. Other than that, the conclusions, I think, are erroneous. First of all, this was the largest, most carefully controlled study of behavioral treatment of alcoholism ever conducted. And it told us several important things. It told us first of all that among the 10 cri-

teria which were selected à priori as patient characteristics for matching with these three very popular and well written up kinds of treatments, none offered particular matching advantage to one arm of the treatment or the other.

On the other hand, it shows the limits of what we can accomplish with contemporary behavioral treatment. It also assures the treatment community that when you consider the dramatic drop in drinking that the patients in all three arms of the treatment showed from the time before they came in to the time they completed the study, that treatment actually is quite effective. Project MATCH demonstrated that any treatment program that delivers one of these treatment modalities in a quality way is likely to do a lot of good for the patient.

The kind of statement which you made, which we've heard occasionally also, simply is not so.

EVALUATIONS OF ALCOHOLICS ANONYMOUS

Mr. PORTER. We discussed the fact last year that Alcoholics Anonymous had never undergone rigorous scientific evaluation. Does Project MATCH provide the scientific evidence that has been lacking, since it included an AA component?

Dr. GORDIS. Not in the strictest sense. But it does shed some light on the AA-related component of Project MATCH. Sometimes people have misunderstood the arm of Project MATCH dealing with 12-step facilitation as meaning, simply sending people to AA. That's not what happened here. All arms of the treatment involve a one-on-one therapeutic series of events between the patient and the therapist.

The one involving 12-step therapy was a detailed examination of the first three steps of Alcoholics Anonymous with the patient by a professional trained therapist. Then the patient would go to AA meetings, was encouraged to do so, and would come back to this professional trained therapist to explore his or her reaction to the meeting, and what attitudinal changes might be suitable in view of these reactions.

That's not the same thing as sending patients to the AA. In fact, if we look at AA's own data from the headquarters office published about six years ago, AA is not a scientific organization but one must commend them for their candor in looking at this issue, AA was very concerned about meetings in general, and about the large loss of people who go to meetings early on. And it turns out that within about three months of the time that people go to their first AA meeting, only about 5 or 10 percent of them are still going to meetings. It doesn't mean that many people don't come back and finally get it together.

But AA is quite aware of the tremendous loss in meeting attendance, even during the first few months. And I must say that the 12-step facilitation arm of Project MATCH did a lot better than that.

The more general answer to the question of effectiveness of AA cannot probably be studied in its pure form. Let me tell you the reason why. If we were to study, for example, a medication, and it's been done with antabuse, which is a drug used in alcoholism treatment to provide an aversity of response to alcohol if you drink, you

don't take people who take the drug and compare them to people who are unwilling to take it. In the antabuse study, which was done by Dr. Richard Fuller of our Institute some years ago in the VA system, he compared patients, all of whom were willing to take antabuse. Some patients got it, some got placebos. This was an excellent study.

Ideally, to study AA, one would want to do the same thing, that is, take a group of people who would be willing to go to AA and some who don't. That kind of idealized situation could probably not be practicably applied to AA. And there are major problems with anonymity, and there are major problems with destroying the very phenomenon you're studying by too much observation.

There have been studies on sponsorship in AA and some ancillary questions like that. But I think in the long run, the kind of rigorous control trial that's been applied to virtually every other aspect of health care, including alcoholism now, probably would be, it would be difficult to do AA studies along those lines, in my view.

Mr. PORTER. Thank you, Dr. Gordis.

Mr. Miller.

MEDICATIONS FOR ALCOHOL TREATMENT

Mr. MILLER. Where do we stand with respect to a medical treatment of alcoholism? What's available?

Dr. GORDIS. If by medical treatment you're talking about medications for alcoholism, there are several. The oldest one dates from the late 1940s. It's called antabuse. And it was a drug which did not obliterate the craving for alcohol. What it did was threaten the patient with an unpleasant reaction if he or she were to drink.

It turns out that although there's been a loss of interest in that drug, because of the excellent control study on antabuse which I just referred to in my response to Mr. Porter's last question, it turns out that probably it needs a little bit more exploration. Because there's some evidence that under supervised conditions, or even in a marriage where one spouse stays in the marriage on the condition that the other takes it, the results can be better. It's a very interesting drug.

And one of the things that we are supporting now is the development of a derivative of the drug. Its metabolism has been studied extensively by Dr. Morris Faimen in Kentucky. And we know now that the first metabolite of antabuse that the body produces is a sulfoxide derivative of the half of the antabuse molecule that is probably the business end of the antabuse molecule. And there's some hope that this would be a more effective use of antabuse and that it would have fewer side effects. So that's one thing we are actually working on. We have contracts out now to prepare the chemically pure new compound, and to try it out for toxicity.

The more hopeful areas that I addressed in my opening remarks have to do with drugs which seem to abolish the hunger for the substance during the time the patient is off it.

Two years ago, the FDA approved naltrexone, which is an opioid antagonist, for the maintenance of sobriety during abstinence after detoxification has been complete. Two things were demonstrated by studies, three, actually. First, naltrexone was not being used independent of counseling but in parallel. That's very, very important.

But the second thing was that among the patients who took naltrexone, it did two things. It lengthened the time to the first abstinence violation or the first relapse. And among the people who did slip, that is, they started experimenting with alcohol again, it reduced the likelihood of them going on to a full-blown binge.

So naltrexone was shown to be effective in these carefully controlled studies by investigators both in Philadelphia and at Yale, and FDA approved it, and now it is increasingly being used in the treatment community, but at a rate which I wish was faster. But it is being generally incorporated, but not to replace counseling, but as an addition to it.

Nalmafene, which is another orally active opioid antagonist, has been studied extensively by Dr. Barbara Mason in Florida. And it turns out to be very promising, indeed.

The drug in Europe called acamprosate, which is calcium acetyl homotaurinate, is a drug which probably acts differently than the other two. Originally thought to react on the GABA receptors, it's now known probably to act on the so-called NMDA receptor, which is a subtype of the glutamate excitatory receptors.

And in European trials, this drug has shown promise also of helping to maintain abstinence. They've had larger numbers of patients in the European trials than here. But the design of the trials and the attention to detail I think were as good as with our naltrexone trial approach.

What's happened is, Lipha Pharmaceuticals, the company that manufactures it, has obtained an IND to begin experiments in this country. And as I said before, the NIAAA is helping them design the experiments to test out this drug in this country. And in fact, the books that were developed with Project MATCH are turning out to be very useful to the pharmaceutical industry in the behavioral side of the treatment.

A CURE FOR ALCOHOLISM

Mr. MILLER. You mentioned a desire to have a cure for alcoholism. What would be the definition of a cure, a realistic one, five years from today?

Dr. GORDIS. I don't think we're going to have it five years from today, but I'm an optimist. The goal is to find a cure, but meanwhile to decrease the consequences of drinking and its abuse. A cure would be, I think ideally a cure would be somebody who either drank or didn't drink at will, who had no tremendous craving to have it, a social drinker, in my definition, is somebody who doesn't really care very much whether he has it or not. And a cure would be to restore alcohol to normal life priorities where it doesn't dominate one's life.

Mr. MILLER. Is that the medical route? The behavioral versus the pharmaceutical route, so you're having, I guess to do them together?

Dr. GORDIS. Yes, I would accept what you said absolutely, with one caveat. It's not versus.

One of the nice things that's happening in research in general now is that this gulf between the behavioral world and the so-called biomedical world is narrowing. We know, for example, that in the case of obsessive compulsive disorder, something outside of

our domain, but somewhat related, that behavioral therapy, when successful, has the same effects in PET scans in the head of the cordite neural regions of the brain as serotonin uptake inhibitors do in those patients who are successfully treated with medications for that disorder.

This just shows that the potent therapy, even of a verbal kind, has the potential of altering the chemistry and the circuits of the brain much as drugs do. Drugs may be more efficient, on the other hand, they're somewhat more global. Behavioral therapy is somewhat more targeted to the behavior you want to change. And I think that this distinction between the two is gradually becoming obliterated, and we need both.

Mr. MILLER. One final question. I was talking with Dr. Leshner about this. The private sector is not spending a lot of effort and money on cocaine addiction. But the private sector, probably, and I hate to assume anything, the private sector is probably pursuing alcoholism, because there is a potential return for them, is that right? Is there a very large effort there?

Dr. GORDIS. There is some effort. I think there's probably more effort in the case of alcohol than there's been in the case of the illegal drugs. You see, naltrexone has been available already for 20 years or so. It was developed originally, of course it's an opioid antagonist, hopefully as a treatment for heroin use. By and large, it has only been slightly successful. Because although it does block the effect of heroin when taken, it does not abolish the craving for the drug, which is the thing that drives the relapse.

So except for a small group of very well-motivated people, say like doctors who are addicted and are threatened with loss of their license, naltrexone has not turned out to be a potent therapy for heroin addiction. But it's interesting, in a confluence of both clinical and basic research, the basic research finding was that naltrexone in animal models inhibited certain kinds of ingestive behaviors, including alcohol and including calories, especially those from carbohydrates.

That animal research, together with an observation made during drug treatment of heroin addicts who were also using alcohol, combined to lead to the experiments using naltrexone for alcoholism. And that's what led to this.

Now, since the drug was already available, it had been manufactured by Dupont Merck under the name Trexan, the drug was made available for the treatment of alcoholism under the new name, naltrexone. We don't have anything in the pipeline in this country for new drugs created just for alcoholism, but there are several existing medications that I didn't mention that are being tried.

Acamprosate, from Europe, is destined to be used only for alcoholism as far as I can see right now; that's a second example.

There probably is some market for acamprosate. And I think as one company succeeds and makes some money, it will be an incentive for other companies to proceed along those same lines.

Mr. MILLER. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Miller.

Mr. Wicker.

PRACTICAL APPLICATIONS FOR GENETICS RESEARCH

Mr. WICKER. Just one question, Dr. Gordis. Your testimony mentions significant strides in demonstration that vulnerability to alcoholism is inherited. And you go on to talk about a study and an assessment about genetics. And strides in chromosomal locations. You say each chromosomal location contains these genes, the next step is to identify the precise genes. So we're not quite there yet?

Dr. GORDIS. That's correct.

Mr. WICKER. If you could just tell me, what do you envision as the practical application for this research, once you finally get the research over with?

Dr. GORDIS. I think there are several practical applications here. Two of the payoffs, I think, which I mentioned briefly earlier, are very practical. The most important one, I think, is that when we find a gene, we find is a recipe for the body's making of proteins. The protein is the functioning part of the body's machinery. The enzymes, the receptors, the structural elements of the cell and so on, much of that is protein.

So the gene is a recipe which tells the body how to make a protein. If the gene is different in alcoholic individuals than it is in normal people, it means that there's something about the protein which is being made which is different. If it's different, it has a slightly altered function. It can be very different, or subtle differences which combine with other genetic changes, cause a whole picture where the patient is sufficiently different to be at risk.

The first payoff from this kind of research will be, once we understand what these genes are and what their function is, to then find medications which are going to interfere with this abnormal function. Genetics research is going to be, I think, one of the most potent routes for developing new medications for the treatment of alcoholism.

A second payoff from genetic research will be prevention. Because it's clear that the highest risk people are the ones most likely to get into trouble. So there will be an aspect of genetic research which will permit us, I think, to target prevention in a more effective way.

GENETICS TESTING

Mr. WICKER. When do you anticipate that individuals, that don't yet have a problem with alcohol, would be tested?

Dr. GORDIS. That remains to be seen, and that raises the whole issue of genetic testing in general. And I don't know if you want me to go into it. Dr. Varmus certainly is a person who has had to discuss these issues in so many ways and in such an articulate way that I don't think I would do as good a job.

But the fact that we can test——

Mr. WICKER. That remains to be seen. [Laughter.]

Dr. GORDIS. The issue of when we do genetic testing for anything is a problem which I think genetics-oriented ethicists are discussing in many spheres of medicine. Even issues which are much closer to a very practical payoff as far as therapy and so on, such as testing for breast cancer genes, are under some debate. I think the issue of alcoholism gene testing is a more complex issue. But we

will wrestle with this when the time comes, bearing in mind all the potential traps there are in the ethics of genetics testing.

Mr. WICKER. I'm guessing that you might have to test children or adolescents?

Dr. VARMUS. You might want to start with children in families where there's a known history of alcoholism. And you probably would want to start at the time when they become of legal age. It depends a little bit on what kind of remedies might be available. At that point, there may be a variety of strategies for trying to employ behavioral methods for averting alcoholism. I think that would be one of the key issues, what's available. That's the issue that we face in other spheres where genetic risk assessment is an issue.

Of course, underlying all of this is the need to have protections in place so that people are not stigmatized, so they don't have a poor self-image, there are a whole host of things that pertain to testing of this kind.

Dr. GORDIS. We share some of the issues which this problem raises such as: discrimination in employment and in insurance. But in our field, there's the extra level of stigmatization, as Dr. Varmus just alluded to. And these are issues we're going to have to deal with. But it's not right down the pike yet.

Mr. WICKER. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Wicker.

Ms. Northup.

COMPARING DRUG AND ALCOHOL USE AND ABUSE

Ms. NORTHUP. Yes, Doctor, I'd like to pursue a line of questioning comparing drug and alcohol use and abuse. Let's just see where you all are going on these questions.

Do you see alcohol as a drug?

Dr. GORDIS. Oh, yes.

Ms. NORTHUP. Okay. And do you see a difference between the other drugs and alcohol?

Dr. GORDIS. Yes, there are many differences.

Ms. NORTHUP. Including, and especially in my mind, rate of addiction?

Dr. GORDIS. Yes, there are differences in that, too. Would you like me to comment on some of the points you just raised?

Ms. NORTHUP. Well, do you have a rate of addiction for alcohol that you would think would be about the average in the adult population in this country?

Dr. GORDIS. Well, one can make some guess of the likelihood of addiction for alcohol, say, compared to cocaine. Cocaine is a far more addicting substance than alcohol, and so is heroin.

Ms. NORTHUP. And tobacco?

Dr. GORDIS. And tobacco is probably also more addictive. The reason why the alcohol problem is bigger as far as number of lives lost and cost is because so many more people are involved with it, and it's a legal substance and much easier to get.

As far as the addiction potential of the substance, alcohol is somewhere in the middle.

Ms. NORTHUP. That's sort of contrary to the statistics that I have used and talked about in the past.

I have heard there is about a 12 percent rate of addiction for alcohol, versus 60, 85 percent depending on what drug you're talking about.

Dr. GORDIS. Well, we know that most adults in this country who drink don't get into any trouble from alcohol.

Ms. NORTHUP. Right.

Dr. GORDIS. Only about 10 percent of them do. So that's telling you something. On the other hand, if you experiment with cigarettes, the chance of becoming an addicted smoker are quite high, and cocaine likewise. So addiction potentials, meaning the odds of any individual becoming addicted once exposed, are higher for tobacco, cocaine and heroin. The size of the alcohol problem is bigger because the population involved is bigger, and there are other reasons, too, such as cost. Alcohol has a whole range of medical complications, which by and large, these other drugs don't have to the same extent.

[CLERK'S NOTE.—Later corrected to "15".]

Ms. NORTHUP. Well, let me ask you about another factor that I think would distinguish them. I sort of forgot where I was going on that.

Dr. VARMUS. I think you're saying the same thing.

Ms. NORTHUP. Yes, I think that you're saying the same thing, too. I guess the question I have is, what is your goal? I know what the other question is. Would you agree that in most other substances, maybe because of the addictiveness of them, and also because of other potencies, that what we would recommend to most people is that they don't use those substances at all.

Dr. GORDIS. Correct.

Ms. NORTHUP. And do you all make that recommendation to the entire population?

Dr. GORDIS. No.

Ms. NORTHUP. Okay. I guess that's the question I'm getting at, that is prevention. Your goal is not to begin recommending to the American public in general that they don't use alcohol?

Dr. GORDIS. Oh, not at all. Let me make another point in line with what you're talking about. You know, alcohol kills more kids and costs more than all the other illegal drugs together. It's the biggest problem for adolescents. But most of these people are not diagnosable alcoholics. You see, there are several aspects to this. When people talk, even among adults, about moderate drinkers, moderate drinkers can get into terrible problems also.

CONSUMPTION

Ms. NORTHUP. Right.

Dr. GORDIS. Because moderate drinking, the way we define these terms, is in terms of average use.

Ms. NORTHUP. Sure.

Dr. GORDIS. So if you drink seven drinks a week, that's one way of doing it. You can have those seven drinks in a two and a half hour period on Saturday night, that's also listed in many of the data analyses as seven drinks a week.

So the issue of concentrated or binge drinking is important, even for the moderate drinkers.

Ms. NORTHUP. Sure.

Dr. GORDIS. But most of the kids who are killed on the highway, get into violence and so on, are not alcoholic by any formal diagnostic criteria.

So the issue of alcohol abuse, which is the misuse of alcohol causing harm short of a dependent syndrome, is a terrible problem which affects adolescents in a very, very big way.

EFFECTS OF ALCOHOL ON DEVELOPMENT

Ms. NORTHUP. I have a question of alcohol and addictiveness. Let's go to addictiveness, do you find that age at which the onset of use of alcohol is a factor? For example, if a 13 year old uses alcohol, are they more likely to become addicted to alcohol?

Dr. GORDIS. Yes, in general that's probably true. I think it's true of alcohol or tobacco, the longer the initial experience with these substances can be postponed, the lower the odds of addiction or dependence setting in.

Ms. NORTHUP. Is there any pathological reason for that, or is it just that a future adult that's going to be attracted to drinking is going to be attracted at an earlier age, and therefore they are more prone to be addicted? Or do you think that the youngness of their cells and so forth actually make the addiction more likely?

Dr. GORDIS. A very deep and complex question.

Ms. NORTHUP. No answer.

Dr. GORDIS. The question you're asking is a developmental one. Is there something in the partially mature, but not completely mature, nervous system and the other organs, which makes the risk of addiction if you initiate alcohol at that time greater than if you initiate it at 20. Or are these issues of simply a psychosocial nature, like for example, by the time you're 20 or 21 or 22, you may be married, and we know that that has a beneficial effect on abusive drinking, short of dependence. You may have a job where the threat of losing it is more severe and so on.

We know that there are indicators of risk in youth from a behavioral standpoint. People with behavioral disorders in youth, a mixture of shyness and aggressiveness at 5 years of age, for example, predict more trouble than at the age of 15 and so on.

But the question you're asking, frankly, I don't know the answer to without looking it up or thinking about it some more. Because the question of the immaturity of the nervous system at age 13 making it more vulnerable for future addiction than at 19 is a very interesting one. And I'm not sure of the answer right now, but I'm certainly going to think about it.

Ms. NORTHUP. This strikes me as very important.

Dr. GORDIS. Yes, I think you're right.

Ms. NORTHUP. Let me ask you another question, though. Do you recommend no drinks to pregnant mothers?

Dr. GORDIS. Absolutely.

Ms. NORTHUP. Okay. And have you disseminated that information?

Dr. GORDIS. Oh, yes, in many, many ways. First of all, the Federal Government has helped us by mandating that on all beverage alcohol, there's a warning label which includes a warning about drinking during pregnancy. NIAAA has supported 20 years of research on this topic, in which we've looked into social aspects of it,

as well as very interesting new neurological or biochemical mechanisms, which define how alcohol damages the fetus.

Our prize winning publication, "Alcohol Health and Research World," published this issue on fetal alcohol effects and drinking during pregnancy a couple of years ago. It's a kind of a bible for the field for people outside science. I think it's wonderful, and I commend it to your attention.

This booklet, "Drinking and Your Pregnancy," has just been prepared. It's being circulated by the thousands, with the help of NOFAS, an organization dedicated to fetal alcohol problems. We have a wide range of research on this topic. I think we're doing a pretty good job of circulation.

Ms. NORTHUP. So any doctor that would tell a patient, one drink a day would go contrary to any sort of evidence you show.

Dr. GORDIS. It's contrary to our recommendations. It is not contrary to everybody's opinion. I must say that there are still a minority of people who feel that since we haven't shown definitively what the threshold for danger is, that to say they shouldn't have one drink a day would impose a fear and a guilt on women and so on. But the tendency in research, based on very sophisticated tests of infant development and, intellectual function, has been to reduce the recommended level of drinking which is safe.

Now, obviously, the heaviest drinkers are the ones who have the most physically malformed children. But there are very subtle and yet important neurological, psychomotor and intellectual development deficiencies which can be shown on a group basis, even at levels of alcohol consumption which are considered moderate.

My own feeling is, and the way I put it is, you've got nine months to make the best baby you can. Save the drinking for later.

Ms. NORTHUP. I agree. Unfortunately, I don't think that's the universal message that is told to every woman in every doctor's office.

Thank you. That's all, Mr. Chairman.

CORRELATION OF HEAVY DRINKING TO FETAL ALCOHOL SYNDROME

Mr. PORTER. Thank you, Ms. Northup.

Let me follow up on that and ask, do researchers have any idea why only about 6 percent of children born to women who drink heavily during pregnancy show signs of fetal alcohol syndrome?

Dr. GORDIS. We don't know the answer to that question yet, Mr. Porter. There are wide ethnic variations in that number, too, by the way. In Native American population, it goes up higher, to 29 percent and higher birth rates with fetal alcohol syndrome. Among African Americans, the incidence is a little bit higher. We know many of the mechanisms now which are purported to cause malformations. And if you're interested in the scientific aspects of this, I'll be happy to answer that.

There may be other factors, those we don't know yet, which contribute to differential risks. Some of them may be environment, such as different nutritional issues. People have different diets, and some of them are not so hot. There's a possibility there's a genetic issue here as well. That is that some of the babies may be born with certain genes, that is, those which deal with the rate of alcohol metabolism. They may even inherit such genes from the father,

rather than the mother, which make them more likely to be vulnerable to fetal alcohol effects, given the same dose of alcohol taken during pregnancy.

This is being explored now, but right now we don't know the answer to that question.

EFFECT OF ALCOHOL ON ESTROGEN

Mr. PORTER. Research findings were reported in December, that even small amounts of alcohol, like half a glass of wine consumed by women taking oral estrogen, causes their estrogen level to rise dramatically. This seems to put women in a dilemma. The combined effect of estrogen and alcohol could be beneficial in preventing osteoporosis and heart disease, but could put women at greater risk of breast cancer, since these outcomes are associated with estrogen levels. What should physicians be recommending for their patients at this stage?

Dr. GORDIS. A very important question. The studies you're referring to are done by Dr. Nancy Mello and her colleagues at Harvard, and there were similar studies done by Dr. Judith Gavalier at Oklahoma. And it turns out that even moderate doses of alcohol, that is, doses of alcohol which bring the blood level up to 30 or 40 milligrams percent, equivalent to say, two or three drinks, were able to kick up the estrogen level rapidly. This was estradiol, the so-called E2, among women who were taking that compound.

And estradiol, of course, has a multiplicity of effects, especially in post-menopausal women. On one hand, it protects against menopausal symptoms, it protects against osteoporosis, the thinning of the bones which can lead to fractures and so on. On the other side, it increases the risk for breast cancer. And even without alcohol use, of course, these things should be explained by the physician to the patient.

With alcohol use, I think the physician is obligated to explain that regular, moderate drinking, will increase, in effect, the dose of estrogen the woman is taking, and therefore probably has a modest increase, I would guess, on the risk of the negative side of estrogen-taking, given all its benefits. And the woman has two options, or the doctor does. One is to reduce the amount of the drinking, which may be the easiest thing to do, because the doctor then is in better control of what's going on. But the doctor might recommend a diminution in estrogen dose.

The problem with that is, since the drinking is irregular and unpredictable, it puts the medical recommendation, I think, in a bit of a limbo. So my recommendation, given the literature that I read on this, and my thinking about it from the point of view of a clinician, would probably be to recommend that the alcohol be taken gingerly.

SEROTONIN

Mr. PORTER. You referred to findings researchers in Oregon reported that in knockout mice, the loss of a single gene that affects the neurotransmitter serotonin is enough to turn healthy rodents into heavy drinkers. The mice were also found to be abnormally aggressive. Serotonin seems to be implicated in a variety of diseases in which impulse control is impaired. Are you working jointly with

the Drug Abuse and Mental Health Institutes in this research field?

Dr. GORDIS. As a matter of fact, serotonin is one of the topics which is being heavily investigated within our intramural program. And there are many collaborations going on, especially with the National Institute of Mental Health, on aspects of serotonin physiology and genetics, which relate to a variety of disorders, other than alcoholism.

The experiments that you're referring to were done by Dr. John Crab and his associates in Portland, Oregon. And what it amounted to was the use of a model mouse where the serotonin 1B receptor had been knocked out by other researchers. So this animal was available. And its aggressiveness was already noted.

But because of the fact that serotonin seems to be involved in many functions, such as sleep, sexual behavior, sedation, and also alcohol use, he decided to see what their behavior would be in relation to drinking. And it turned out that compared to the wild type animals from which the knockouts were derived, the animals drank about twice as much alcohol as their wild type colleagues.

And there was another very interesting finding here, and that was that the physical dependence and withdrawal upon cessation of alcohol and tolerance could be distinguished. The animals which were the knockouts developed tolerance to the effect of alcohol much more slowly than the wild type animals. And yet, the ability of these two kinds of animals to demonstrate physical withdrawal upon cessation of chronic alcohol use was identical.

This is a very important issue, because the question of whether tolerance and withdrawal share the same neural circuits has been argued in literature for a long time. And this experiment tends to distinguish them as far as their neural circuits not being identical.

In the presence of Dr. Varmus, I hate to talk about an issue which is so close to his great skills on knockouts. It suggests that the serotonin 1B receptor is involved in the behavior relating to alcohol preference. It's not an iron-clad proof. Because as we know from knockout experiments, whether it's the lack of a serotonin receptor or the compensations that the animal may undergo by virtue of not having it since birth, which may affect other systems aside from the 1B receptor, is not certain yet. But certainly, it's a very promising avenue of research.

LIVER TRANSPLANTATION FOR ALCOHOLIC LIVER DISEASE

Mr. PORTER. Your Institute co-sponsored a meeting with NIDDK last year on liver transplantation for alcoholic liver disease. What were the conclusions from that meeting?

Dr. GORDIS. Well, the conclusions were those which have been collecting in the literature over a period of several years. About 25 percent of liver transplants for chronic liver disease, which is going to be fatal without transplantation, are done for alcoholic end stage liver disease in this country. There are about 3,000 done a year, and about 700 were done for alcoholic liver disease.

It turns out that the survival rate and rejection rate of these patients with alcoholic liver disease is no different than the best survival groups for other categories of liver disease. That's number one. The second conclusion was that the recidivism rate to drinking

again is considerably lower in this group than it is in general treatment programs, a question that you asked me about before.

The reason for that second finding is likely to be the selection bias by which patients are selected and sorted before they enter the transplant program. Most programs demand a several month period of sobriety. When we're talking about trends we say that once you get through the first three months of sobriety, your likelihood of remaining sober later, is better. Second of all, they often are required to have efficient social supports and be involved already in some sort of treatment for alcoholism.

So it turns out that among these patients, the survival rate was good as any other. Their return to drinking was less, and among those who died, it wasn't drinking which killed them, it was the same reasons that killed other people who died after liver transplant, rejection, failure, viral infection and so on.

As for suggestions for the future, several recommendations were made. And in fact, we're now engaged in a collaborative effort with the National Institute on Diabetes, and Digestive and Kidney Diseases to put out a grant announcement on several issues which are of common interest to both Institutes.

I think the two prominent questions which we'd like to investigate following this liver transplant issue are number one, can we improve the results if what we've learned about the efficient ways of doing alcoholism treatment can be brought to this community. There are two worlds here. There's the alcoholism treatment community on one hand, and then there is the liver transplant community on the other.

But all the techniques that we've learned about treatment of alcoholism have really not been applied in a systematic way to post-transplant care. And that's one area where we really ought to do some research, although in answer to one of the questions before, one of the grants we have on naltrexone is actually studying the use of naltrexone in post-transplant patients, just as an aside.

The second issue, which is probably more difficult to do and more expensive, has to do with whether the genetic background of a donor liver has any effect on its survival in the alcoholic recipient. And I think you can see the implications of this, both as far as the theory and as far as the dimensions of such a project. But it's been raised as something that might be worth considering.

Mr. PORTER. Dr. Gordis, listening to you, it's like an encyclopedia on everything that's transpired in the field. You're obviously extremely knowledgeable and we appreciate the excellent job you're doing at NIAAA. Thank you for your testimony this afternoon.

Dr. GORDIS. Thank you very much.

Mr. PORTER. The subcommittee will stand in recess until 10:00 a.m. tomorrow.

[The following questions were submitted to be answered for the record.]

SAFE AND DRUG FREE SCHOOLS

Mr. Porter: Dr. Gordis, I understand that, in a presentation before state drug treatment administrators last December, you were asked a question about the Safe and Drug Free Schools program to which you responded by turning your thumbs down. You apparently suggested that, given limited funding, substance abuse prevention efforts should be focused on the children of individuals with substance abuse problems - that these are the people for whom we can have the greatest impact. Is this an accurate description of the meeting last December, and could you expand on your discussion of the most effective way to expend safe and drug-free schools money?

Dr. Gordis: NASADAD's (National Association of State Alcohol and Drug Abuse Directors) Board of Directors invited me to speak at the December, 1996 meeting. At this meeting, I provided the state directors with a 25 year retrospective of alcohol research then presented an overview of recent alcohol research findings and possible new directions in areas such as genetics, neuroscience, medications development, and health services research. Considerable time was spent discussing alcohol abuse and alcoholism prevention and treatment, focusing on comparisons of current clinical field practice and the most current scientific findings regarding prevention and treatment. This presentation gave the state directors a thorough overview of alcoholism and alcohol abuse research.

In my discussions of successful prevention efforts I mentioned several school-based intervention projects which focus on delaying, preventing and reducing adolescent alcohol use by clarifying peer alcohol use, minimizing the effects of peer pressure and increasing self esteem. Examples of these community and educational interventions which have been effective for reducing adolescent alcohol abuse are Project Northland, Life Skills Training (LST), and Alcohol Misuse Prevention Study (AMPS).

Mr. Porter: You were apparently particularly critical of the DARE program in your presentation. What do you see as the major problems with the DARE program and how could funding best be spent in that program?

Dr. Gordis: The DARE Program is under the purview of the Department of Education. As such, all questions regarding the effectiveness and funding levels for DARE should be directed to the Department of Education.

The NIAAA has, however, supported a program with the same goals as DARE and I will be happy to provide comments on the effectiveness of this program. A multi-component, school and community-based research intervention, Project Northland, has shown success in delaying, preventing, and reducing alcohol use and related problems among adolescents. It includes social-behavioral curricula, peer leadership, parental involvement/education, and community wide task force activities. The first 3 years of intervention, conducted in grades six through eight, resulted in significantly lower prevalence of past-month and past-week alcohol use among students in intervention communities compared with controls. These beneficial effects were particularly notable

among students who had not yet begun experimenting with alcohol when the program began.

MODERATE DRINKING

Mr. Bonilla: Dr. Gordis, it has been claimed that moderate drinking has health benefits. At the same time, alcohol causes many health problems. Could you please discuss the trade-off between the risk and benefit of alcohol consumption?

Dr. Gordis: Current understanding of the consequences of moderate alcohol consumption is limited; therefore, NIAAA is supporting increased research to determine both beneficial and harmful effects of moderate alcohol consumption. The dichotomous view that alcohol is either only beneficial or only harmful appears to be too simplistic. Research will inform patients and clinicians on how to appraise their individual situation and the associated risks and benefits of alcohol consumption. With a few exceptions, the decision to drink is best made after an individual assessment of personal and family medical history. There are those, however, for whom drinking is not recommended. Examples of such exceptions to this rule are women who are pregnant or trying to conceive; people who plan to drive or engage in other activities requiring attention or skill; people taking medication, including over-the-counter medications which interact with alcohol; recovering alcoholics; and persons under the age of 21.

What we know is that data from numerous epidemiologic studies indicate that moderate consumption of alcohol may have beneficial cardiovascular effects for some people. However, the cellular and molecular mechanisms by which alcohol may reduce the risk of coronary artery disease are still not clearly understood. For instance, we know that whereas alcohol induces changes in high-density lipoproteins (HDL)--the so-called "good cholesterol"--alcohol also induces changes in low-density lipoproteins (LDL)--the so-called, "bad cholesterol." We also know that chronic alcohol consumption leads to significant reductions in platelet functioning, resulting in increased bleeding time. Ironically, while this reduction in platelet functioning may contribute to the protective affect of alcohol against heart disease, this reduction may also contribute to an increased risk of alcohol-induced hemorrhagic stroke. Acute alcohol consumption has also been shown to increase circulating triglycerides (fatty acids) which many suspect aid in the development of atherosclerosis which is a primary cause of heart disease and stroke.

Even moderate amounts of alcohol consumption affect hormonal regulation, especially in women. Osteoporosis affects 4-6 million older Americans, especially postmenopausal women. Moderate amounts of alcohol have been shown to increase circulating levels of estradiol, a metabolite of estrogen, in postmenopausal women. This increased estradiol may have beneficial effects by protecting from both heart disease and osteoporosis. However, alcohol has been shown to interfere with normal bone metabolism and, in fact, can be directly toxic to juvenile bone cells. Furthermore,

there is some evidence that increased estrogen in postmenopausal women may place them at risk for breast cancer. NIAAA is therefore, continuing to support research to evaluate the impact of various levels of alcohol consumption on hormonal regulation.

The detrimental effects of alcohol on the fetus resulting in fetal alcohol syndrome are well known. Although, not all women who drink give birth to babies with alcohol-related birth defects, we do not yet know how to identify those who will. Therefore, the safest course is to recommend that pregnant women not drink. In this instance, clearly the risks to the fetus outweigh any potential benefits to the mother.

In certain social contexts, alcohol may have a beneficial effect for some by easing social tensions and increasing relaxation. However, too much alcohol may lead to serious consequences such as traffic accidents, unintentional injuries, and violence.

In conclusion, it is clear that under some circumstances, alcohol exhibits a beneficial effect for some people, whereas under other circumstances, alcohol exhibits a detrimental effect. The NIAAA manages a prominent research portfolio dedicated to searching for solutions to the questions of who will be affected, by what amount, and in what way.

PROMISING MEDICATIONS

Mr. Bonilla: Are there any other promising medications such as naltrexone in the pipeline that someday may prove successful in treating alcoholism?

Dr. Gordis: The most promising medication in the pipeline is acamprosate. Acamprosate, which is calcium acetyl homotaurinate, acts on the NMDA receptor in a different way than naltrexone. In European trials, acamprosate has shown great promise in helping to maintain abstinence. The drug has been approved in approximately 12 European countries and recently, Lipha Pharmaceuticals obtained an investigational new drug approval from FDA. NIAAA is assisting Lipha Pharmaceuticals with the design of the clinical trials to test this drug in the United States. These trials will determine which groups of patients are most responsive to this medication.

Another focus of medications development research is determining which medications, used singularly or in combination, effectively treat alcoholic patients. Alcoholism is a complex disease, with no single medication working for every patient. The NIAAA is supporting research to study the efficacy of combinations of medications. These mixtures of medications may have an additive effect, thus being more effective than any single medication.

NEW OPPORTUNITIES FOR DEVELOPING NEW DRUGS

Mr. Bonilla: As you are aware, there has been an investment explosion in the biotech and pharmaceutical industries because advances in cellular and molecular biology provide a powerful way to develop new and more effective drugs. Can you tell me about advances in molecular research in the alcohol field that open new opportunities for developing new drugs?

Dr. Gordis: Progress in neuroscience forms the foundation for the development of effective pharmacotherapies for alcoholism treatment which is a top priority at NIAAA. Advances in the field of neuroscience continue to elucidate how alcohol acts on the brain to produce the fundamental phenomena of alcoholism--tolerance, withdrawal, impaired control over drinking, and craving--and how these phenomena can be interrupted or controlled. A standard problem in drug development is finding a compound with actions as specific as possible while minimizing undesirable side effects. Investigators use their knowledge of basic cellular structure and function to design an exact fit of the medication to the target cell. Thus, studies of membrane structure, receptors, and studies of the cell's response to the binding of chemical messengers are essential to this type of "exact fit" drug development.

Current research into the underlying mechanisms of alcohol-seeking behavior and reinforcement suggests that specific brain areas and neurotransmitter systems, such as GABA, NMDA, dopamine, serotonin (5-HT), and opioid peptides, initiate and maintain excessive alcohol consumption. Detailed molecular research is showing just how important small differences in receptor subtypes and subunits are in producing the different effects of alcohol on the brain. Recent advances have provided clues toward understanding which subunit assemblies of receptors are most sensitive to alcohol.

Recent studies suggest that alcohol may directly interact with specific neurotransmitter receptor proteins to cause their affect. However, the precise molecular region of the receptor protein with which alcohol interacts was not known. Investigators at NIAAA's intramural program used molecular biological methods to construct a single receptor from two different types of neurotransmitter receptors, forming a chimera. Until now, specifying the particular portion or subunit of the serotonin receptor involved in modulating alcohol-related behaviors has eluded scientists. The data provide substantial evidence that alcohol interacts with the last nitrogen molecule on the receptor protein that protrudes from the cell membrane, thus providing a target for designing medication to fit exactly.

Another recent advance makes use of molecular genetics to breed mice that are lacking a specific serotonin receptor, 5-HT_{1B}. These mice display enhanced aggressiveness and altered serotonin receptors in many areas of the brain. Recent studies demonstrate that partial dopamine agonists and $GABA_A$ agonists reduce alcohol consumption. On the other hand, knockout of the serotonin receptor, 5-HT_{1B}, increased

alcohol consumption, whereas 5-HT_{1A} agonists reduced consumption. This study demonstrates that the 5-HT_{1B} receptor subtype is involved in regulating the consumption of alcohol in mice.

Advances such as these are providing clues for the types of medications that could be effective in treating alcohol abuse and alcoholism. NIAAA is expanding the drug development program to capitalize on findings in cellular and molecular biology in order to quickly find promising compounds for clinical trial.

Mr. Bonilla: Can we expand funding in these areas?

Dr. Gordis: NIAAA has an ongoing commitment to the development of pharmacotherapy for treating alcoholism. Thus, this January NIAAA issued an RFA calling for applications in this area. Individual medications, as well as medications in combination with other medications or behavioral therapies are envisioned. Another area that is ripe for expansion is the discovery of prototypic medications. Investigators can take advantage of new technology in order to develop prototypic medications to a stage where they could be tested in clinical trials. Such studies might include novel forms of drug delivery to cross the blood brain barrier; or, perhaps means by which specific receptor subunits in the brain can be modified.

PREVENTION RESEARCH VERSUS BEHAVIORAL RESEARCH

Ms. Northrup: Please provide the percentage of your budget which is focused on prevention research versus behavioral research?

Dr. Gordis: Since the misuse of alcohol is a behavioral issue, and the Institute's prevention efforts are directed at preventing alcohol abuse, all of the NIAAA prevention research is behavioral research. Approximately 20% of the Institute's budget supports prevention research and about 40% of the budget is spent on behavioral research. The remaining balance of the Institute's funds support biomedical research.

PROJECT NORTHLAND: POSITIVE OUTCOME AND LOWER DRUG USE

Ms. Northup: Please talk about your results in the Northeast Minnesota trial. Is there any indication that the decrease in alcohol abuse was replaced by an increase in drug use?

Dr. Gordis: Project Northland is an efficacy trial with the goal of preventing or reducing alcohol use among young adolescents by using a multilevel, community-wide approach. At the end of 3 years, fewer students in the intervention communities had started drinking than in the communities where the community-wide interventions had not been used. The differences were particularly notable among those who were nonusers at the beginning of the project. Combining classroom and community interventions to prevent alcohol use by young adolescents showed results, reducing the onset of alcohol use by 28 percent in the intervention communities relative to other communities. The prevalence of drinking in the prior month was 19 percent lower in the intervention communities. This two-prong approach appears to have reduced peer-pressure and may be expanded to develop culturally sensitive interventions. The results of Project Northland suggest that multilevel, targeted prevention programs for young adolescents are effective in reducing alcohol use.

Regarding other drug use, the percentage of cigarette use was 19% lower in the intervention districts, and the difference was notable at the end of the eighth grade. For baseline nonusers of alcohol, the percentages of students reporting cigarette use and marijuana use were significantly lower in the intervention districts. In addition, less smokeless tobacco use occurred at the end of the eighth grade.

INCIDENCE BY GENDER

Ms. Northup: Dr. Gordis, if I read correctly, your justification mentioned that the incidence of alcohol abuse was the same for men and women yet the article you provided "The Economic Cost of Alcohol Abuse and Alcohol Dependence: 1990" states that 10.3 percent of employed men and 4.1 percent of women were alcohol dependent. Would you care to comment on this?

Dr. Gordis: I believe what you are referring to is a statement in the FY 1998 Congressional Justification that says "...investigations show strong evidence for an

important genetic influence on the development of alcoholism and the evidence is equally strong for men and women." This statement is supported by family studies which have found no evidence for a different genetic influence on alcoholism in women compared with men. The second statement notes that there is a difference in rates of alcoholism between men and women (10.3 percent of employed men and 4.1 percent of women are alcohol dependent). We believe this difference may be due to environmental influences, such as greater availability of alcohol, greater social acceptance of drinking among men vs. women and job status. NIAAA will continue to support research to identify factors that affect alcoholism in both men and women so that we may develop specific prevention and treatment strategies keyed to gender differences.

COORDINATION

Ms. Northrup: What is your coordination with NIDA? SAMSHA? Centers for Disease Control?

Dr. Gordis: The NIAAA coordinates their research efforts with NIDA, SAMSHA, and the Centers for Disease Control (CDC) through joint program staff participation in program initiatives, workshops, interagency task forces such as the Interagency Coordinating Committee on Fetal Alcohol Syndrome, progress review boards, and editorial boards. The NIAAA also co-funds a number of research projects with these agencies.

The NIAAA is currently co-funding three grants with NIDA. One grant is examining the developmental histories of drug and alcohol use as well as the histories of other risks and the relationship of these histories to the outcomes and consequences of alcohol/drug abuse in adulthood. Two other grants are studying contributing factors, including alcohol and drug use, to violent relationships. In addition to supporting research grants of mutual interest, the NIAAA is collaborating with NIDA and the American Society of Addiction Medicine to include alcohol related topics and alcohol researchers in the state of the art conference, "The Neurobiology of Protracted Abstinence: Cognitive, Emotional, and Behavioral Effects in Addictive Disorders". The NIAAA and NIDA are also collaborating on a research project, "Estimating the Economic Costs of Alcohol and Drug Abuse".

The NIAAA and SAMSHA have also cofunded several projects. Among these are three large scale community demonstration trials. The objectives of these trials are to reduce alcohol-related trauma, to reduce the access of youth to beverage alcohol, and to prevent drinking and driving. Results from completed research indicate that community-based interventions can be successfully implemented even when they involve policy changes affecting the availability of alcohol.

The NIAAA advises CDC on the inclusion of alcohol-related questions in epidemiological surveys regarding injury control, chronic diseases, and nutrition and, conducts epidemiological studies in conjunction with the CDC. One recent study focuses on alcohol-related suicide; the CDC is currently examining the results of this study.

CHROMOSOMES ASSOCIATED WITH ALCOHOLISM

Ms. Northup: Please provide for the record more details about Hot Spots and chromosomes associated with alcoholism.

Dr. Gordis: Early family, twin and adoption studies provided strong evidence that alcohol dependence is inheritable. Other factors affect whether a person with the genes for developing alcoholism will, in fact, do so. However, the identification of the genes responsible for the heritable portion of alcoholism would provide scientists with information leading to the development of effective therapuetics and new prevention and treatment strategies.

The Cooperative Agreement on the Genetics of Alcoholism (COGA) is showing significant progress toward finding genes underlying the development of alcoholism. The recent discovery of promising chromosomal "hot spots" is quite exciting. Hot spots are areas on the chromosome where genes of interest are likely to be found. Suggestive areas for the location of genes influencing alcohol dependence are on chromosomes 1, 4, 8, and 16. Genes for possible protective factors may be located on chromosomes 1 and 4 for persons without alcohol dependence, but with some vulnerability. Neurophysiologic traits, such as specific brain wave patterns, may be located on chromosomes 2, 6, and 8. Personality variables suggest potential linkage at many regions scattered throughout the genome, including a region for "harm avoidance" on chromosome 8. Chromosomal regions of interest are now being more densely mapped, and the "second half" of the collected samples will replicate and extend the current findings.

EXTENT OF THE PROBLEM

Mr. Stokes: According to the Institute, more Americans misuse alcohol than any illegal drug, and the economic and social destruction wrought by alcohol abuse and alcoholism in the United States equals or exceeds that associated with other contemporary medical problems. Are we making any real progress in this area of research -- especially as it relates to effective treatment control, and prevention -- more specifically, what can you tell us this year that you could not tell us last year?

Dr. Gordis: Alcohol research is progressing rapidly and the scientific advances and opportunities in our field are very encouraging.

Exciting advances have been made in the development of both medications and behavioral interventions to treat alcoholism. Among the former are naltrexone and acamprosate. The latter group includes motivationally-based, targeted behavioral, and interpersonal support treatments. These two classes of treatment strategies are not competitive but rather,- complementary. Recent research suggests that pharmacologic agents may be combined effectively with psychosocial interventions and that their combination further enhances treatment outcome.

Prevention/ intervention research is also reporting major advances. Results from a recent survey indicate that greater than one quarter of the adolescents surveyed used alcohol on a weekly basis. Initial findings from the NIAAA-supported Northland study show that multilevel, targeted prevention programs for young adolescents are effective. Participating communities in the project offer students school-based skills training to help resist peer influences and alcohol-free extracurricular activities. Programs to engage and educate parents and the community also are important components of this project. Combining classroom and community interventions to prevent alcohol use by young adolescents showed striking results, reducing the onset of alcohol use by 28 percent in the intervention communities relative to control communities. The prevalence of drinking in the prior month was 19 percent lower in the intervention communities. This two-prong approach appears to have reduced peer-pressure and may be expanded to develop culturally sensitive interventions.

Mr. Stokes: In you professional judgement, are we investing enough in this area of research?

Dr. Gordis: There are always more opportunities for research than available resources. Nevertheless, NIAAA strives to achieve a program balance that invests in new research opportunities, in both basic and applied research , while sustaining productive ongoing research with existing resources.

MAJOR RESEARCH OPPORTUNITIES

Mr. Stokes: What major research opportunities, that are ready to be exploited, will the Institute initiate in FY 1997 and FY 1998?

Dr. Gordis: The major research opportunities of NIAAA in the upcoming year are: 1) to identify the genes influencing human predisposition to alcoholism and answer many of the questions in the gene versus environment controversy; 2) to determine the genetic basis for neurological characteristics which may identify persons who are susceptible to the development of alcoholism; 3) to find a reasonable mechanism for alcohol's deleterious effects on human fetal development, leading to the manifestations of fetal alcohol syndrome (FAS); 4) to determine how alcoholism treatment medications work (the mechanism of action), the potential therapeutic value of using pharmacotherapy over a longer period of time, and which subsets of patients are most likely to benefit from new pharmacological treatments and finally, 5) to enlarge the intervention and prevention research efforts in minority populations, particularly directing efforts for the prevention of FAS. The payoff for this research is the development of new, effective medications, prevention programs that selectively target those individuals most at risk, and a precise understanding of environmental influences on the development of alcoholism.

SIGNIFICANT RESEARCH OPPORTUNITIES

Mr. Stokes: What are the most significant research opportunities that will go unfunded in FY 1998?

Dr. Gordis: The FY 1998 request enables the Institute to begin expansion of the knowledge gained in FY 1997 and in previous years, addressing our most significant research opportunities and supporting high quality applications in our priority areas.

FETAL ALCOHOL SYNDROME

Mr. Stokes: I understand that it has been reported that the incidence of fetal alcohol syndrome is several times higher in poorer and disadvantaged communities. What is the extent of this very serious public health problem?

Dr. Gordis: Fetal Alcohol Syndrome (FAS) is a serious health problem. It is one of four leading known causes of mental impairment in the United States. FAS stands out as the only birth defect that is completely preventable. It is costly to treat FAS; 1990 estimates indicated the direct costs of FAS as approximately 2.1 billion dollars. Various studies reporting the occurrence of FAS range from 0.6 to 3 births per 1,000 in most populations, with some communities having much higher rates. Despite general population declines in drinking during pregnancy, the incidence of FAS is significantly higher among known alcoholics, African Americans, and some Native American groups.

Among African Americans, the risk for FAS is approximately seven times that of whites. Rates as high as 10 per 1,000 among some Native American populations and 120 per 1,000 among Canadian Indian populations, where the rate of alcohol abuse is high, have been reported.

Mr. Stokes: What research, research training, and related activities are underway at the Institute to control and prevent Fetal Alcohol Syndrome?

Dr. Gordis: NIAAA has long supported a large portfolio of basic research in animal models that investigates the mechanisms of FAS. Basic research in animal models elucidates the mechanisms of alcohol teratogenesis and leads to pharmacologic or other strategies for amelioration of alcohol's effects. Several promising areas of investigation have recently come to light. One is the discovery that alcohol impairs cell to cell "stickiness" or adhesion which is necessary for proper neuronal development. Another recent development is that alcohol impairs signal transduction, the biochemical process whereby developmental genes are activated. A third area of major interest follows the finding that alcohol induces oxidative stress causing the formation of free radicals; this process can disrupt normal cellular functioning and lead to cell death.

NIAAA will continue to support basic science research that is directed towards elucidating the mechanisms by which alcohol induces cellular injury. Basic approaches may include the use of appropriate *in vivo* models, including transgenic animals and recombinant inbred lines, cell culture techniques, molecular biology, and behavioral techniques to correlate biochemical events with cognitive and behavioral deficits. As our understanding of the underlying molecular mechanisms of damage progresses, we will support studies to develop and test therapeutic interventions in utero and postnatally.

Beginning in FY 1997, NIAAA will focus research on three types of prevention and intervention strategies to reduce alcohol consumption by women of child bearing age in high risk populations. They include tests of community-based prevention strategies among selected Native American tribes; tests for culturally sensitive prevention strategies in urban African American communities; and studies of the alcohol-related screening and advice practices of primary care physicians who treat pregnant patients and other women in their child-bearing years. A program announcement issued in 1996 solicits applications in these areas.

Another aspect of prevention is the training of professionals in alcohol-use screening techniques and in the conduct of appropriate interventions. One Small Business Innovation Research project will design and evaluate a package of training materials for primary care health providers who treat pregnant women who drink. A videotape will be produced to train providers in motivational interviewing skills designed for use in a brief intervention. The NIAAA's Scientific Communications Branch has recently produced a pamphlet, *Drinking and Your Pregnancy*, aimed at low literacy women. The pamphlet has been tested in focus groups and work has begun on adapting it especially for Hispanic and Native American women.

This year the NIAAA will collaborate with National Institute on Child Health and Human Development on the District of Columbia Infant Mortality Study. This collaboration will support a feasibility study on alcohol as a risk factor for infant mortality and morbidity. This study will be developed and conducted collaboratively with the Howard University and several other sites in Washington. From this study we anticipate determining how screening for alcohol use and the evaluation of alcohol-related pregnancy outcomes can be incorporated into the health care system in an effective manner. The information from the feasibility study will provide the foundation for effective intervention and prevention strategies in the District of Columbia which could then serve as a model for other communities.

Mr. Stokes: To what extent will the NIH investment initiative on the "Biology of the Brain" help the Institute to further advances in this (FAS) critical area of research?

Dr. Gordis: Alcohol is one of a number of chemical compounds that are toxic to the developing central nervous system of humans. Of all drugs of abuse, alcohol produces by far the most serious neurobehavioral effects in the fetus. The Biology of the Brain initiative will shed light on the normal formation of brain tissue, as well as on abnormal development. Throughout gestation, the fetus is in a continual state of orderly biochemical and structural transitions during which new tissues are being formed and spatially rearranged. At any time in the total span of development, these ongoing processes can be subtly deflected, severely perturbed, or abruptly halted causing the characteristic features of fetal alcohol syndrome, FAS, craniofacial defects of the eyes, upper lip, and jaw, arising from improper development of the cranial neural crest during embryogenesis. There are also functional, as well as structural abnormalities, in children with FAS. NIAAA researchers are conducting clinical trials to identify children exposed prenatally to alcohol as compared to normal children and children born with Down syndrome. The children receive magnetic resonance imaging (MRI) and electroencephalography (EEG) scans to help provide clues about impaired behavioral and cognitive function. Based on preliminary results, it may be possible to distinguish FAS from other forms of mental retardation.

What can we hope to learn from expanded research in this area?

We hope this expanded research will increase the understanding of the embryonic mechanisms involved in the development of FAS and will lead to the development of treatment strategies to ameliorate, treat, or prevent this disease. Progress in understanding the mechanisms by which alcohol perturbs the developing neural systems of the fetus has been encouraging in recent years. Last year we reported that NIAAA sponsored scientists have demonstrated that large concentrations of alcohol compete with retinol (vitamin A) for oxidation by class IV alcohol dehydrogenase (ADH). This finding has implications for the eventual development of therapeutics that may ameliorate or possibly reverse fetal damage by alcohol.

During embryonic development, new cells are guided to exactly form specific organs. Cells migrate and come together in a specific sequence that ultimately forms brain tissue, nerves, heart muscle and so on. An interesting question is how cells know where to migrate. Specific molecules have been identified that, during embryonic development, guide cells to the proper location. NIAAA supported scientists have demonstrated that alcohol, at doses equivalent to one drink, can inhibit this process of cell-cell adhesion. Another finding is that alcohol induces excessive cell death through the formation of free radicals in pre-migratory neural crest cells resulting in subsequent malformation. The addition of a free-radical scavenger, for example, superoxide dismutase (SOD), can ameliorate alcohol-induced cell death. This type of research is expected to provide avenues for the development of new treatment and prevention strategies.

Mr. Stokes: It appears that a concentrated effort designed to prevent Fetal Alcohol Syndrome is needed for at-risk communities. Will the Institute go beyond the pilot study being planned in Washington, D.C., and if so, explain, and if not, why?

Dr. Gordis: The NIAAA is collaborating with National Institute on Child Health and Human Development (NICHD) and the Office of Research on Minority Health (ORMH) on a pilot study on alcohol as a risk factor for infant mortality and morbidity.

This study will be developed and conducted collaboratively with the Howard University and several other sites in Washington. From this study we plan to determine how screening for alcohol use and the evaluation of alcohol related pregnancy outcomes can be incorporated into the health care system in an effective manner. The information from the D.C. feasibility study will provide the foundation for an effective FAS/FAE intervention and prevention effort in Washington. These efforts, combined with the valuable insights provided by FAS research conducted at the NIAAA's alcohol research center at Wayne State University in Detroit, Michigan, will serve as a model for other at-risk communities.

NIAAA is also addressing FAS/FAE in at-risk communities with strategies developed in the Interagency Coordinating Committee on FAS. This committee is comprised of staff representing NIAAA, NICHD, Centers for Disease Control (CDC), Health Resources and Services Administration (HRSA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Agency for Health Care Policy Research (AHCPR), and the Indian Health Service (IHS).

PREGNANCY

Mr. Stokes: What are the major health and related implications of alcohol use during pregnancy?

Dr. Gordis: Misuse of alcohol, of all drugs of abuse, produces by far the most serious neurobehavioral effects in the fetus. Alcohol has been found to be acutely toxic to the fetus and prenatal alcohol exposure, which is one of the leading known causes of mental retardation in the Western World, is the only preventable cause of this disability. It is generally accepted that the adverse effects of prenatal alcohol exposure exist along a continuum, with the complete FAS syndrome at one end of the spectrum, including serious psychomotor consequences, and incomplete features of FAS, including more subtle cognitive-behavioral deficits, on the other end. The effects of alcohol exposure during specific stages or "critical periods" of development cause the characteristic features of FAS: craniofacial defects of the eyes, upper lip, and jaw, arising from improper development during embryogenesis.

While the physical abnormalities are unfortunate, the mental impairments and hyperactivity are probably the more debilitating aspects of FAS. Problems with learning, attention, memory, and problem solving are common, along with incoordination, impulsiveness, and speech and hearing impairment. Deficits in learning skills, such as mastering aspects of daily life; judgment, problem solving, and memory, persist even into adolescence and adulthood.

The direct costs of FAS to the Nation were estimated for 1990 at $2.1 billion. To avoid this waste of human resources, and because we do not know at what point alcohol damage begins, it is prudent to suggest that pregnant women abstain from alcohol use.

Mr. Stokes: Doctor, are we making much progress in helping to dramatically reduce this public health problem?

Dr. Gordis: Yes, we are making progress. The NIAAA continues to support a broad range of research on the epidemiological, biomedical, and behavioral aspects of full-blown FAS and the lesser effects of alcohol-related birth defects. This research has spawned a number of public health measures, including health cautions to hospitals, clinics, public health workers, and other health care professionals; practical guides for OB/GYN physicians and nurses; dietary guidelines recommending limited alcohol consumption for pregnant women; and warning labels about drinking and pregnancy and drinking and driving on alcoholic beverages.

These health care education activities, based upon NIAAA-supported research, were largely directed at the general population, and were likely responsible for a decline in drinking among pregnant women (from 32-20 percent). Research indicates that this cost effective approach increased knowledge about the risks of alcohol use in pregnancy, but has not modified drinking behavior among those women who drink the most heavily. This finding clearly indicates the need for increased prevention efforts focused on women at highest risk. Despite general population declines in drinking during pregnancy, the incidence of FAS is significantly higher among known alcoholics, African Americans, and some Native American groups. These groups are more difficult to reach and require innovative approaches.

In order to address these issues, NIAAA retains prevention research as a priority. The goal of this research is to obtain scientifically objective and measurable effects attributable to specific interventions. To ensure the acquisition of meaningful results, these studies employ rigorously defined scientific methodologies including random selection and control communities.

NIAAA is focusing research on three types of prevention and intervention strategies to reduce alcohol consumption by women of child bearing age in high risk populations. This includes tests of community-based prevention strategies among selected Native American tribes, tests of culturally sensitive prevention strategies in urban African American communities and studies of the alcohol-related screening and advice practices of primary care physicians who treat pregnant patients and other women in their child-bearing years. NIAAA is encouraging applications for a randomized clinical trial that measures the effectiveness of reducing FAS by combining generalized health education messages on alcohol and pregnancy with specific, individual-focused interventions for pregnant women using alcohol. NIAAA is making it a priority to target communities that are not being reached by educational efforts. A program announcement, "Intervention Research to Prevent Alcohol-Related Problems", has been issued to stimulate the design, development, and/or testing of interventions that have the potential to prevent FAS and other alcohol-related problems.

In addition to prevention research, investigations of the mechanism of alcohol-induced teratogenesis are expected to lead to successful treatment strategies. We have made significant progress in understanding the molecular mechanisms by which alcohol exerts its teratogenic effects. There are now three main hypotheses for this mechanism: interference during embryogenesis with retinoic acid metabolism; induction of excessive cell death through the formation of free radicals in pre-migratory neural crest cells; and complete inhibition of specific cell adhesion molecules, even at clinically relevant levels. Research on effective medications is built upon findings such as these.

Mr. Stokes: To what extent are there outreach activities underway and/or planned in this area?

Dr. Gordis: The Institute has issued a program announcement to solicit applications for research on prevention and intervention strategies to reduce alcohol consumption by women of child bearing age in high risk populations. One aspect of this proposal involves training primary health care providers to screen for alcohol problems and provide appropriate interventions.

The NIAAA has also developed, in collaboration with the National Organization on Fetal Alcohol Syndrome (NOFAS), a low literacy brochure Drinking and Your Pregnancy for high risk American women. This research based pamphlet is designed to reach women who may not be aware of the problems associated with alcohol during pregnancy. Two culturally sensitive spinoff publications are in progress: one for Hispanic women; the other for Native American women.

NIAAA is also addressing FAS/FAE in at-risk communities with strategies developed in the Interagency Coordinating Committee on FAS. This committee is comprised of staff representing NIAAA, NICHD, Centers for Disease Control (CDC), Health Resources and Services Administration (HRSA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Agency for Health Care Policy Research (AHCPR), and the Indian Health Service (IHS).

DISSEMINATION OF RESEARCH FINDINGS

Mr. Stokes: As the Institute indicated last year, 30 percent of all suicides, 50 percent of all homicides, and 30 percent of all accidental deaths are attributable to alcohol. In addition, up to 40 percent of all patients in urban public hospitals have medical conditions resulting from their drinking regardless of the condition that brought them to the hospital. Thus, as I am sure you would agree, alcohol abuse and alcoholism take a tremendous toll on families across this country, and from all walks of life, no family or community is immune to this very serious public health problem. Alcohol abuse and alcoholism present tremendous challenges to the health care providers who treat patients suffering from these diseases. Many health care providers are extremely frustrated. How does the Institute go about disseminating its research findings?

Dr. Gordis: Strategies used to disseminate research findings include print and nonprint publications such as peer-reviewed scientific journals, quick response bulletins, monographs, reports, and brochures that convey state-of-the-art information on a variety of topics specific to alcohol abuse and alcoholism research. Alcohol Health & Research World is the Institute's quarterly, peer-reviewed scientific journal. The issue on the Genetics of Alcoholism was awarded first place in a recent competition in the category of publications for a technical audience. Alcohol Alerts, which are distributed to approximately 35,000 readers, serve as a rapid response bulletin to communicate important research findings to clinicians and allied health professionals. NIAAA also publishes various informative pamphlets, including The Physician's Guide to Helping Patients with Alcohol Problems, which includes screening and brief intervention procedures, as well as a companion brochure for patients, including concrete advice on how to recognize that one might have a drinking problem and how to cut down on one's drinking. Another brochure, Alcoholism: Getting the Facts, offers useful, general advice about the scope of the problem, as well as definitions, guidance and factual material on

decision making regarding treatment approaches, and some references for additional information. NIAAA's world wide web site contains up-to-date information including press releases, announcements of meetings and conferences, publications (many available in full text), and links to other organizations and associations providing alcohol-related information.

Press conferences and press releases announce the results of current and highly promising alcohol research. Each year NIAAA sponsors approximately 20 workshops and symposia to bring together researchers and practitioners from a variety of disciplines to exchange ideas and formulate new strategies for the prevention and treatment of alcohol abuse and alcoholism.

Mr. Stokes: Are there any specific initiatives or projects underway and/or planned to better prepare health care professionals to address alcohol abuse and alcoholism in their patients?

Dr. Gordis: This past year NIAAA published and disseminated 75,000 copies of The Physicians' Guide to Helping Patients with Alcohol Problems. At the request of the Office of National Drug Control Policy (ONDCP), an additional 165,000 copies were printed for distribution by ONDCP. DuPont Pharma is also significantly aiding in this effort at their own expense by printing and distributing through their field representatives an additional 60,000 copies to primary care physicians nationwide. Another brochure, How to Cut Down on Your Drinking, is a companion to The Physicians' Guide to Helping Patients with Alcohol Problems. This pamphlet is used by health care professionals to counsel patients to reduce their alcohol intake. The NIAAA has also recently published Alcoholism: Getting the Facts which helps individuals and families answer common questions about alcohol problems, defines alcohol abuse and alcoholism, symptoms of each, when and where to seek help, treatment choices, and additional resources. This pamphlet is widely distributed and the full text is available on NIAAA's world wide web page.

INSTITUTE OF MEDICINE ASSESSMENT

Mr. Stokes: I understand that the Institute of Medicine has made several significant recommendations with regard to the Institute's Fetal Alcohol Syndrome (FAS) research portfolio. IOM has called for the establishment of task force, increased neurological abnormalities and neurobiological research, expanded clinical research, and the development of biological markers. IOM has also asked the Institute to consider the potential role of fetal alcohol exposure in developmental disabilities studies. Can you bring the committee up-to-date on the Institute's efforts to implement these Institute of Medicine recommendations?

Dr. Gordis: The NIAAA is funding research according to several of the IOM recommendations. NIAAA researchers are conducting clinical research to identify potential structural and functional abnormalities in children with Fetal Alcohol Syndrome

(FAS) or Fetal Alcohol Effects (FAE) and correlating these abnormalities with cognitive or behavioral dysfunction. These studies use magnetic resonance imaging (MRI) and electroencephalography (EEG) scans, as well as a variety of sophisticated neuropsychological tests that help provide clues about impaired behavioral and cognitive function. Based on preliminary results of this research, it may be possible to develop clinical protocols for the detection of alcohol-related brain damage and improved diagnosis of FAS and FAE.

Recommended prevention strategies include basic research in animal models to elucidate the mechanisms of alcohol teratogenesis, which might lead to pharmacologic or other strategies for amelioration of alcohol's effects, and which may suggest biological markers to identify fetuses at greatest risk. Recent promising areas of investigation include alcohol-induced impairment of cell adhesion molecule function, which is necessary for proper neuronal development; alcohol-induced impairment of signal transduction, the biochemical process whereby developmental genes are activated; and the induction of oxidative stress (free radicals) by alcohol, a process that can disrupt normal cell function and lead to cell death.

Research to examine the underlying neurobiological mechanisms of behavioral and environmental interventions is supported. In one basic research study, animals with deficits on motor tasks resulting from moderate alcohol exposure were able to improve their motor skills after a period of therapeutic motor training. Preliminary morphological data indicated that alcohol caused the loss of certain cells in the cerebellum, the brain region which controls motor function. Rehabilitative training of alcohol-exposed animals restored function by increasing cell connections among the surviving cells.

In response to the IOM's recommendation that an interagency task force be established to coordinate national efforts on FAS, Alcohol Related Neurodevelopmental Disorders, and Alcohol Related Birth Defects, the NIAAA has organized an interagency coordinating committee comprised of relevant Federal agencies. The first meeting was held in October 1996 and another was held in January 1997. The agencies are identifying activities which are complementary to the NIAAA's research and research dissemination activities.

NALTREXONE RESEARCH

Mr. Stokes: According to the Institute, FDA approval of naltrexone marked the first medication approved for alcoholism treatment in 40 years. This marked a first step forward. To what extent is there clinical research underway with regard to this medication and thus far, what are the major side effects of this medication?

Dr. Gordis: We have considerable follow up research going on with respect to naltrexone. In fact, more than twelve studies are currently underway. Researchers are working to understand the mechanism of action of naltrexone in humans, its use in different populations, the impact of treatment of longer duration, and the usefulness with

different behavioral groups. So far, there have been no significant adverse side effects noted in humans. The main side effect has been mild nausea, which has been managed by phasing the patient on to the medication gradually.

TOBACCO AND ALCOHOL USE

Mr. Stokes: Last year the Institute indicated that there are many lines of converging data which suggest that alcohol and tobacco consumption are correlated, and that the co-occurrence of smoking and excessive drinking have important implications. What are the latest research findings with regard to the alcohol and tobacco relationship, and how is that research knowledge being used to further reduce their use and consumption?

Dr. Gordis: Indeed, it is still true that many lines of converging data suggest that alcohol and tobacco consumption are correlated. For example, smokers consume more alcohol than nonsmokers and alcohol consumers smoke more than nondrinkers. In addition, a large majority of alcoholics smoke heavily and often experience the life-threatening medical consequences of long-term conjoint use, including cardiovascular disease, and cancers of the mouth, larynx, and pharynx. Also, co-occurrence of smoking and excessive drinking has important treatment implications. Evidence reveals that the reduction of drinking improves the prospects for successful smoking cessation. Likewise, smoking cessation prior to formal alcoholism treatment appears to improve subsequent drinking outcome.

It is of interest that results from a recent study found that although a previous alcohol use disorder (AUD)or tobacco dependence (TD) diagnosis increases the likelihood of being diagnosed with the other disorder at a later time, comorbid AUDs and TD do not affect the likelihood of recovery from either disorder. The particular study is conducted on Children of Alcoholics, thus bringing to mind that there are family interaction variables, individual personality patterns, and possible genetic factors involved.

In terms of further action, last year NIAAA issued a Request for Applications on "The Role of Tobacco Dependence in Alcoholism Treatment". The objective of this RFA was to encourage research that would lead to improved strategies for treating alcohol and nicotine dependence. The RFA elicited a strong response and 41 applications were reviewed. Nine were funded. Thus a major program was initiated. Research areas targeted in a program announcement this year include identification and testing of relevant clinical intervention strategies, and identification of reinforcement mechanisms underlying both alcohol and tobacco that have implications for relapse prevention or better understanding of the alcoholism treatment process.

IMPROVING THE HEALTH OF MINORITIES

Mr. Stokes: African Americans and other minorities continue to suffer disproportionally from a tremendous number of diseases and disorders -- from cancer to cardiovascular diseases to AIDS to diabetes. It is thought that fuller participation of minorities in the biomedical research enterprise, -- from the conduct of research to research training to research decision making on the front-end, would help to dramatically close this long standing gap in health status. What is the institute doing to increase minority representation in basic research and research training?

Dr. Gordis: The NIAAA has a long tradition of encouraging the training and recruitment of African American and other minority scientists and has participated fully in all of the existing NIH programs. Significant efforts and advances have made to facilitate and encourage minority participation in our research program, expanding existing alcohol research efforts on the problems of ethnic minorities and enhancing and extending the alcohol research activities of minority scientists as young as the high school level. This is accomplished through actual hands on experience in a laboratory or participation in workshops to gain technical experience in grant application preparation and submission. The following is a listing of the various grant programs that the Institute supports:

- Administrative Supplements for Underrepresented Minorities
- Minority Predoctoral Fellowship Program
- Program Announcement: Developmental Grants for Collaborative Projects
- Research Project and Training Awards to Historically Black Colleges and Universities (HBCUs)
- Research Project and Training Awards to Hispanic Serving Institutions (HSIs)
- Minority Access to Research Careers (MARC) Program and the Minority Biomedical Research Support (MBRS) Program (both programs are cofunded through the National Institute of General Medical Sciences)
- Minority Technical Assistance Workshops
- Support of the National Hispanic Youth Initiative (NHYI) Program

The Administrative Supplements for Underrepresented Minorities Program is the largest program the Institute utilizes to increase the number of minority investigators in alcohol research. During FY 1996, the Institute spent $1.1 million, almost a 50% increase over FY 1995. This program offers support for high school level students through Investigator levels to work in established laboratories and gain invaluable research experience. The Institute also supports minority trainees through the Minority Predoctoral Fellowship Program.

In addition to these specific programs, the Institute supports several regular research grants in which minority members of the study population are collaborators. These collaborators may be MD/PhD's or students looking to gain additional research experience or learn how to prepare a grant application. Including members of the study population in the actual conduct of the research has opened many doors for individuals that may not have existed otherwise.

CLINICAL RESEARCH

Mr. Stokes: Clinical research is a critical component of the research continuum, as its findings are one of the most important means of determining what constitutes appropriate medical care or treatment. What portion of the Institute's budget is invested in clinical research and how does this compare with the basic research investment?

Dr. Gordis: Clinical research is research in which an investigator directly studies human subjects. Studies may include interviews, the administration of therapeutic agents, the collection of body fluids or tissues, psychological or other medical testing, or the testing of treatment and prevention strategies. Clinical trials, a subset of clinical research, are experiments which test the efficacy of a specific therapy. Clinical research is frequently the direct application of findings from basic research.

In FY 1996 NIAAA spent about $87.0 million, or about 44% of the Institute's budget, on clinical research and approximately $90 million on basic research.

Mr. Stokes: Obviously, the relevance of clinical research findings is greatly enhanced when the study group is representative of the nation's population as a whole. What is the institute doing to ensure minority representation in its clinical research?

Dr. Gordis: The NIAAA adheres in full to the NIH-wide policy on the inclusion of minorities and women in its clinical trials and other studies. In fact, the Institute's substantial efforts to improve our understanding of the effects of alcoholism in minority populations predate implementation of this policy by several years. NIAAA investigators have long realized that the drinking population is not a homogeneous group. The racial and ethnic diversity of the American population requires an understanding of the unique social, health, and cultural needs of various groups.

In order to ensure proper representation of women and minorities in all studies, the Institute gathered epidemiologic data that would make it possible to identify differences in the incidence and prevalence of alcohol use and alcohol-related problems in minority groups. The NIAAA-supported National Longitudinal Alcohol Epidemiologic Survey (NLAES) is the largest nationwide prevalence study on alcohol abuse and dependence ever undertaken. Investigators purposely over-sampled minority populations so that reliable, statistically significant data for characterizing drinking patterns and their correlates among these important subgroups could be obtained.

The most complex randomized clinical trial ever undertaken in alcohol treatment, Project MATCH, was recently completed. This study was funded before the original guidelines for inclusion of minorities and women were in place. Nonetheless, the investigators made aggressive efforts to recruit minorities at all sites, focusing recruitment where the underepresented populations reside, and succeeding in their goal of attracting at least 20% minorities. Project MATCH set a new standard for the conduct of clinical trials in alcoholism treatment by virtue of its methodological rigor and administrative excellence.

In addition to statistical over sampling, investigators are focusing on populations primarily comprised of single ethnic groups, e.g., African Americans, or Hispanics, or Native Americans. This method ensures an in-depth study of the group of interest. For instance, NIAAA also supports a large-scale cooperative research project on the genetics of alcoholism (COGA) which is looking at the multiple genetic factors involved in vulnerability to alcoholism and other disorders as they relate to alcoholism. Because African Americans are considered to be at high risk for alcohol-related disease, investigators have recruited heavily from this population. In addition to COGA, the NIAAA Intramural Research Program has several ongoing studies that are focusing on specific Native American tribes where the prevalence of alcoholism is high. These studies will help discover the genetic and environmental factors that influence this population's vulnerability to alcohol abuse and dependence.

Finally, our Extramural Program has issued two Program Announcements, "Preventing Alcohol-Related Problems among Ethnic Minorities" and "Intervention Research to Prevent Alcohol-Related Problems", which address the critical need for preventive intervention research focusing on understudied populations, including racial/ethnic subpopulations. One of the primary objectives is to expand the limited information available about the prevention of alcohol-related problems among ethnic minorities, with a focus on the culturally-appropriate development/adaptation of interventions within minority settings.

KNOWLEDGE "BOTTLENECKS"

Mr. Stokes: The Director of NIEHS, Dr. Olden, spoke about a "Bottleneck" when referring to the problems of identifying environmental hazards that contribute to human disease and illness. With regard to the diseases and disorders under the purview of your Institute, what are the most significant "Bottlenecks" in the Institute's knowledge base, and what are the health implications?

Dr. Gordis: The critical research needs of NIAAA in the upcoming year are: 1) to identify the genes influencing human predisposition to alcoholism and answer many of the questions in the gene versus environment controversy; 2) to determine the genetic basis for a neurological characteristic which may identify persons who are susceptible to the development of alcoholism; 3) to find a plausible mechanism for alcohol's deleterious effects on human fetal development, leading to the manifestations of Fetal Alcohol

Syndrome (FAS); 4) to determine how alcoholism treatment medications work (the mechanism of action), the potential therapeutic value of using pharmacotherapy over a longer period of time, and which subsets of patients are most likely to benefit from new pharmacological treatments and finally; 5) to enlarge intervention and prevention research efforts in minority populations, particularly directing efforts for the prevention of FAS.

This increased knowledge has great potential for enabling the development of effective medications that can intervene with the harmful effects often associated with alcohol abuse and alcoholism and can be used productively to design prevention/intervention programs that selectively target those individuals most at risk.

Mr. Stokes: To what extent will the FY 1997 appropriations allow the Institute to address the "Knowledge Bottleneck" problem, and how much is included in the FY 1998 budget request for such?

Dr. Gordis: The FY 1997 appropriations allows the Institute to continue ongoing programs, many of which address these critical areas and support high quality applications in priority areas of research.

Mr. Stokes: In your professional judgement, is the proposed funding level adequate to address the "knowledge bottleneck", explain?

Dr. Gordis: These special areas of emphasis are also included in the Institute's FY 1998 request, enabling the Institute to begin expansion of the knowledge gained in FY 1997 and in previous years.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists' cloning of adult sheep, and Oregon researchers cloning monkeys. These articles expressed excitement with regard to opportunities for advances in medical treatments, and concern with regard to misuses of the technology and the possibility of human cloning. This is another area where we must now be certain to examine and address the ethical, legal, and social issues of research on the front-end. As a leading researcher and as an Institute director, what is your professional opinion of this technology and what are your most serious concerns?

Dr. Gordis: Professionally, I am in complete agreement with Dr. Varmus on the subject. I believe this technology heralds a major opportunity for advancing medicine. Cloning technology offers the potential for major advances in animal husbandry, the development of novel therapeutics, the production of medically useful products, increased understanding of gene regulation, and increased success with transplantation. The sheep experiment represents a major advance in our understanding of genetics and opens a field of remarkable possibilities that require exploration. Although, the idea of cloning a

human being is repugnant, and fairly useless as an experimental strategy, I am concerned that a rush to legislations will inhibit needed discussion and absorption of the details by the scientific community. I am also in complete agreement with the President's referral of this topic to his National Bioethics Advisory Commission.

Mr. Stokes: With regard to the diseases and disorders studied by your Institute, what are the most significant benefits that the cloning technology would yield?

Dr. Gordis: NIAAA's research will benefit in largely the same way as all health research. This type of investigation is expected to lead to the development of new therapeutics, animal models that more closely mimic human disease, and an increased understanding of the influence of genetics and the environment on the development and maintenance of disease.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are currently underway, and what are the expected benefits to be achieved from this investment?

Dr. Gordis: The most significant clinical trials that the NIAAA currently supports are determining which medications, used singularly or in combination, effectively treat alcoholic patients. Alcoholism is a complex disease and no single medication works for every patient. NIAAA supported investigators are determining the efficacy of combinations of medications. These medication combinations may have an additive effect, thus being more effective for some people than any single medication. Various medications are also being studied for patients with co-occurring psychopathologies such as depression, panic disorder, or post traumatic stress. This "two-pronged" approach may, in some cases, be effective in treating alcoholism as well the co-occurring psychiatric disorders. This research will determine how alcoholism treatment medications work (the mechanism of action); the potential therapeutic value of using pharmacotherapy over a longer period of time; and which subsets of patients are most likely to benefit from new pharmacological treatments. The prospects for improved alcoholism treatment have never been better.

Mr. Stokes: Dr. Gordis, what major clinical trials that are ready to be implemented will the FY 1998 budget request allow the institute to pursue, and what are the expected benefits to be achieved?

Dr. Gordis: We will be conducting a multi-center trial to assess the efficacy and safety of combined behavioral and pharmacologic interventions in the treatment of alcohol dependence. The behavioral interventions will build, in part, on the results of MATCH which employed motivational, coping skills, and 12-step therapeutic

approaches. Recent advances in pharmacotherapy have led to the development of several promising medications to prevent or reduce drinking, including naltrexone and acamprosate. We expect that the combined pharmacologic-behavioral intervention will increase the success of treatment outcome for alcoholism.

BRAIN FUNCTION IN ADOLESCENTS

Ms. DeLauro: What types of research is NIAAA conducting on brain function in adolescents who use alcohol and their ability to learn?

Dr. Gordis: For ethical reasons, NIAAA does not recruit human adolescents to study the effects of alcohol on their learning and cognitive abilities. Animals are excellent surrogates for examining and controlling experimental details that cannot be ethically examined or controlled in humans. NIAAA is therefore, developing and expanding our research portfolio that examines the effects of alcohol on animals.

So far, we know that for both humans and animals, neurobiologic systems continue developing during the period of late childhood and adolescence. Although final brain size and available neurons are largely fixed early in infancy, the brain continues to grow and develop during adolescence. Synaptic connections, neurotransmitter systems, and the rate of brain electrical and metabolic activity mature. Animal studies suggest that adolescents have different physiological responses to alcohol than do adults. For example, research funded by NIAAA indicates that alcohol affects the ability of adolescent rats to learn their way out of a maze to a greater extent than for adult animals. Research on the neuro-developmental effects of alcohol on youth continues to be of substantive interest to the NIAAA.

WELFARE REFORM

Ms. DeLauro: Recent welfare reform measures have eliminated SSI payments for people addicted to drugs and alcohol. Individuals who received SSI under this law were required to seek treatment. Now many of these individuals will be disconnected from the treatment community. How does your institute address research on hard to target populations?

Dr. Gordis: Research methodology employs several approaches to ensure the recruitment of hard-to-reach populations. Over sampling is a statistical technique that enrolls a sufficiently large number of hard-to-reach individuals to ensure statistical validity of the results. For instance, one study is examining the number and type of injuries related to alcohol consumption. These data for youth are particularly difficult to obtain; therefore, the investigators are over sampling youth within their target population. Investigators also hire people who are familiar with the community under study to recruit and interview study participants. These specially trained interviewers may be community members, community outreach workers, or people simply familiar with the location of shelters, soup kitchens, and so on--where hard to reach populations can often be found. Sometimes investigators can sample a hard-to-reach population by accessing a community or school event or a specific locality.

Ms. DeLauro: According to the SSA, some of this disenfranchised SSI population will qualify for benefits because the secondary symptoms of their alcohol abuse are so disabling. Does your institute address research on the secondary health effects of alcohol abuse?

Dr. Gordis: The Institute conducts multiple investigations on the secondary health effects, called medical sequelae, of alcohol abuse. Excessive alcohol consumption has consequences for nearly every part of the body. In large doses, alcohol is highly toxic to the heart, brain, liver, pancreas, bone, breast, bowel, and endocrine and immune systems. NIAAA maintains an active research portfolio on all the medical complications associated with alcohol, including research on prevention and treatment. The health effects of alcohol abuse may be more severe in populations with less access to medical care and who may be less healthy, in general, than the population not in need of economic assistance. At this time, NIAAA is encouraging applications to study the effects of new welfare regulations on those seriously affected by alcohol and previously receiving SSI or other forms of welfare.

COORDINATION OF RESEARCH FINDINGS

Ms. DeLauro: As a sister organization to SAMHSA, how do your two agencies coordinate to ensure that the research done at NIAAA is applied to the field through SAMHSA?

Dr. Gordis: The NIAAA provides all research findings, scientific publications, monographs, and monthly updates of our bibiliographic database to SAMHSA's National Clearinghouse for Alcohol and Drug Information (NCADI). The NIAAA and NCADI also work together in updating and maintaining the *Alcohol and Other Drugs Thesaurus.* The NIAAA world wide web (www) links to NCADI's www which also serves to transfer research information to NCADI and its users.

NIAAA staff are members of the SAMHSA, Center for Substance Abuse Treatment's editorial board for their Treatment Improvement Protocols which recently reviewed a primer on alcohol and drug abuse for primary care clinicians Staff also participate in planning group meetings of the Prevention Enhancement Protocols System, supported by the Center for Substance Abuse Prevention (CSAP); and co-chair the Ethnic/Minority Research Progress Review with CSAP.

SAMHSA has staff representation on the NIAAA-coordinated Interagency Task Force on Fetal Alcohol Syndrome (FAS). SAMHSA and NIAAA staff work together on the editorial board of *Frontlines*, a health services research newsletter. Staff from both agencies contributed to the Health Services Research Review Panel Report which summarized recommendations for health services research and managed care research development.

NIAAA has also collaborated with SAMHSA on several productive research projects, including community demonstration trials. The objectives of these trials were to reduce alcohol-related trauma, to reduce the access of youth to beverage alcohol, and to prevent drinking and driving.

FETAL ALCOHOL SYNDROME AND EARLY CHILDHOOD DEVELOPMENT

Ms. DeLauro: What research has your institute done on Fetal Alcohol Syndrome and early childhood development?

Dr. Gordis: Fetal Alcohol Syndrome (FAS) which is one of four leading known causes of mental impairment in the United States stands out as the only birth defect that is completely preventable. FAS is a serious disorder with physical and mental deficiencies that are costly to treat and rehabilitate and which often require long-term care. In fact, 1990 estimates indicate the direct costs of FAS are approximately 2.1 billion dollars; the largest part of this is expense is residential care and treatment for mentally retarded patients over the age of 21. Since 1972, the NIAAA has supported a broad range of research on the epidemiological, biomedical, and behavioral aspects of FAS and the lesser effects of alcohol-related birth defects. Prior to 1973 the cause of mental and physical defects seen in some babies was unknown. Early NIH-funded research demonstrated birth defects in the offspring of rodents that were fed alcohol during pregnancy. This effect was demonstrated in humans when in 1973-74 investigators reported clusters of specific birth defects appearing in infants born to mothers who abused alcohol during their pregnancy. The full syndrome is characterized by prenatal and postnatal growth retardation, a characteristic constellation of craniofacial anomalies, central nervous system dysfunctions and major organ system malformations.

NIAAA is supporting several longitudinal prospective studies of children with various levels of prenatal alcohol exposure. These studies are providing new information about specific deficits; cognitive, behavioral, and social functioning; and the impact of the postnatal environment in affected individuals across the lifespan. This information is being used to design specific strategies for ameliorating the adverse consequences in affected children.

NIAAA continues to support basic science research that is directed towards elucidating the mechanisms by which alcohol induces cellular injury. Basic approaches include the use of appropriate *in vivo* animal models, including transgenic animals and recombinant inbred lines, cell culture techniques, molecular biology, and behavioral techniques to correlate biochemical events with cognitive and behavioral deficits.

Progress has recently been made in elucidating the molecular events responsible for the teratogenic effects of alcohol. Recent findings yield two new hypotheses about this mechanism. One is that alcohol interferes with the ability of fetal cells to "stick" to each other to form functional organs. The second is that when fetal cells are exposed to alcohol, they undergo premature cell death as a result of exposure to free radicals. NIAAA researchers have also made significant advances in examining the brain of FAS affected children with magnetic resonance imaging. In conjunction with bio-behavioral assessment, these studies show structural abnormalities that underlay the behavioral deficits associated with FAS and differentiate children born with FAS from children diagnosed with Down's Syndrome. As our understanding of the underlying molecular mechanisms of damage progresses, we will support studies to develop and test therapeutic interventions *in utero* and postnatally.

NIAAA researchers are expanding studies that have effectively conveyed the dangers of drinking during pregnancy. Some of these studies are informational, while others are clinical interventions. Building on these results, investigators are developing multi strategy approaches which include culturally appropriate media messages for vulnerable populations. Despite general population declines in drinking during pregnancy, FAS still has an incidence estimated at 1 to 3 infants per 1,000 live births, and among known alcoholics, African Americans, and some Native American groups, the incidence is significantly higher. Previous educational prevention measures have been more successful with slightly older and more educated women and less successful with other groups who are more difficult to reach.

NIAAA is focusing research on three types of prevention and intervention strategies to reduce alcohol consumption by women of child bearing age in high risk populations. This includes tests of community-based prevention strategies among selected Native American tribes, tests of culturally sensitive prevention strategies in urban African American communities and studies of the alcohol-related screening and advice practices of primary care physicians who treat pregnant patients and other women in their child-bearing years. NIAAA is encouraging applications for a randomized clinical trial that measures the effectiveness of reducing FAS by combining generalized health education messages on alcohol and pregnancy with specific, individual-focused interventions for pregnant women using alcohol. NIAAA is making it a priority to target communities that are not being reached by educational efforts. A program announcement, "Intervention Research to Prevent Alcohol-Related Problems", has been issued to stimulate the design, development, and/or testing of interventions that have the potential to prevent FAS and other alcohol-related problems.

In response to a recent Institute of Medicine report on FAS which recommends that an interagency task force be established to coordinate national efforts on FAS and other alcohol-related birth defects, NIAAA established the Interagency Coordinating Committee on Fetal Alcohol Syndrome with members from SAMHSA, HRSA, IHS, NIH, and CDC. The interagency coordinating committee first convened in October 1996 and then again early in 1997. The recommendations in the report and input from the Committee will help focus current research efforts and guide new initiatives. NIAAA has also initiated an NIH-wide interest group focusing on the teratology of alcohol and other birth defects in an effort to foster communication and collaboration on FAS and FAS-related research between alcohol researchers and other developmental biologists.

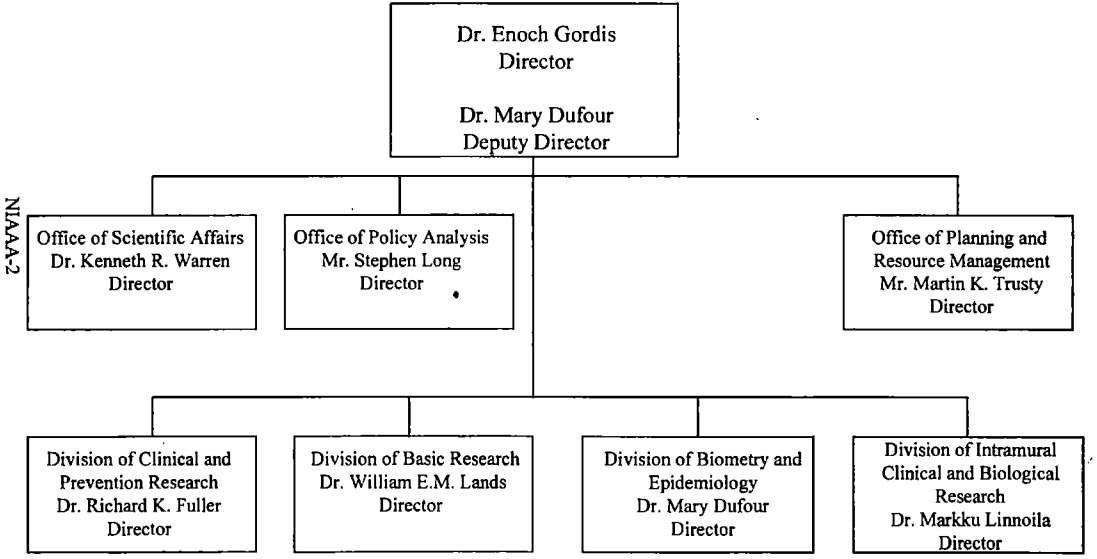
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

FY 1998 Budget	Page No.
Organization Chart	2
Appropriation language	3
Amounts available for obligation	4
Justification	5
Budget mechanism table	18
Budget authority by activity	19
Summary of changes	20
Budget authority by object	22
Administrative costs	23
Significant Items from the House and Senate Appropriations Committee Reports	24
Authorizing legislation	29
Appropriation history	30
Detail of full-time equivalent employment (FTE)	31
Detail of end-of-year employment	32

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

For carrying out section 301 and title IV of the Public Health Service Act with respect to alcohol abuse, and alcoholism, [$212,004,000] *$208,112,000.*

(Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriation Act, 1997, P.L. 104-208.)

40-478 97 - 37

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$198,607,000	$212,004,000	$208,112,000
Rescission in accordance with P.L. 104-134	(195,000)	—	—
Reduction in accordance with P.L. 104-208	—	(134,000)	—
Subtotal, Adjusted Appropriation	198,412,000	211,870,000	208,112,000
Real transfer from: Other NIH Institutes through the NIH Director's one percent transfer authority	192,000	0	0
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	(10,135,000)	(11,051,000)	0
Subtotal, adjusted budget authority	188,469,000	200,819,000	208,112,000
Unobligated balance, lapsing	(111,000)	0	0
Total obligations	188,358,000	200,819,000	208,112,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1996 - $2,655,000; FY 1997 - $2,700,000; FY 1998 - $2,700,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research: FY 1998 - $11,234,000.

Note: Excludes $ 2,077 in FY 1996 and $ 2,000 in FY 1997 for royalties.

Justification

National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation:	Section 301 and Title IV, Sections 464H(d) and 487 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
225	$188,469,000	225	$200,819,000	225	$208,112,000	--	+$7,293,000

General Statement

This document provides justification for FY 1998 Non-AIDS activities of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Justification of NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled, "Office of AIDS Research (OAR)".

Mission

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the foremost Federal agency supporting biomedical and behavioral research directed towards improving the prevention and treatment of alcohol abuse and alcoholism and reducing associated health, economic, and social consequences. The NIAAA funds 90 percent of all alcohol research in the United States and provides leadership in the country's effort to combat these problems, by developing new knowledge that will decrease the incidence and prevalence of alcohol abuse and alcoholism, and associated morbidity and mortality.

Improvements in the Quality of Life from Alcoholism Research

Genetic studies clearly have the potential to improve the quality of life of people affected by alcoholism by leading to the development of effective prevention and treatment strategies for alcoholism. Advances in neuroscience and basic physiology can be built upon the steps established by basic genetic research. Every research finding that brings us one step closer to preventing or treating alcohol abuse and alcoholism has tremendous potential to affect the quality of life of nearly every American. Alcohol is used by more Americans than any other drug, including cigarette tobacco. The social and economic destruction wrought by alcohol abuse and alcoholism in the United States far exceeds the loss associated with any other contemporary

medical or social problem. Although a dollar figure cannot adequately reflect the devastation wrought by these illnesses, it is estimated that the costs to society from alcoholism and alcohol abuse exceed $100 billion annually (Rice, D.P.; Kelman, S.; Miller, L.S.; and Dunmeyer, S. *The Economic Costs of Alcohol and Drug Abuse and Mental Illness: 1985.* 1990).

Alcohol abuse and alcohol dependence affect about ten percent of adult Americans; unfortunately, they are not the only affected group. Approximately 6.6 million children under 18 years of age live in households with at least one alcoholic parent. Children growing up in homes where one or more household members abuse alcohol can suffer seriously. They may be at risk for neglect, as well as physical, sexual, and/or emotional abuse and this may place them at risk for a range of emotional and behavioral problems, including conduct disorders, depression, and anxiety. Unborn children may suffer as well. Fetal Alcohol Syndrome (FAS) is a serious disorder with physical and mental deficiencies that are costly to treat and rehabilitate and that often require long-term care. This type of research has the potential for making significant contributions to allied fields, as well. Thus, alcoholism research has the potential for making substantial contributions to the quality of life for all citizens.

Story of Discovery: The Genetics of Alcoholism

The idea that alcoholism runs in families is an ancient one. In recent decades, science has advanced this idea from the status of folk-observation to systematic investigation. Data from controlled family studies have conclusively demonstrated that alcoholism does indeed run in families. The data further indicate that alcoholism is a complex disease, the development of which is influenced by both genes and environmental factors. The genetic analysis of alcoholism is confounded by several factors, such as genetic heterogeneity, contributions by more than one gene, and strong environmental influences. Scientists know that the picture is far from simple and that many genes may exert an influence over the disease process. Furthermore, because alcohol affects all cells in the body, the potential for genetic variability is enormous.

The ultimate goal of genetic research in alcoholism is to understand which gene(s) influences the development of the complex behavioral trait, alcoholism and to what degree. Scientists are quite excited by the huge potential of genetics research for aiding in the development of effective treatment and prevention methods. Once genes controlling the events that combine to cause alcoholism are identified, new treatment strategies become apparent; the ability to identify those who are susceptible opens the door for highly targeted prevention efforts; understanding abnormal processes increases our understanding of normal physiologic and neuropsychiatric functioning; and the contribution of the environment to this complex disorder can be ascertained. NIAAA has always and will continue to support studies of the genetics of alcoholism using a range of techniques, from analyzing the genetic distribution of specific populations to the latest methods of molecular analysis.

The influence of the environment and the influence of inherited factors in the development of addiction used to stir much controversy. Now we know that both genes and the environment play a role. In an effort to discover the proportional contributions of inheritance and of the environment to the development of alcoholism, early investigations employed two primary

strategies, adoption and twin studies. Adoption studies compare the risk of alcoholism in an adopted child who has alcoholic biological relatives but who is raised in a non-alcoholic environment. Twin studies compare the risk of alcoholism in identical or fraternal twins reared in the same environment.

Identical twins have identical genetic composition, i.e., 100 percent of their genes are the same. Fraternal twins, however, have only roughly 50 percent of the same genes. Through the application of specific statistical techniques and theoretical models, investigators compare the rates of alcoholism for the two types of twin pairs. When a disease, such as alcoholism, appears more frequently in identical twin pairs than in fraternal twin pairs, genetic influences in the origin of the disease are implied.

Both lines of investigation show strong evidence for an important genetic influence on the development of alcoholism and the evidence is equally strong for men and women. Furthermore, extensive and detailed reviews of data from many different studies have shown conclusively that genetics plays an important role in the development of alcoholism. Also, these results are remarkably consistent despite major differences among research methods. Results such as these stimulated investigators to develop methods to isolate the responsible genes and thus lay to rest the gene versus environment controversy.

NIAAA is working towards the goal of identifying the contributions by genetic and environmental factors on the development of alcoholism through support of a highly sophisticated, complex study of entire families who suffer from alcoholism. The Cooperative Agreement on the Genetics of Alcoholism (COGA) is a major multi- disciplinary, collaborative research study on the genetics of alcoholism. The project involves six research institutions throughout the Nation and is resolving the genetic factors involved in a person's susceptibility to developing alcoholism. COGA is a pedigree (family lineage) study that uses extensive interviewing, complex psychiatric instruments, and molecular biological techniques to carefully describe the physical and psychological characteristics of families who have several alcoholic members.

COGA is a huge undertaking. Accurate, valid, reliable, and specific information is essential for successful family and genetic studies in alcoholism and other psychiatric diseases. To address the limitations of existing methodology, COGA investigators developed several comprehensive interviewing tools, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) and its companion version for children (C-SSAGA-C) and adolescents (C-SSAGA-A). These new interviewing tools represent a major advance in currently available psychiatric interviewing techniques by covering a wide range of diagnostic classification systems, by paying close attention to different diagnoses, and by providing an array of items suitable for the broadest descriptions of psychiatric characteristics. These important new techniques can assess the time when alcoholic drinking began, identify drinking patterns, determine the severity of the alcoholic disorder, identify subtypes of alcoholics, and provide evidence of co-existing psychiatric disorders. COGA data can now be compared with existing family, epidemiologic and genetic data sets, thus allowing confirmation of findings from earlier studies. These diagnostic

interviewing tools developed by NIAAA-supported scientists are now used internationally and are one example of the extensive benefits of alcoholism research.

Ultimately, detailed data on several hundred families will be available. By fall, 1996, 7511 interviews of alcoholics and their family members had been conducted; 287 pedigrees had been established; and cell lines from 2,446 individuals are now available for genetic analysis. Biochemical, neurophysiological, and neuropsychological characterization of more than 1500 individuals enhances the extensively detailed clinical assessment of recruited subjects.

From its inception, the COGA project included the ambitious goal of searching the entire genome for genes affecting the risk of alcoholism. This approach offers the highest probability of finding the relevant genes. Genotyping of 900 subjects at more than 100 genetic markers has already begun. This systematic screening process also includes hunting for proposed "candidate" genes. These are genes that on the basis of other studies are already hypothesized to be inherited with alcoholism. Once researchers locate a region of the genome that appears to contribute to the risk for alcoholism, they will examine other potential "candidate" genes within that region to confirm the initial finding. This appears to be a very powerful and promising approach to identifying the genetic basis of a complex disease, such as alcoholism.

The importance of specifically identifying genes is that genes control the production of specific factors that influence a person's susceptibility to alcoholism. Prevention of the development of alcoholism in susceptible persons would be a major break through in the treatment of this disorder. Success in uncovering the genes involved will enable the identification of persons at high risk for alcoholism, thus permitting early intervention in alcohol-related pathologies. This knowledge will also aid in the development of new treatments for alcohol-related problems by providing new insights into the physiological mechanisms of the disease.

To-date, one of the most exciting findings is the identification of "hot spots," possible areas of the chromosome that may contribute to alcoholism. The identification of these "hot spots" is quite encouraging and is expected to eventually lead to the precise identification of the genes. Once the genes for alcohol dependence are identified, and the contribution of the environment is understood, even more effective prevention and treatment programs can be designed, yielding meaningful gains for the Nation's health.

Another exciting finding from the COGA projects is the determination of the genetic basis for a neurological characteristic which may identify persons who are susceptible to the development of alcoholism. This neurological characteristic is a specific type of brain wave pattern known as, P3. P3 amplitude may actually occur before the development of alcohol dependence and thus may be useful for assessing an individual's risk. Reliable neurological, physiological, or physical characteristics can be used productively in designing prevention programs that selectively target those individuals most at risk.

The present COGA arrangement will come to an end as a distinct project on August 31, 1999. During its tenure it will have created a number of important, unique resources, such as, Cell and Data Repositories, which can be maintained *in perpetuity*, and which will be available to all

qualified investigators for further study. These resources include diagnostic and pedigree data on 3000 individuals belonging to about 300 families with alcoholism, along with corresponding biochemical, genetic, and neurophysiological data. There will also be a collection of DNA samples and immortalized cell lines derived from these individuals. By the end of 1999, these resources will be available for the benefit of the entire scientific community and represent a major resource for future genetic studies.

Research on the genetics of alcoholism does not stop with family, twin, and adoptive studies. Animal studies have also proven valuable. Experimental animal models that mimic human disease greatly simplify complex statistical genetic analysis and provide the means to circumvent complex patterns of inheritance and environmental influences that complicate the analysis of human multi-gene illnesses. In mice, as in humans, alcohol preference is a genetically influenced behavior the study of which may shed light on the development of human alcoholism. Molecular biology studies employ sophisticated genetic analyses to locate the genes that predispose certain animals to addictive drinking and have been supported by NIAAA for several years. These techniques give investigators the ability to define the contribution of a single gene to complex behaviors that are determined by the interaction of many genes, called quantitative trait loci (QTL).

Alcohol drinking in mice is a quantitative trait influenced by quantitative trait loci (QTL). Finding the location of genes which influence such traits is technically difficult, and has become possible only relatively recently. A variety of very encouraging results suggest that the process of identifying mouse QTL influencing alcohol preference is well underway. In some very elegant work, NIAAA-sponsored investigators have discovered and identified the location of two sex-specific genes influencing alcohol consumption in mice. One QTL (*Alcp1*) is active only in males; the other (*Alcp2*) is active only in females, and only when inherited through the mother. Both QTL are recessive and both are located on chromosomes previously identified in other mice.

Although the neuroscience of addiction is complex, advances in molecular genetics are helping scientists to very selectively breed animals that exhibit differing degrees of responses to alcohol. Neurons in the brain communicate among themselves by transmitting and receiving specific chemical messengers called neurotransmitters. Serotonin is a neurotransmitter that appears to be involved in controlling alcohol consumption in animals and humans. When the right combination of neurotransmitters and specific receptor types is present in the brain, the consumption of alcohol tends to perpetuate consumption; thus alcohol is said to be reinforcing. The reinforcing properties of alcohol are partly responsible for addiction and are reported to be mediated by serotonergic and other neurotransmitter systems in the brain.

Studies in the Institute's laboratories are pursuing the structure and control of genetic expression, and the variation of genes involved with serotonin. Serotonin is involved in the regulation of appetite, sleep, and body temperature, and is implicated in impulsive behavior and alcoholism. Diseases in which impulse control is impaired and where serotonin appears to be involved include alcoholism, drug abuse, eating disorders, suicidal tendency and antisocial personality disorder. Thus, studies such as these may have far-reaching ramifications.

Until now, specifying the particular portion or subunit of the serotonin receptor involved in modulating alcohol-related behaviors has eluded scientists. The identification of this specific receptor subtype has profound implications for the development of treatment and prevention strategies, as well as the development of diagnostic tools for identifying those at risk. Knowledge of the specific receptor subtype is valuable for developing medications designed to interact with this specific receptor and, thus may be useful for helping individuals reduce their alcohol consumption.

NIAAA-supported scientists have used molecular genetics to breed mice that are lacking a specific serotonin receptor, 5-HT_{1B}. Mice lacking a functional 5-HT_{1B} serotonin receptor, as a result of this artificially induced mutation, drank about twice as much alcohol as genetically unaltered mice in which this receptor was functional. The increased consumption was fairly specific for alcohol, since consumption of water, food, and sweet (either caloric or noncaloric) and bitter solutions was normal.

This study suggests that the 5-HT_{1B} serotonin receptor functions in a pathway mediating alcohol consumption in mice. These findings also generate the testable hypothesis that some human alcoholics might, in part, owe their susceptibility to alcoholism to a defect in a similar receptor type (or to a defect in some other step of a pathway in which it functions). Increases in understanding the molecular basis of alcohol addiction should provide a foundation for the future development of therapeutic strategies for treating alcohol abuse and alcoholism. This type of research will also increase our understanding of the functioning of neurotransmitter receptors on a molecular level.

To study the molecular mechanisms involved in alcohol addiction, investigators must first understand the molecular action of alcohol on the brain and remaining parts of the nervous system. A recent study provides important new data on the molecular basis for alcohol's effects in the nervous system and establishes a basis for future investigations on the molecular basis of addiction to alcohol. Although alcohol's behavioral effects are well known, the cellular and molecular mechanisms that underlie those actions are poorly understood. For almost a century, it has been thought that alcohol's behavioral effects result only from non-specific actions on the fatty components of cell membranes in the central nervous system.

Recent studies, however, have suggested that alcohols may directly interact with specific neurotransmitter receptor proteins to cause their effect, rather than non-specifically interacting with the fatty molecules in the cell membrane. However, the molecular region of the receptor protein with which alcohol interacts was not known. In order to answer this question, investigators in this study used molecular biological methods to construct a single receptor from two different types of neurotransmitter receptors. The elucidation of the exact location where alcohol binds to different receptors will lead to new medical therapies.

Other Research of Significance

Fetal Alcohol Research

In addition to genetic research, other advances are making major contributions to our understanding of how alcohol affects the body. One of the most tragic consequences of excessive alcohol consumption during pregnancy is the development of fetal abnormalities resulting in serious birth defects.

During embryonic development, new cells are guided to exactly form specific organs. Cells migrate and come together in a specific sequence that ultimately forms brain tissue, nerves, heart muscle and so on. An interesting question is how cells know where to migrate. Specific molecules have been identified that guide cells during embryonic development to the proper location. One of these molecules, called L1, helps cells "find" each other and then to stay together in a process called cell-cell adhesion. If this process is interrupted, serious birth defects can result.

A recent study demonstrates that doses of alcohol equivalent to one drink can inhibit this process of cell-cell adhesion. This demonstration that alcohol at clinically significant levels completely inhibits the activity of L1, suggests one reasonable mechanism for alcohol's effects on human fetal development leading to the manifestations of fetal alcohol syndrome (FAS). Children with FAS exhibit retarded growth, facial malformations and other neurological abnormalities. Coming to an understanding of the mechanism of alcohol disruption in cellular development and functioning may lead to effective strategies for reducing problems associated with FAS, a totally preventable public health problem.

In addition, L1 plays a role in the adult part of the brain where learning and memory reside. Disruption of the activities of L1 may play a role in the memory and cognitive disruptions sometimes seen in alcoholics. Because L1 also plays a role in cellular interactions in the adult brain, the mechanism hypothesized by this study may contribute to the development of medications that can intervene with alcohol-associated memory disorders.

Neuroscience Research

Alcohol interacts with other compounds in the brain, as well. The physiological affects of steroids, such as testosterone, estrogen, corticosteriods, and others, on bodily functions have been well documented for some time. Recently, however, steroids specific to the brain, called neurosteroids, have been discovered. These neurosteroids are potent agents of neural activity and are useful for enhancing our understanding of the neuro-mechanism of alcohol withdrawal. This increased understanding also has great potential for enabling the development of effective therapeutics that can intervene with the harmful effects often associated with alcohol withdrawal and alcohol-seeking behavior.

Chronic alcohol consumption leads to the development of alcohol dependence and tolerance. Abrupt cessation of alcohol use may result in often profound withdrawal symptoms, including agitation, anxiety, and an enhanced susceptibility to seizures. Drugs from the benzodiazepine family, e.g., Valium, have been used to treat these withdrawal symptoms, but often because of

cross-tolerance between alcohol and these drugs, they are less effective. In other words, heavy alcohol consumption can reduce the ability of the brain to respond to the ameliorating effects of the benzodiazepine family of drugs on alcohol withdrawal.

Chronic alcohol exposure reduces the anti-seizure properties of benzodiazepines. Recent research has found that the neurosteroid called THP, reduced the susceptibility in rats to alcohol-related seizures during withdrawal. Thus, neurosteroids have the potential to alleviate alcohol-related symptoms-and at lower doses than previously used medication. Thus, this neurosteroid shows promise as a new agent for managing withdrawal symptoms in humans, possibly providing a better alternative to currently used medications. Other studies suggest that neurosteroids can also reduce alcohol consumption and improve cognitive deficits resulting from chronic ethanol exposure.

Treatment Research

Research on the psychological treatment and prevention of alcoholism and alcohol-related problems is also a priority a NIAAA. Effectively treating alcoholism has the potential to substantially reduce morbidity and lower health care costs. This can be significant for an illness that costs the nation nearly $100 billion annually (Rice et al. 1990) and affects nearly 10 percent of the adult population. Recent treatment advances include the completion of a large clinical trial, Project MATCH, which compared the effects of different treatment types when matched to specific patient characteristics. Project MATCH was the largest, most complex randomized clinical trial ever undertaken in alcoholism treatment.

A number of alternative treatments are available for alcohol problems, ranging from brief, motivational interventions to "broad spectrum" treatments, such as social skills training, and Minnesota model (12-step, including Alcoholics Anonymous) therapies. Frequently two or more treatment types are combined in one therapeutic approach. The hypothesis tested in Project MATCH, was that patients with differing characteristics would do better in a treatment type that better fit their specific characteristics. Patients were randomly assigned to well-specified treatment strategies and treatment outcome based on patient characteristics and treatment type was assessed. A total of 1728 patients were recruited from nine states, with ample representation of women (25%) and minorities (20%). Three specific treatment approaches were tested: Twelve Step Facilitation; Cognitive-Behavioral Coping Skills Therapy; and Motivational Enhancement.

The findings were somewhat unexpected, but nonetheless quite encouraging in many respects. The three treatments achieved comparable outcomes and the data indicate that each treatment type resulted in substantial reductions in drinking. This reduction in drinking was generally sustained for 12 months. Treatment also resulted in fewer alcohol-related problems, and less other drug use and depression. Improvements in liver functioning were also seen. Except for patients with serious psychiatric problems, it does not appear necessary to match patients on the basis of patient characteristics to currently available treatments. The results indicate that treatment modalities with skilled counselors, based on the 12-step model, which is the most widely used treatment model in the United States, yet the least studied, is effective. The results

with Motivational Enhancement Therapy suggest that comparable post-treatment results may be obtained with less intensive therapies.

These findings run counter to the belief that treatment gains are inconsequential and short-lived. In addition, on a broader level, these data indicate that treatment programs do not need to markedly change treatments that staff are skilled in administering. This study demonstrates that well-designed treatments, in combination with good training of therapists, contribute to excellent retention rates in treatment.

Prevention Research

Prevention research is also a priority at NIAAA. NIAAA-supported investigators have demonstrated that prevention experiments can be conducted in a scientifically sound and rigorous manner. Research has shown that the design and implementation of relatively inexpensive prevention programs is highly feasible and promises great rewards in terms of saved lives, reductions in injuries, and reductions in medical costs associated with traffic accidents.

The "Saving Lives" project, in particular, has clearly demonstrated that communities can successfully plan, organize, and implement programs that reduce fatal automobile crashes related to drunken driving and speeding. This example of the utility of comprehensive multi-strategy community programs is responsive to the recommendations made by the 1989, Institute of Medicine evaluation of treatment and prevention strategies for alcohol-related health problems; it is based on other successful community interventions, such as, reducing cardiovascular mortality, smoking, and high blood pressure.

The purpose of the study was to assess the effectiveness of a five year community planned, organized, and implemented program to reduce alcohol-impaired driving, related driving risks, and traffic deaths and injuries. Multiple city departments and private citizens were involved in the "Saving Lives" prevention program. Community prevention programs were implemented in six Massachusetts communities. Five comparable communities that did not have similar state-supported traffic prevention programs, and the rest of Massachusetts served as comparison sites.

A full-time coordinator from the mayor's office organized a task force of concerned private citizens, organizations, and officials from various city departments. Approximately $1 per inhabitant was granted annually in program funds. Voluntary efforts played a key role; an average of 50 organizations participated in each city and active task force membership ranged from 20 to more than 100 persons. Each community designed its own prevention program.

Results were dramatic in the program cities during the five program years compared to the previous five. Fatal crashes declined 25% relative to the rest of Massachusetts. Fatal crashes involving alcohol showed a 42% relative decline. Furthermore, visible injuries per 100 crashes showed a 5% greater decline in the intervention communities than in the rest of Massachusetts. During the program, the proportion of 16 to 19 year olds who reported driving after drinking in the month prior to their interview, declined by 40% in the program communities relative to the rest of Massachusetts. Based on these findings, it is clear that relatively inexpensive prevention

activities organized by multiple city departments and private citizens can significantly reduce driving after drinking, related driving risks, and traffic deaths and injuries.

However, prevention efforts must begin when people are much younger than driving age. Despite encouraging declines in the prevalence of alcohol consumption in adolescents, youthful drinking remains a major public health problem. Alcohol use among teens is widespread, in spite of its illegality. Motor vehicle crashes are the leading cause of death for this age group, with one-third to one-half of such crashes involving alcohol. Furthermore, data show that the early onset of alcohol and tobacco use is a risk factor for progression to more serious drug use. A recent study nearing completion may provide a model alcohol use prevention program that can be implemented in communities around the country. It may also provide a model for ways of intervening with other behaviors of young adolescents that are causing concern.

The Northland study employed a multi-component, multi-year, community trial to delay, prevent, and reduce the prevalence of alcohol use and alcohol-related problems among a group of adolescents from 22 school districts in northeastern Minnesota. The project targets the Class of 1998 and has been ongoing for five years, beginning with students in the sixth grade and following them through grade 10. Interim results look quite hopeful. At the end of three years of program (grade 8) the rates of alcohol use were significantly lower among students in the program school districts compared to the reference districts. When compared to reference districts, 19% fewer students who received the program used alcohol in the past month, and past week use was 29% lower. Of great significance is the fact that overall fewer students initiated alcohol use. For instance, past month alcohol use by 8th graders who did not drink in grade 6 was 28% lower in program communities than in reference communities. Furthermore, the program effectively reduced peer influence on the use of alcohol; altered expectations about how many young people drink; enhanced parent-child communication about the consequences of alcohol use; and increased the number of personal reasons for not using alcohol.

Research Goals

Our goals for the upcoming fiscal year are to continue with the very promising genetic research begun by the Cooperative Agreement on the Genetics of Alcoholism (COGA) and animal studies. NIAAA will continue to support the use of COGA resources to confirm and enlarge upon the project's initial findings. Potential areas of research include: the identification of genes and their products initially found by COGA; mapping of new genes; more detailed characterization of subtypes of alcoholism; and the elucidation of the genetic bases for different alcoholic subtypes. Validation of COGA's genetic findings will require replication in independent studies using subject samples distinct from those of COGA. Some of these studies could be conducted using existing collections of twins and families, while others will require the recruitment of new collections of siblings and parents.

In addition, now that Project Match is complete, we are planning follow-up clinical trials that will include new medications along with standardized psychological strategies. Naltrexone, an FDA approved drug, and acamprosate, a drug that showed highly promising results in Europe are ready for additional testing. Exciting advances have been made in the development of both

medications and behavioral strategies to treat alcoholism. Among the former are naltrexone, nalmefene, and acamprosate. The latter group includes motivationally-based, targeted behavioral, and interpersonal support treatments. These two classes of treatment strategies are not competitive. Rather, recent research suggests that pharmacologic agents may be combined effectively with behavioral strategies and that their combination further enhances treatment outcome.

NIAAA is conducting research on specific strategies under each category, as well as combining the two approaches. To date, the bulk of investigations have employed small sample sizes, failed to consider the role of patient differences in responding to treatment, and have not considered the joint impact of treating alcoholism with medications and behavioral approaches simultaneously. Therefore, NIAAA is planning a multi-site clincial trial to follow up on Project Match findings. The rationale for a mult-site trial to evaluate various medications combined with behavioral treatments is that large numbers of patients can be accrued rapidly, great diversity of the subject pool is expected, statistical power is high, and the very structure of the Cooperative Agreement support mechanism promotes collegial alliances among experts, senior non-Federal researchers and Institute scientists. This approach is likely to generate considerable enthusiasm from the behavioral and pharmacologic research communities, as well as from clinical practitioners.

Priority-Setting Process

The NIAAA funds 90 percent of all alcohol research in the United States. The processes used to determine which areas of science are the most promising are similar to other NIH institutes. NIAAA has an extensive priority setting process involving the scientific community, clinicians and other health care providers, the public, and the Institute Director. This process recognizes the evolving nature of the scientific enterprise and includes not only identifying priorities, but also establishing their relative ranking in the context of the emerging alcohol research opportunities and available resources. In determining the award of individual research grants, NIAAA has specific criteria which include the scientific merit of a grant application as determined by the peer review process, program balance within the Institute's overall research portfolio, and scientific relevance to Institute research objectives. The NIAAA develops and adjusts research goals and objectives and establishes criteria for both intramural and extramural research programs with continuous, authoritative input from the scientific community, clinicians, the public, and specialized, impartial expert panels.

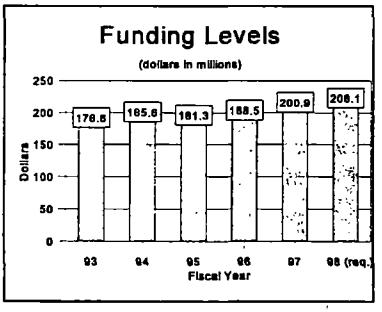
The Institute's National Advisory Council has a primary role in developing NIAAA's research priorities. The National Advisory Council reviews the Institute's program plans as well as key planning and budgetary policies. In 1989, the Extramural Scientific Advisory Board (ESAB), then a component of the Advisory Council, completed a review of the Institute's entire extramural research portfolio. These review findings have been used by Program Staff in making funding decisions. In 1996, this cycle began again. A Council subcommittee will again conduct in-depth reviews of progress in the field as well as the Institute's research accomplishments, priorities and future plans.

In identifying key priority areas, the Institute has frequently utilized the Institute of Medicine (IOM) of the National Academy of Sciences to conduct detailed studies on its goals and objectives and to identify long term scientific opportunities. This year the IOM provided a congressionally-directed report on the Fetal Alcohol Syndrome and Fetal Alcohol Effects (FAS/FAE) to NIAAA that identifies areas of research priority and opportunity. Following the IOM recommendations and Congressional interest, the NIAAA established an interagency committee on FAS/FAE. This committe represents the NIAAA, NICHD, CDC, IHS and other relevant agencies. It will focus on a variety of activities that will be enhanced by increased collaboration among the participants. A report to Congress will be submitted in Spring of 1997.

The Institute has also prepared and published comprehensive research plans. Alcohol Research: Promise for the Decade was prepared in response to a request from the Chairman of the Senate Appropriations Subcommittee on Labor-Health and Human that NIAAA outline research directions in the alcohol field for the next ten years. The document highlights findings in various disciplines and presents research initiatives through 2001 that promise to advance our understanding of the nature of alcoholism and expand efforts to develop new and improved methods to prevent and treat the disease. The report was submitted to Congress, and has been widely circulated to the research and the health care communities.

Overall Budget Policy

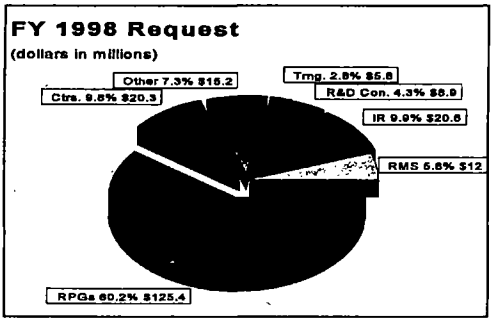
The FY 1998 President's Budget Request for NIAAA is $208,112,000, an increase of $7,293,000 or 3.6 percent over the FY 1997 estimate of $200,819,000.



NIH policy links RPG average cost increases to total program budget requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for research project grants (RPGs). In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs would increase by up to two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP). These levels will maintain stability of support within the extramural grantee community while providing new research opportunities by supporting 143 competing RPGs and 532 total RPGs, an increase of 33 total RPGs over FY 1997.

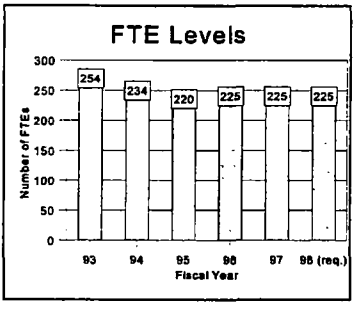
Research centers' support for 13 awards would be $20,300,000 under the FY 1998 request, the same level as FY 1997.

Other research grants would be supported at $15,201,000, a 2 percent increase over the 1997 estimate. This includes 55 research career awards at $5,290,000; $9,120,000 for cooperative agreements; $321,000 for Minority Biomedical Research Support grants; and $470,000 for 5 awards comprised of science education, conference and scientific evaluationgrants.



The FY 1998 request includes $5,775,000 for 203 full-time training positions, the same number of training positions the FY 1997 estimate and a funding increase of $114,000. These additional funds would provide a proposed stipend increase for post-doctoral fellows with 0 and 1 years of experience.

Research and development contracts would receive $8,900,000, an increase of $1,132,000 over the 1997 estimate. Additional funds for contracts would support the establishment of pedigree, diagnostic, and genetics databases and a cell line repository to expand on findings from the Cooperative Agreements on the Genetics of Alcoholism (COGA).



The FY 1998 request includes $20,595,000 for intramural research, a 1.5 percent increase over the FY 1997 estimate, and $11,956,000 for research management and support, the same level as the FY 1997 estimate. In FY 1998, 225 FTEs are requested, the same as the 1997 estimate.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	311	$77,975,000	358	$87,977,000	373	$89,107,000
Administrative supplements	(26)	946,000	(29)	1,230,000	(29)	1,230,000
Competing:						
Renewal	32	9,579,000	30	9,250,000	35	10,800,000
New	99	18,767,000	92	16,717,000	106	19,730,000
Supplemental	2	558,000	2	500,000	2	510,000
Subtotal, competing	133	28,904,000	124	26,467,000	143	31,040,000
Subtotal	444	107,825,000	482	115,674,000	516	121,377,000
SBIR/STTR	14	1,957,000	17	4,274,000	16	4,008,000
Subtotal, RPGs	458	109,782,000	499	119,948,000	532	125,385,000
Research Centers						
Specialized/comprehensive	13	19,767,000	13	20,300,000	13	20,300,000
Clinical research						
Biotechnology						
Comparative medicine						
Research centers in minority institutions						
Subtotal, Centers	13	19,767,000	13	20,300,000	13	20,300,000
Other Research						
Research careers	50	4,727,000	55	5,290,000	55	5,290,000
Cancer education						
Cooperative clinical research	12	8,510,000	12	8,820,000	12	9,120,000
Biomedical research support						
Minority biomedical research support		194,000		321,000		321,000
Other	2	530,000	5	465,000	5	470,000
Subtotal, Other Research	64	13,961,000	72	14,896,000	72	15,201,000
Total, Research Grants	535	143,510,000	584	155,144,000	617	160,886,000
Training	FTTPs		FTTPs		FTTPs	
Individual	43	812,000	44	888,000	44	906,000
Institutional	163	4,455,000	159	4,773,000	159	4,869,000
Total, Training	206	5,267,000	203	5,661,000	203	5,775,000
Research & development contracts	27	7,681,000	26	7,768,000	28	8,900,000
(SBIR/STTR)	(5)	(1,514,000)	(3)	(350,000)	(4)	(750,000)
	FTEs		FTEs		FTEs	
Intramural research	94	20,051,000	94	20,290,000	94	20,595,000
Research management and support	131	11,960,000	131	11,956,000	131	11,956,000
Cancer prevention & control						
Construction						
Total, ICD	225	188,469,000	225	200,819,000	225	208,112,000
(Clinical Trials)		(16,498,000)		(17,300,000)		(17,500,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Alcohol Biomedical and Behavioral Research		$156,388		$168,573		$175,561		
Subtotal, Extramural research		156,388		168,573		175,561		6,988
Intramural research	94	20,031	94	20,290	94	20,595	0	305
Research management and support	131	11,939	131	11,956	131	11,956	0	0
Total obligations	225	188,358	225	200,819	225	208,112	0	7,293
Unobligated balance lapsing		111		0		0		0
Total, Budget Authority	225	188,469	225	200,819	225	208,112	0	7,293

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Summary of Changes

1997 Estimated budget authority	$200,819,000
1998 Estimated budget authority	208,112,000
Net change	7,293,000

	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$7,341,000		97,000
b. Annualization of January 1997 pay increase		7,341,000		61,000
c. January 1998 pay increase		7,341,000		154,000
d. Legislative proposal, 1.51% increase in the CSRS rate		7,341,000		31,000
e. Service and supply fund		1,008,000		26,000
f. Increased cost of laboratory supplies, materials, and other expenses		11,941,000		152,000
Subtotal		20,290,000		521,000
2. Research Management and Support:				
a. Within grade increase		9,606,000		166,000
b. Annualization of January 1997 pay increase		9,606,000		79,000
c. January 1998 pay increase		9,606,000		202,000
d. Legislative proposal, 1.51% increase in the CSRS rate		9,606,000		46,000
e. Service and supply fund		72,000		2,000
f. Increased cost of laboratory supplies, materials, and other expenses		2,278,000		48,000
Subtotal		11,956,000		543,000
Subtotal, Built-in		32,246,000		1,064,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Summary of Changes - continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	358	89,207,000	15	1,130,000
b. Competing	124	26,467,000	19	4,573,000
c. SBIR/STTR	17	4,274,000	(2)	(266,000)
Total	499	119,948,000	32	5,437,000
2. Centers	13	20,300,000	0	0
3. Other research	72	14,896,000	0	305,000
4. Research training	203	5,661,000	0	114,000
5. Research and development contracts	26	7,768,000	2	1,132,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes	83	17,790,000	0	(216,000)
b. Special emphasis areas	11	2,500,000	0	0
Subtotal, intramural	94	20,290,000	0	(216,000)
7. Research management and support	131	11,956,000	0	(543,000)
Subtotal, program		200,819,000		6,229,000
Total changes				7,293,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Object

	FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	225	225	0
Full-time equivalent of overtime and holiday hour	1	1	0
Average ES salary	$118,000	$118,000	$0
Average GM/GS grade	10.9	10.9	0
Average GM/GS salary	$54,804	$56,338	$1,534
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)			
Average salary of ungraded positions			

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	10,780,000	11,777,000	$997,000
11.3	Other than Full-Time Permanent	1,545,000	984,000	(561,000)
11.5	Other Personnel Compensation	382,000	350,000	(32,000)
11.8	Special Personal Services Payments	1,259,000	990,000	(269,000)
11.9	**Total Personnel Compensation**	**13,966,000**	**14,101,000**	**135,000**
12.0	Personnel Benefits	2,970,000	2,980,000	10,000
13.0	Benefits for Former Personnel	11,000	11,000	0
	Subtotal, Pay Costs	**16,947,000**	**17,092,000**	**145,000**
21.0	Travel & Transportation of Persons	239,000	244,000	5,000
22.0	Transportation of Things	79,000	74,000	(5,000)
23.1	Rental Payments to GSA	1,218,000	1,280,000	62,000
23.2	Rental Payments to Others	200,000	160,000	(40,000)
23.3	Communications, Utilities & Miscellaneous Charges	409,000	409,000	0
24.0	Printing & Reproduction	137,000	115,000	(22,000)
25.1	Consulting Services	20,000	20,000	0
25.2	Other Services	1,221,000	1,040,000	(181,000)
25.3	Purchase of Goods & Services from Government Accounts	10,380,000	10,486,000	106,000
25.4	Operation & Maintenance of Facilities	614,000	618,000	4,000
25.5	Research & Development Contracts	5,678,000	6,810,000	1,132,000
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	579,000	581,000	2,000
25.8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**18,492,000**	**19,555,000**	**1,063,000**
26.0	Supplies & Materials	1,678,000	1,810,000	132,000
31.0	Equipment	540,000	544,000	4,000
32.0	Land and Structures	7,000	0	(7,000)
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	160,805,000	166,761,000	5,956,000
42.0	Insurance Claims & Indemnities	66,000	66,000	0
43.0	Interest & Dividends	2,000	2,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**183,872,000**	**191,020,000**	**7,148,000**
				0
	Total Direct Obligations	**200,819,000**	**208,112,000**	**7,293,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$10,780,000	$11,777,000	$997,000
Other Than Full-Time Permanent (11.3)	1,545,000	984,000	(561,000)
Other Personnel Compensation (11.5)	382,000	350,000	(32,000)
Special Personal Services Payments (11.8)	1,259,000	990,000	(269,000)
Total Personnel Compensation (11.9)	**13,966,000**	**14,101,000**	**135,000**
Civilian Personnel Benefits (12.0)	2,970,000	2,980,000	10,000
Benefits to Former Personnel (13.0)	11,000	11,000	0
Subtotal, Pay Costs	**16,947,000**	**17,092,000**	**145,000**
Travel (21.0)	239,000	244,000	5,000
Transportation of Things (22.0)	79,000	74,000	(5,000)
Rental Payments to Others (23.2)	200,000	160,000	(40,000)
Communications, Utilities and Miscellaneous Charges (23.3)	409,000	409,000	0
Printing and Reproduction (24.0)	137,000	115,000	(22,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	20,000	20,000	0
Other Services (25.2)	1,221,000	1,040,000	(181,000)
Purchases from Govt. Accounts (25.3)	7,789,000	7,895,000	106,000
Operation & Maintenance of Facilities (25.4)	614,000	618,000	4,000
Operation & Maintenance of Equipment (25.7)	579,000	581,000	2,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**10,223,000**	**10,154,000**	**(69,000)**
Supplies and Materials (26.0)	1,678,000	1,810,000	132,000
Subtotal, Non-Pay Costs	**12,965,000**	**12,966,000**	**1,000**
Total, Administrative Costs	**29,912,000**	**30,058,000**	**146,000**

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

1997 House Appropriations Committee Report Language

Item

Genetics - The Committee states that past studies in genetic epidemiology provide compelling evidence for the influence of genetics on the predisposition to alcoholism. Recent findings from the Cooperative Study on the Genetics of Alcoholism (COGA) have identified several chromosomal regions of importance. NIAAA plans to initiate additional research to precisely map the location of the genes, isolate them, and identify their protein products. The Committee strongly supports the continued funding of this important research, which will provide the foundation for the development of new methods to prevent and treat alcoholism.

Actions Taken or to be Taken

The NIAAA remains strongly committed to furthering valuable knowledge gained by the (COGA) investigators. In FY 1997, the NIAAA is supporting research to more densely map the chromosomal regions identified as promising "hot spots" for linkages of alcohol dependence. The Institute will also be supporting additional research by COGA scientists to confirm evidence that a particular brain wave's amplitude is a determinant of one's susceptibility to alcoholism as well as promising new research that has identified the location of gender-specific chromosomes that influence alcohol consumption in a certain strain of mice. These advances will continue to facilitate the identification of genes influencing a human predisposition to alcoholism and will, potentially, lead to early diagnosis and timely prevention and intervention strategies.

Item

Fetal alcohol syndrome - The Committee states that fetal alcohol syndrome is the leading preventable cause of mental retardation in the United States. Research funded by NIAAA has led to important discoveries on the molecular mechanisms underlying alcohol-induced birth defects, the effects of moderate drinking during pregnancy on the intelligence and behavior of children, and strategies for the prevention of drinking during pregnancy. The Committee encourages the NIAAA to consider the recommendations of the Institute of Medicine in its funding of fetal alcohol syndrome research.

Actions Taken or to be Taken

The NIAAA supports a broad spectrum of Fetal Alcohol Syndrome (FAS) research and has expanded the research grant portfolio to implement recommendations in the Institute of Medicine (IOM) report. The Institute supports basic research on animal models to elucidate the mechanisms of alcohol teratogenesis, that might lead to pharmacologic or other strategies for amelioration of alcohol's effects. The NIAAA also funds research to examine the underlying neurobiological mechanisms of behavioral and environmental interventions. Other research areas recommended by the IOM include developing methods of identifying those women most at risk for alcohol problems and developing appropriate interventions for them.

The Institute has issued a program announcement to solicit applications for research on prevention and intervention strategies to reduce alcohol consumption by women of child bearing age in high risk populations. One aspect of this proposal involves training primary health care providers to screen for alcohol problems and provide appropriate interventions. The NIAAA is also developing a publication, *Drinking and Your Pregnancy,* for high risk African American women. After it is completed and evaluated, the pamphlet will be adapted for Hispanic, Native American, and other high risk women.

The IOM recommended that NIAAA establish and chair an Interagency Coordinating Committee on FAS. The committee, which represents the NIAAA, the National Institute of Child Health and Human Development (NICHD), the Centers for Disease Control (CDC), the Health Resources and Services Administration (HRSA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Agency for Health Care Policy Research (AHCPR), and the Indian Health Service (IHS) has been established and has met several times to discuss research, prevention, and treatment proposals in this important area.

Item

Moderate drinking - The Committee understands that NIAAA has received an extensive number of research applications on the health effects of moderate drinking to further investigate the potential role of beer, wine, and distilled spirits alcohol in an optimal diet and lifestyle. . . . The Committee believes that this research is important and encourages the NIAAA to continue its efforts in these areas. The Committee looks forward to learning in next year's hearing about the volume and types of research projects that have been funded.

Actions Taken or to be Taken

In late FY 1996 the NIAAA funded 12 new research projects for $2.2 million to study the risks and benefits of moderate drinking. These projects address a broad range of topics including: the impact of alcohol on coronary artery disease; potential cardioprotective effects of alcohol; the effects of alcohol on osteoporosis; alcohol and prescription drug reactions in the elderly; and alcohol's effects on estrogen replacement therapy in women. Findings from this research will elucidate both risks and benefits of moderate alcohol consumption.

Item

Training - The Committee states that since behavioral factors are important to alcoholism and alcohol abuse, the Committee encourages NIAAA to consider an initiative to support junior behavioral researchers, such as the B/START (Behavioral Science Track Awards for Rapid Transition) program which has been used by other Institutes.

Actions Taken or to be Taken

The NIAAA is currently restructuring programs that support junior investigators, including behavioral researchers. Several old programs are being consolidated into an integrated activity that promotes novel, small projects and includes features that will enable a smooth transition to research for new investigators.

Item

Treatment matching - Committee states that it is interested to learn that Project MATCH, NIAAA's clinical trial of patient-treatment matching and treatment effectiveness, is approaching completion, and requests a report on the results of this important research as soon as it becomes available.

Actions Taken or to be Taken

The NIAAA will submit a full report on the findings of Project MATCH prior to the FY 1998 hearings. The purpose of Project MATCH was to test whether it is important for alcoholism treatment providers to match their patients to particular treatments based on the individual's needs and special characteristics.

A press conference to announce the study findings was held at the National Press Club on December 17, 1996. Essentially, the clinical trial demonstrated that all patients, regardless of which of three study treatments they received, experienced significant and sustained improvement with a higher percentage of days abstinent and a decreased number of drinks on days when drinking occurred. Patients who participated in the study also showed decreased use of drugs, less depression, and fewer alcohol related problems as well as improved liver function. These improvements were maintained throughout the 12 months following treatment and demonstrate the effectiveness of treatment. The clinical trial confirmed one of the hypothesized patient treatment matches found in previous studies and did not confirm the others, leading researchers to challenge the notion that patient-treatment matching is necessary in alcoholism treatment. Project MATCH researchers will continue to analyze and publish additional findings. A logical next step for alcoholism treatment research is to test behavioral treatments in conjunction with promising pharmacological treatments for alcoholism.

1997 Senate Appropriations Committee Report Language

Item

Fetal alcohol syndrome - The Committee recommends that funds be made available to implement the recommendations of the recently published the Institute of Medicine's report to increase research on fetal alcohol syndrome.

Actions Taken or to be Taken

The NIAAA supports a broad spectrum of Fetal Alcohol Syndrome (FAS) research and has expanded the research grant portfolio to implement recommendations contained in the Institute of Medicine (IOM) report. The Institute supports basic research on animal models to elucidate the mechanisms of alcohol teratogenesis, that might lead to pharmacologic or other strategies for amelioration of alcohol's effects. The NIAAA also funds research to examine the underlying neurobiological mechanisms of behavioral and environmental interventions. Other research areas recommended by the IOM include developing methods of identifying those women most at risk for alcohol problems and developing appropriate interventions for them.

The Institute has issued a program announcement to solicit applications for research on prevention and intervention strategies to reduce alcohol consumption by women of child bearing age in high risk populations. One aspect of this proposal involves training primary health care providers to screen for alcohol problems and provide appropriate interventions. The NIAAA is also developing a publication, *Drinking and Your Pregnancy,* for high risk African American women. After it is completed and evaluated, the pamphlet will be adapted for Hispanic, Native American, and other high risk women.

The IOM recommended that NIAAA establish and chair an Interagency Coordinating Committee on FAS. The committee, which represents the NIAAA, the National Institute of Child Health and Human Development (NICHD), the Centers for Disease Control (CDC), the Health Resources and Services Administration (HRSA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Agency for Health Care Policy Research (AHCPR), and the Indian Health Service (IHS) has been established and has met several times to discuss research, prevention, and treatment proposals in this important area.

Item

Behavioral research - The Committee is interested to learn that Project MATCH, the Institute's clinical trial of patient-treatment matching and treatment effectiveness, is approaching completion and requests that the NIAAA be prepared to report the results of this important research during the fiscal year 1998 budget hearings.

Actions Taken or to be Taken

The NIAAA will submit a full report on the findings of Project Match prior to the FY 1998 hearings. The purpose of Project MATCH was to test whether it is important for alcoholism treatment providers to match their patients to particular treatments based on the individual's needs and special characteristics.

A press conference to announce the study findings was held at the National Press Club on December 17, 1996. Essentially, the clinical trial demonstrated that all patients, regardless of which of three study treatments they received, experienced significant and sustained improvement with a higher percentage of days abstinent and a decreased number of drinks on days when drinking occurred. Patients who participated in the study also showed decreased use of drugs, less depression, and fewer alcohol related problems as well as improved liver function. These improvements were maintained throughout the 12 months following treatment and demonstrate the effectiveness of treatment. The clinical trial confirmed one of the hypothesized patient treatment matches found in previous studies and did not confirm the others, leading researchers to challenge the notion that patient-treatment matching is necessary in alcoholism treatment. Project MATCH researchers will continue to analyze and publish additional findings. A logical next step for alcoholism treatment research is to test behavioral treatments in conjunction with promising pharmacological treatments for alcoholism.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
			>	$195,158,000	>	$202,337,000
			a/		b/	
National Institute on Alcohol Abuse and Alcoholism	Section 464H(d)	42§258n(d)				
National Research Service Awards	Section 487(d)	42§288(d)	a/	5,661,000	b/	5,775,000
Total, Budget Authority				200,819,000		208,112,000

a/ Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208).
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	n/a	n/a	$180,169,000	$176,619,000 2/
1994	$173,615,000	$184,700,000	184,700,000	185,617,000
1995 3/	182,498,000	181,328,000	181,328,000	181,256,000 4/
1995 Rescission				(106,000)
1996	185,712,000 3/	198,607,000	183,733,000 3/	198,607,000
Rescission				(195,000)
1997	192,280,000 3/	212,079,000	195,891,000 3/	211,870,000 5/
1998 3/	208,112,000			

n/a = Not applicable.

1/ Reflects enacted supplementals, rescissions, and reappropriations. Prior to the FY 1993 Senate Allowance, NIAAA was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of $1,430,000, $61,000, and $601,000.

3/ Excludes funds for HIV Research Activities consolidated in the NIH Office of AIDS Research in FY 1995, FY 1996 and FY 1997.

4/ Excludes enacted administrative reductions of $117,000, $4,000, and $68,000.

5/ Excludes enacted administrative reductions of $134,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	10	10	10
Office of Planning and Resource Management	44	44	44
Office of Scientific Affairs	21	21	21
Office of Policy Analysis	4	4	4
Division of Clinical and Prevention Research	25	25	25
Division of Basic Research	14	14	14
Division of Biometry and Epidemiology	13	13	13
Division of Intramural Clinical and Biological Research	94	94	94
Total, NIAAA	225	225	225
	Average GM/GS Grade		
1993	10.6		
1994	10.8		
1995	10.8		
1996	10.9		
1997	10.9		
1998	10.9		

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism
Program Administration

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	0	0	0
ES-5	2	2	2
ES-4	3	3	3
ES-3	0	0	0
ES-2	0	0	0
Subtotal	5	5	5
Total - ES Salary	$590,000	$590,000	$590,000
GS/GM-15	20	20	20
GS/GM-14	42	42	42
GS/GM-13	22	22	22
GS-12	17	17	17
GS-11	18	18	18
GS-10	1	1	1
GS-9	19	19	19
GS-8	8	8	8
GS-7	21	21	21
GS-6	7	7	7
GS-5	9	9	9
GS-4	3	3	3
GS-3	2	2	2
GS-2	0	0	0
GS-1	0	0	0
Subtotal	189	189	189
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Director Grade	6	6	6
Senior Grade	6	6	6
Full Grade	3	3	3
Senior Assistant Grade	0	0	0
Subtotal	15	15	15
Ungraded	26	26	26
Total permanent positions	198	198	198
Total positions, end of year	235	235	235
Total full-time equivalent (FTE) employment,end of year	225	225	225
Average ES level	4	4	4
Average ES salary	$118,000	$118,000	$118,000
Average GS/GM grade	10.9	10.9	10.9
Average GS/GM salary	$53,038	$54,804	$56,338

WEDNESDAY, MARCH 5, 1997.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

WITNESSES

PHILLIP GORDEN, M.D., DIRECTOR, NIDDK
L. EARL LAURENCE, DEPUTY DIRECTOR
CHARLES R. ZELLERS, FINANCIAL MANAGEMENT OFFICER
HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DENNIS WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTRODUCTION OF WITNESSES

Mr. PORTER. The subcommittee will come to order.

We're pleased to welcome Dr. Phillip Gorden, the Director of the National Institute of Diabetes and Digestive and Kidney Diseases, to testify. And Dr. Gorden, would you please introduce the people who are with you at the table and then proceed with your statement.

Dr. GORDEN. Thank you, Mr. Chairman.

To my far left is Mr. Charles Zellers, our Budget Officer; Mr. Earl Laurence, our Deputy Director; Dr. Varmus and Mr. Williams I think you know.

OPENING STATEMENT

Mr. Chairman, Mr. Wicker, members of the committee. The NIDDK leads the national biomedical research effort to combat some of the most important, chronic and costly diseases in this country, including diabetes, endocrine, and metabolic diseases; digestive diseases and nutritional disorders; and diseases of the kidney, urologic tract and blood.

In meeting this challenging research mission, we forge collaborations with other NIH components as well as with non-profit foundations and commercial enterprises. Our approach is to deploy resources and capitalize on emerging technologies across the spectrum of the diseases we address. We seek to understand the underlying cause and course of disease, and develop effective treatments and preventive strategies.

At different points in time, based on scientific opportunities, we pursue all or some of these avenues, ranging from the most basic studies of molecular biology to major clinical trials.

As a special way to emphasize this broad NIH approach, Dr. Varmus and I will co-sponsor a conference in the near future related to diabetes research. The conference will include all Institutes involved in diabetes research and will focus on special opportuni-

ties and directions that this broad interdisciplinary approach brings to diabetes research.

This forum will offer a special opportunity for the Director of NIH and a number of ICD directors to meet directly with leaders of the diabetes research community. We believe this will be a constructive and informative approach.

This continuum of research, from clinical science to very basic science, to which I have referred, is best illustrated by a few examples. Let me describe the point on this continuum that is closest to medical practice. For example, we are currently engaged in four multicenter clinical trials, all of which were made possible through knowledge derived through basic and pre-clinical research about biologic mechanisms. In diabetes, one trial focuses on immune modulation, to halt or delay the onset of insulin-dependent diabetes in high risk children and adolescents.

A second diabetes trial centers on the use of drug therapy and lifestyle changes to prevent or delay the onset of non-insulin dependent diabetes, which usually occurs in later life and disproportionately affects minorities.

Fundamental research also made possible our ongoing trials studying methods to ameliorate the course of kidney function deterioration in African-Americans with hypertension and to pursue non-surgical approaches to treating benign prostatic hyperplasia, or BPH, one of the most prevalent conditions in our aging population.

At the middle of the continuum, we are funding cutting edge research where clinical applications appear promising but are not yet completely feasible. A prime example is found in the NIH special emphasis area, "The Genetics of Medicine." This includes NIDDK studies to sequence and clone the disease-causing genes; identify proteins they produce; and develop the means to replace or repair them, or circumvent the defects they cause.

Diseases targeted here for which major discoveries have occurred include cystic fibrosis, polycystic kidney disease, diabetes, hemochromatosis, and hereditary pancreatitis. Other cutting edge research relates to the special emphasis area, "The Biology of the Brain." This includes the NIDDK funded discovery of the obesity gene and its hormone product, leptin, which works in the brain to regulate both energy intake and utilization. Spinoff research has had an enormous positive impact on the U.S. pharmaceutical and biotechnology industries.

Also at the center of the NIDDK research continuum are studies focused on the special emphasis area, "New Approaches To Pathogenesis." An excellent example is research following up on the discovery that the bacterium, *H pylori,* is a causative agent of peptic ulcer disease, and possibly gastric cancer.

In closing, I would like to turn to the first part of the NIDDK research continuum, the engine of basic science that drives all of our success stories. One example is transgenic technology. Another example is the development of experimental mouse models in which a particular gene has been deleted or "knocked out" to confirm hypotheses about disease-causing genes and to help researchers then develop and test therapeutic strategies. Examples here include models for Tay-Sachs disease, inflammatory bowel disease, bone developmental abnormalities and many others.

Another technology of the future is structural biology, which enables us to visualize the three-dimensional architecture of molecules in order to study drugs to inhibit or to enhance activity in a very special way. Major examples of this technology include the integration of the AIDS virus; the mechanism of tumor suppressors; and the action of inflammatory mediators. It is the continuum of research from fundamental science to clinical science that we will vigorously support with our 1998 appropriation.

Mr. Chairman, the budget request for the NIDDK for fiscal year 1998 is $821,164,000. I would be very pleased to answer any questions you may have.

Thank you very much, Mr. Chairman.

[The prepared statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Statement of the Director
National Institute of Diabetes and Digestive and Kidney Diseases

Mr. Chairman and Members of the Committee, I am pleased to testify on behalf of the research programs, progress and opportunities of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Our institute has responsibility for the national biomedical research effort to combat some of the most important, chronic diseases in this country, including diabetes, endocrine and metabolic diseases; digestive diseases and nutritional disorders; and diseases of the kidney, urologic tract and blood. These diseases inflict tremendous suffering and health care costs on the American people because they are life-long, debilitating, and often relentless.

In meeting this challenging research mission, we have forged collaborations with other NIH components, as well as with nonprofit foundations and commercial enterprises. Our approach is to deploy resources and capitalize on emerging technologies across the spectrum of the diseases we address. We seek to understand the underlying cause and course of disease and to develop effective treatment and preventive strategies. At different points in time, based on scientific opportunities, we pursue all or some of these avenues, ranging from the most basic studies of molecular biology to major clinical trials.

This "continuum"of research is best illustrated by a few examples. To illustrate this process, let me describe the point on this continuum that is closest to medical practice: clinical trials. In diabetes, we are currently conducting two multicenter primary prevention trials in an attempt to arrest or delay disease onset. The first trial focuses on immune modulation to halt or delay the onset of insulin-dependent diabetes in high-risk children and adolescents. The second trial is focusing on the use of drug therapy and lifestyle changes to prevent or delay the onset of noninsulin-dependent diabetes, which usually occurs in later life and disproportionately affects minorities. These two trials would not have been possible without the knowledge base we have acquired on the cellular mechanisms of insulin action; the demonstration that special pharmacologic approaches can prevent the onset of insulin-dependent diabetes in experimental animals; the development of highly accurate tests for predicting the risk of developing diabetes; the design of insulin-sensitizing drugs; and the discovery of sophisticated methods for monitoring metabolic control. Our studies have also been bolstered by the results of the Diabetes Control and Complications Trial (DCCT), which clearly demonstrated the efficacy of metabolic control in preventing the nerve, eye, and kidney complications of diabetes--a message that we are broadly disseminating through our diabetes outreach program.

Another example from the NIDDK research continuum is our ongoing clinical trial of methods to ameliorate the course of kidney function deterioration in African Americans with hypertension. This study would not have been possible without basic research to develop improved methods of measuring kidney function; to understand the

natural history and progression of kidney disease; and to develop and demonstrate the protective effect of drugs that affect the microcirculation of the kidney.

A third example from our research continuum is our current study of non-surgical approaches to treating benign prostatic hyperplasia or BPH, one of the most prevalent conditions in our aging population. This trial would not have been possible without the development of drugs that affect prostate size and bladder outlet function.

While we are pursuing clinical trials made possible by our science base, we are also supporting other types of research in the middle of the research continuum, where clinical applications appear promising, but are not yet completely feasible. Here we find rapidly emerging cutting-edge research. These are central discoveries--largely derivative of recent technologic advances--with broad potential application to multiple diseases. A prime example of this cutting-edge science is found in the NIH Special Emphasis Area, "The Genetics of Medicine," which includes studies to sequence and clone disease-causing genes; identify the proteins they produce or regulate; and develop the means to replace, repair or circumvent the defects they cause. Derivative of these new genetic technologies, NIDDK-supported researchers continue to seek new therapeutic approaches to cystic fibrosis by building upon the landmark discoveries of the gene and defective transport protein responsible for this disease. On a parallel track, other researchers have recently discovered two major defects that lead to polycystic kidney disease--one of the most common genetic diseases and a major cause of end stage renal disease. Moreover, this year, four major genetic discoveries have elucidated defects in two forms of maturity-onset diabetes of the young; hereditary pancreatitis; and the iron-storage blood disease, hemochromatosis. It is critical to emphasize that the importance of these discoveries goes far beyond the specific single-gene diseases to which they directly apply. Importantly, they will also allow us to understand mechanisms applicable to more complex diseases such as noninsulin-dependent diabetes and cancer.

Another excellent example from our continuum of cutting-edge research relates to the NIH Special Emphasis Area, "The Biology of Brain Diseases." This includes the NIDDK-funded discovery of the obesity gene and its hormone product, leptin, which works in the brain to regulate both energy intake and utilization. Almost immediately following this landmark advance, a host of related fundamental discoveries were made related to receptors for leptin and neurobiologic connections within the brain that orchestrate the effects of the body's energy-regulation system. This spinoff research has had an enormous positive impact on U.S. pharmaceutical and biotechnology industries. The leptin story is one of the best ways to illustrate the tightly dovetailed relationship between the national investment in NIH science and the national benefits flowing from its commercial application. These burgeoning discoveries have obvious relevance to appetite control and obesity, and--as is often the case in science--are likely to lead to clinical applications for other medical problems such as diabetes, nutritional disorders, infertility, and developmental abnormalities.

Also at the center of the NIDDK research continuum you will find studies focused on pinpointing the causes, natural history, and onset of disease. These relate to the NIH Special Emphasis Area, "New Approaches to Pathogenesis." Here an excellent example is research following up on the discovery that the bacterium H. pylori is a

causative agent of peptic ulcer disease. As a result of this finding, several combinations of antibiotic therapy were approved by FDA this past year for eradication of this bacterium, thus preventing costly, recurrent attacks of peptic ulcer. Also approved was a simple, easy and inexpensive breath test for diagnosing the bacterium in patients--without endoscopy. In NIDDK, we are now building upon these clinical developments to help us focus on remaining research questions of disease pathogenesis, including the mechanisms by which H. pylori leads to ulcer disease and, possibly, to gastric cancer.

In closing, I would like to turn to the first part of the NIDDK research continuum--the engine of basic science that drives all our success stories. Because its ultimate use is largely unknown, the critical importance of such fundamental science is sometimes difficult to convey, other than by giving the types of examples I have described today.. What are some of these "technologies of the future" in which NIDDK is investing today? One is transgenic technology, which enables us to alter genes in laboratory animals in order to study their function. One aspect of transgenic technology is the development of experimental mouse models in which a particular gene has been deleted or "knocked out." One effective way knock-out mice are used is to confirm hypotheses about disease-causing genes and to help researchers then develop and test therapeutic strategies. For example, NIDDK researchers have developed "knock-out" animal models of inflammatory bowel disease which both elucidate putative causes of the disease and also suggest the possibility of therapeutic approaches to protect the intestine from injury and possibly prevent the cellular initiation of intestinal cancer. A second use of transgenic technology is to observe the effects of genes whose function in health and disease is unknown and has not even been hypothesized. Here, we are exploiting molecules just discovered in patients with lung cancer, but now known to be important in bone development, with possible relevance to bone diseases such as osteoporosis. While these types of laboratory studies are extremely preliminary, they illustrate the vast but as yet unknown future clinical application of impressive basic science technologies to diseases afflicting the American public.

Another "technology of the future" is structural biology, which enables us to visualize the three-dimensional architecture of molecules. With this knowledge, researchers can then rationally design drugs to closely fit and attach to a molecule in order to inhibit or enhance its activity. Already, structural biologists in the NIDDK intramural program have contributed to elucidating the structure of the p53 tumor suppressor gene widely believed to play a major role in protecting against many forms of cancer. They have also solved the structure of integrase, a protein essential to the cellular integration and replication of the AIDS virus.

Our investment in "technologies of the future" also includes support for the development of vectors for the delivery of gene therapy. One promising delivery system on which we are working is the adeno-associated virus. Another potential vehicle for gene therapy is the primitive, undifferentiated stem cell. Stem cells might be used to introduce healthy genes to the body and to replace or repair defective ones in a host of genetic diseases. Stem cells also offer opportunities for replenishing the bone marrow in a variety of cancers, as well as other potential applications.

Another example of "technologies of the future" is our support of basic research to understand signal transduction--that is, the cellular communication pathways and cascades, through which disease processes are mediated. Here, we are intensely studying a class of signaling proteins called "G-proteins." These proteins were first discovered in an intramural NIDDK laboratory and now have application in essentially every aspect of our clinical science program.

Mr. Chairman, today I have described the continuum of NIDDK research efforts. This continuum encompasses promising multicenter clinical trials. It contains impressive cutting-edge research within NIH Special Emphasis Areas. It is also made up of a significant base of untargeted fundamental research involving "technologies of the future." We deploy our resources at every point on this continuum. We always recognize, however, that basic science--coupled with replenishment of a cadre of talented scientists--remains the essential underpinning of all our efforts. I am confident that this strong commitment to basic science will lead to major medical progress, which will improve the health of all Americans as we prepare for the twenty-first century.

Mr. Chairman, the budget request for NIDDK for FY 1998 is $821,164,000.

DIABETES EMPHASIS

Mr. PORTER. Thank you, Dr. Gorden, for your fine statement.

As we discussed last week, I don't want to participate in a body count approach to Institute funding allocations. I agree with the position of the NIH leadership of identifying and funding cross cutting areas of scientific emphasis. But I think it is legitimate for the committee to try to ensure that all diseases share in these areas of specific emphasis to the extent their scientific promise permits. For example, diabetes research seems to dovetail nicely with at least three of the areas of scientific emphasis: new approaches to pathogenesis, new preventive strategies and genetic medicine.

Dr. Gorden, do you plan to apply the $10 million increase in your Institute's budget for areas of special emphasis to diabetes research?

Dr. GORDEN. Yes, we certainly do, Mr. Porter. Of course, this will have to be balanced to some extent with our other programs. But certainly those areas are ones that diabetes research is included in.

Mr. PORTER. Dr. Varmus, we have already heard from the Eye, Genome and Allergy Institutes on their diabetes research. From your perspective of looking at NIH research in the aggregate, is diabetes increasingly a campus-wide effort with more institutes involved, and who are the other institute players in diabetes research?

Dr. VARMUS. Well, there have always been a large number of institutes involved in this research. In fact, I recently had a look at a report by the National Diabetes Research Coalition, which lists at the end of the document about nine offices, centers and institutes that play a role in diabetes research.

As Dr. Gorden mentioned, he and I have decided to have a workshop in the near future, not so much to hear the latest findings as to define the various areas of diabetes research, including research on diabetes complications in the kidney, the eye, and the heart. We want the fundamental aspects of diabetes research aired in a trans-institute setting so that institute directors and program officers, as well as other scientists and advocacy groups, can hear about the opportunities that exist and assess the degree to which we are adequately supporting them.

IDENTIFYING AREAS OF RESEARCH EMPHASIS

Mr. PORTER. Dr. Gorden, when the NIH leadership meets to discuss the areas of scientific emphasis that will be reflected in the budget, have you proposed new areas that would match your Institute's research portfolio well?

Dr. GORDEN. We certainly try to, Mr. Chairman. We put forward what we think are the most promising areas of research across the five or six particular categorical areas. And we believe very strongly in pursuing those areas, and we will do our very best to pursue them.

BUDGET INCREASE

Mr. PORTER. Do you think a 2.2 percent increase in your budget is sufficient to pursue them?

Dr. GORDEN. Well, it will basically permit us to continue the things that we have in motion. It will not permit us to add any really substantially new items to our research agenda without something else having to give in its place.

STRESS IN DIABETES

Mr. PORTER. Dr. Gorden, regarding type II diabetes, we often hear discussions of weight, diet, exercise and the like in reference to this form of diabetes. Has any research been done relating to stress and the ability of the individual to handle stress in their lives and whether this has a role in this disease?

Dr. GORDEN. There have been a number of studies that relate to glucose control and various aspects of stress in relationship to this. This is a somewhat difficult area to get a complete handle on. But there's no question that one's ability to care for themselves and one's ability to maintain the regimen that they are placed on is governed to some extent by what kind of stress they suffer in their lives, or they are exposed to.

Certainly, stress is something that stimulates certain endogenous functions such as the sympathetic nervous system. The sympathetic nervous system has a great deal to do with glucose homeostasis, that is, the levels of glucose in the blood. So there are lots of indirect reasons that we could relate to stress, and certainly, it's a promising and important area that we need to consider.

Mr. PORTER. Is there any research being done now in this area?

Dr. GORDEN. We have several grants that relate generally to stress and glucose control.

Mr. PORTER. Thank you, Dr. Gorden.

Mr. Wicker.

IMMUNE MODULATION IN DIABETES

Mr. WICKER. Thank you, Mr. Chairman.

Dr. Gorden, it's good to have you before the subcommittee. And members of the subcommittee will note from Dr. Gorden's vitae that he was born in Baldwyn, Mississippi, which is in the first Congressional district. And I'm mighty proud to see him testifying so well before the subcommittee.

I have a particular personal interest in the subject of diabetes, because of my little niece, Rebecca, who lives in Virginia Beach, and who was diagnosed several years ago with diabetes. She's doing quite well. She takes insulin every day.

And I guess I would want you to comment on what progress has been made in that type of diabetes. I notice in your testimony you say there's a trial that's focused on the immune modulation to halt or delay the onset of insulin dependent diabetes in high risk children and adolescents. And you mentioned knowledge gained in that regard concerning the development of highly accurate tests for predicting the risks of developing diabetes.

I wonder if you could elaborate for the subcommittee on that subject.

Dr. GORDEN. There are several aspects, Mr. Wicker. The first is that the individual who has diabetes already is one that clearly should, I think, gain an enormous comfort from a recent study

called the Diabetes Control and Complications Trial, which was one of the largest clinical studies ever conducted in diabetes research.

In fact, it was the largest. It was completed approximately three years ago. It was a multicenter trial involving 1,440 patients. It demonstrated unequivocally that careful glucose control can ameliorate or prevent the eye complications of diabetes by about 75 percent, the kidney complications by about 50 percent, and the neurologic complications by about 60 percent.

So that this is the first time that we have known that therapeutic intervention clearly can ameliorate the rate at which these complications occur. So that we can tell this young woman that there's a great future for her, in a much more solid and positive way than we could before.

This opens up the question, we now know that this is very effective. So we have two different kinds of problems. First, we have a problem related to any particular siblings that she may have. And that is, the possibility that they could develop diabetes. And so this is what this prevention trial refers to. It refers to the development of technologies to recognize children at high risk for developing diabetes. And it falls back on some really very imaginative research having to do with what we call tricking or modulating the immune system.

Now, conventionally, we use words like vaccination or immunization and that has kind of a general meaning. We know we can prevent the measles and other things like that. For diseases like diabetes, it's possible to think about it in that way. So exposing a child prone to developing diabetes to an antigen, meaning something that might be related to triggering the disease, insulin in this case, which is a somewhat complicated explanation, but this is one that is being used, could be devised in some way to block this immune response. That's what we mean by immune modulation.

That clinical trial is in effect. We have two phases of it. The second phase has just begun. So the first research issue is developing methods to recognize these children, and the second is having an intervention strategy, based on a lot of fundamental research and some results in animal models that suggest feasibility. So that's the second aspect of this pursuit.

Now, the third aspect is one that we're really in the midst of right now. And it's a terribly important area. We refer to it as the Diabetes Prevention and Treatment Initiative. Because the Diabetes Control and Complication Trial, which was so seminal in its results, doesn't tell us how to achieve its effects. And for your young niece, she takes insulin, and we know that that's a very difficult thing for her. There are a lot of things about treatment regimens that this trial has taught us that we can transfer to her to make it easier. But we know it's still difficult. We've got to close that therapeutic gap. We've got to find ways to make that treatment more achievable and easier. And that's the goal of what we're really into right now. That's a difficult area. But it's one that we must and we will pursue.

Mr. WICKER. If somehow we could have known years ago, before this little girl came down with diabetes, we could have known that she was at high risk, do we now have the technology to prevent,

do we now have the knowledge to actually prevent that child from coming down with diabetes?

Dr. GORDEN. This is the nature of the experiment. And we don't know the outcome. The only thing that I can tell you is that, in animal models that simulate the human condition, the maneuvers that we're using will prevent diabetes in these animal models. And it is that basis primarily that has led us into the human experiment. We don't know the outcome. It's too early for us to get a hint about what this is going to be.

But we're convinced that we're on the right track. We're convinced that this is an appropriate approach. If this is the wrong reagent, it's the one that is safe now and we have approval to use the forms of treatment that we're using. But there are others in the pipeline, and they may prove to be the right trigger. But this is a real thrust of research, and we think we're clearly going in the right direction. And the answer, we hope, will be a very positive one, which we clearly could not have given to you several years ago.

Mr. WICKER. As a scientist, are you willing to speculate about a time line?

Dr. GORDEN. I'm always hesitant, Mr. Wicker, because I like to talk to you as I would to a patient. And I don't want to create a sense of false hope about setting a time because I don't really know if I could deliver, and I wouldn't know quite what to say to you then.

RESTORING INSULIN PRODUCTION

Mr. WICKER. What about research in the area of restoring the defective organ, I guess it's the pancreas?

Dr. GORDEN. Yes.

Mr. WICKER. How are we doing on that?

Dr. GORDEN. There are fundamentally two approaches, each of which has a set of ramifications. First, it's clinically possible to do pancreas transplantation. It is being done, and, in fact, it works. It is not a type of transplantation that we would do, except under very special conditions. And so it's generally done in the context of kidney transplantation, which has been a great miracle for the diabetic patient.

There has been some experimentation using pancreas transplantation without kidney transplantation. But at the present time, for a child, this would involve very toxic immunosuppressive agents. Because we do have alternatives, we would not want to use that approach.

The other approach is to use what we call islet cells, that is, the insulin producing cells of the pancreas. And there are techniques to isolate those cells and there have been very successful animal experiments in which this has been carried out.

There are two fundamental problems. One problem is the immune problem, that is, the same problem you have with any transplantation where the body will attempt to reject something that it sees as foreign. That's one problem. And there's a set of approaches that are being taken to deal with that. One is some sort of shielding device that one might use. One is a sort of an immune policeman that would sit there and help guard those cells against the at-

tack by the immune system. And there are a number of examples of that that I could elaborate on.

Mr. WICKER. There you're talking about transplanting a few cells——

Dr. GORDEN. Yes.

Mr. WICKER [continuing]. Into a non-functioning organ?

Dr. GORDEN. Exactly. The cells would be transplanted into some other area, not the pancreas, where they normally exist. We put them in the liver or some other place in the body. And this is actually being done.

But just to mention the second problem. One problem there is the immune rejection, the second problem is the ability to sustain the growth of these cells. That is, these cells don't appear to like particularly being isolated themselves and growing in a sustained way. So the problem really has been not getting it to work. It does work at a clinical level, and it works in patients. But it works over a relatively short term, and we don't have very many examples where we've been able to get this to go out, say, a year. We have a few, and so that offers us an approach. So that this is an area that we continue to look at and we continue to support, and we continue to recognize the problems. It's really not moved quite as fast as we would like to see it move. But we're still encouraging this area of research. So this is something I think we will look forward to, but we can't give you, as a final clinical product.

PREVALENCE OF DIABETES

Mr. WICKER. Is it true that the number of Americans with diabetes has skyrocketed since 1983, and to what would you attribute this?

Dr. GORDEN. Well, certainly the prevalence of diabetes, that is, the total number of diabetic patients has increased. There's another term that we use, we call it incidence, which has to do with the rate of new people entering the system. We believe that this is due largely to the fact that people are healthier and living longer, there are more diabetics of an older age, that this would increase the prevalence of the disease, if diabetics are not dying at a younger age, and doesn't necessarily infer that there's an infusion of something that's causing more people to have diabetes.

We think that's relatively stable, although we do know that certain groups are more prone to develop diabetes. For example, Native Americans, Hispanic Americans, and African Americans, have a higher prevalence of diabetes. So in particular areas, particular regions where there are larger populations like this, then one will see an increase in the prevalence of diabetes, because of the population admixture.

Mr. PORTER. Thank you, Mr. Wicker.

Mr. Dickey.

Mr. DICKEY. Dr. Gorden, how are you doing?

Dr. GORDEN. Fine, thank you, sir.

Mr. DICKEY. I knew who you were, I didn't have to look at your name.

Dr. GORDEN. You could just tell when I spoke. I just wanted to get a little credit, if I could, because the Chairman wanted to be certain that I had spoken at the Rotary Club in Baldwyn, Mis-

sissippi, and Mr. Wicker and Mr. Lott can attest to the fact that I've done that. And so I want the Chairman to know that, and thank you.

Mr. DICKEY. Now, can we get on with other things?

Dr. GORDEN. That's right. [Laughter.]

FUNDING FOR DIABETES RESEARCH

Mr. DICKEY. In the last 10 years, overall funding at NIH grew by 63 percent, or 7.25 percent per year, while funding at NIDDK grew by just 40 percent or 4.95 percent a year. When diabetes is the fourth leading cause of death by disease, can you explain why NIDDK did not receive the same rate of growth as NIH as a whole?

Dr. GORDEN. Well, Mr. Dickey, I think that what's important for us and what's expected of us is to take the resources that we have and do the very best job we can. I believe that's what the Director of NIH expects of us, and I believe that's what you expect of us. And that's what we try to do.

I can't really explain beyond telling you what we're trying to do and telling you of the directions that we're trying to take, and to tell you how we're trying to make things really happen with the resources that we have, and how we're trying to augment those resources in a variety of ways.

Mr. DICKEY. Does this reflect, this reduction in your increase, your decision or your Department's decision, or is it happening without your consent or against your request?

Dr. GORDEN. Mr. Dickey, as you know, we take the appropriations that we receive that start with the Administration and end in the Congress and that's what we basically use as our resource base. We have a variety of inputs into that at various times. But as I say, in the end, I think our responsibility is to do the very best with what we have.

Mr. DICKEY. Are you saying that we as laymen could better decide how much you could spend adequately to combat——

Dr. GORDEN. No, what I'm saying is that I think our fundamental responsibility is to use the appropriation that we receive in the very best way that we can.

PROFESSIONAL JUDGMENT BUDGET

Mr. DICKEY. Have you ever asked for any more than you've received?

Dr. GORDEN. Well, we do submit a professional judgment budget at the very early phase of the process. And that budget is something that we routinely do, and it clearly is larger than the budget that we receive, so that we do clearly ask for things that we do not receive, yes, sir.

Mr. DICKEY. How much more did you ask for this year than the President's budget provided?

Dr. GORDEN. I could give you a percentage. The professional judgment budget that we submitted was an 11.4 percent increase over the 1997 budget, and our President's budget is approximately 2.23 percent. I believe that's correct. The number of dollars is $75 million.

Mr. DICKEY. Thank you.

What are you having to not do because of this 9.2 percent reduction from your request? Let me ask you this, particularly. How much of that has had to be taken away from the research that has as its target the finding of a cure for diabetes?

Dr. GORDEN. Well, I think that fundamentally, our search for the cure, as you have put it, is framed in a number of different ways. It's framed around clinical trials and it's framed around very basic research. And so it's very important that we continue some balance in these two areas.

Just to give you an example of what we've tried to do to maintain a momentum, Mr. Dickey, we were just discussing two clinical trials that we have in operation now. One is an attempt to prevent Type I or juvenile onset diabetes. We were just discussing the nature of that trial and some of the ingredients in it.

We had also discussed a trial called the Diabetes Control and Complications Trial, which was a major multicenter trial, which was very expensive. We knew that we could not begin new trials until we ended the first trial, because of the expense of this trial. As that trial ended, we began to focus on what we were going to do next, and how we were going to focus that money.

So we planned on two separate clinical trials, one in non-insulin dependent diabetes, the adult onset diabetes which we had further developed and had this ready to go. But then, our basic science research was really showing some promise, and indicated some ways that we might interdict the process of Type I, the juvenile onset diabetes.

Now, what do we do? We felt we needed to go ahead and do a study of Type I. We basically put a plan into motion. We asked two institutes to help us, the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases. We asked the Juvenile Diabetes Foundation, the American Diabetes Association, and we asked for some industry support. We told them why we wanted to do this and what this was all about, and we received support.

Then we got to the Type II trial. We actually had just received, in addition to this kind of support, funds from two different NIH Institutes, just to give you a flavor of the multi-institute collaboration, and the way that we go about trying to get things done. We've completed a negotiation with industry because of a new drug that has just been approved by the FDA, which we think has a great promise in treating diabetes, and in possibly preventing Type II diabetes. But we had no budget to include that trial. So we went to industry. We told them what we wanted to do; we said it would be very important to include them in our trial. And we've used the Federal Technology Transfer Act to achieve that kind of balance, so that we can address some of the concerns that they have.

My major point is that diabetes is a very difficult problem. There are many people who suffer from it. There are children, adults, and their families. Research needs to be supported.

Our responsibility is to get things done across NIH and within our Institute. We're the lead Institute for diabetes research. It's our responsibility to get things done. We feel that's our responsibility to you and to the Director of NIH. And that's the way we're trying to do it.

Now, there's no question that we need resources and we certainly want to emphasize the fact that that continues to be important. Because it's a very, very mature and very moving research agenda.

GENETICS OF DIABETES

Mr. DICKEY. What is the state of research into the genetics of diabetes?

Dr. GORDEN. We've made several, I think, important discoveries. Sometimes when we use the word diabetes, it sounds as if we're talking about a single thing. When we talk about, say, high cholesterol or high blood pressure, we think we're talking sometimes about a single disease. In fact, these are manifestations of multiple different kinds of things, and so is diabetes.

So we broadly separate diabetes into, we call it insulin-dependent Type I and non-insulin dependent Type II diabetes, and that, there are two different diseases. But the blood sugar goes up and there are complications in the eye and the kidney and the nerves that are the same. And that seems to be a sequel to the fact that the blood sugar is very high and it's not what the body is accustomed to having.

So there are different sets of genes involved in these two different conditions. So we've made a lot of progress in identifying the locus, that is, the place in the human genome that these genes exist. And to some extent, we've identified genes in Type I diabetes.

In Type II diabetes, we've identified at least four causes, that is, we've identified the insulin receptor, which is a major component of how insulin works, as a genetic abnormality in diabetes. In the last year, we've identified three genes in what's called "Maturity Onset Diabetes of the young."

And we've also made, I think, as much progress in the area of what we call "complex genetic diseases." When we talk to you about a disease like cystic fibrosis, this disease is due to a single gene. You injure that gene and you have this disease.

Non-insulin dependent diabetes seems to be a complex genetic disorder, that is, you have susceptibility areas that get weakened within the genome. And there may be three, there may be five, there may be ten. We really don't know.

But we've made progress in beginning to try to identify where some of these genes are, and we think we have an approach to this. And so it's a terribly important area, it's one that's very important in hypertension and Alzheimer's disease and depression. Those are diseases that are fundamentally this type of complex genetic disorder. And I think that is one that we're clearly in the forefront of, but it's one that we can't sort of bring to final fruition right now.

DIABETES EDUCATION PROGRAM

Mr. DICKEY. I understand that NIH will be participating in the diabetes education program. What additional funds will be needed to carry out this important endeavor,and will the funds be taken out of diabetes research?

Dr. GORDEN. What we've done, Mr. Dickey, as I mentioned, at the completion in 1993 of the Diabetes Control and Complications Trial, which showed such a dramatic effect on control, that is, how you control your blood sugar, we began to hear from the community

we felt that there was a need for us to develop models similar to what had been developed in cholesterol and hypertension, which had been so successful. We started what we called an "outreach program," and we started in a small way to deal with aspects of diabetic foot care.

But in the last year, we have sort of begun to call this an "education program," and we have put funds in it up to approximately $1 million. We have also gotten co-funding from the CDC for this project. And we're looking for some other support. We think it's very important to get this message out to the public and to the practicing physicians about the importance of glucose control.

And so yes, funds for everything we do come from essentially the same place. So this program does affect our research budget. And we're trying to do this in a measured way, so that we can really achieve the most practical effect from it with the least impact on our research budget possible. We have clearly got it moving, and we will build on it as we have the opportunity to build on it.

Mr. PORTER. Thank you, Mr. Dickey. Did you have a follow-up question, a short one?

Mr. DICKEY. Mr. Chairman, I don't have any more questions.

Mr. PORTER. Well, I would say to members, the ones who were here early like Mr. Dickey got extra time, you got 13 minutes, Mr. Dickey.

Mrs. Lowey.

SPECIAL RESEARCH AREAS IN DIABETES

Mrs. LOWEY. Thank you, Mr. Chairman.

And I do want to apologize to you, Dr. Gorden, Dr. Varmus and colleagues, for being detained. But I'm delighted to be here today.

One of the questions I'd like to begin with is whether you think there are any particular areas of research in diabetes that deserve special emphasis that currently are underfunded.

Dr. GORDEN. Well, there are a number of areas, and we've talked about two fundamental areas, that is the clinical science arena, the numbers of clinical trials we have, and the sort of basic science arena. As I mentioned in my statement, this sort of continuum which is, and diabetes research is well-represented by that, from the very fundamental basic science.

And we have certain areas, as everyone does, where opportunities sort of lend themselves to more immediate application and some that move at different rates. So that it's difficult, there are certain areas that we were talking about before that have to do with prevention and treatment. These are very important areas for us to pursue.

UPCOMING DIABETES CONFERENCE

And one of the things that we plan to do in the very near future, Dr. Varmus and I plan to co-sponsor a conference in which multiple NIH Institutes, which are involved in diabetes research, will be present, and we will interface, essentially, with leaders in the diabetes research community that relate to all these different components that we have and other Institutes have.

And we'd like to kind of see what the meeting of the minds would bring out. We clearly have an agenda that is ongoing. We'd like to

see where that agenda perhaps ought to be turned or moved or enhanced in one way or another. And this would be one of the important goals of this particular conference that we will certainly be talking to you about more in the future.

LOCATING DIABETES INFORMATION

Mrs. LOWEY. One of the questions I have asked in past years is whether there is, is there a national directory, does NIH actually have a directory of research projects? The response I have gotten in past years is that there are forms and people who are working in an individual area, whether through the internet or their own journals, really know what other people are working on.

But is there any national directory, I would say, for all research, or for diabetes research, so that you really have a handle on who is doing what?

Dr. GORDEN. NIDDK is the lead Institute for diabetes research. We have a home page in which one can feed into and really get a great deal of the information base that either would give you the information that you would be seeking or lead you in a direction in which you could get that information. I think most Institutes do have that kind of facility available. And I think that now that this sort of thing is being utilized more and more, this is probably a good avenue for one to approach this. It would be difficult to sort of encompass all of NIH research in one place. I think it would have to be decentralized to some extent.

But as long as one would simply focus on where the lead application of that kind of research was coming from, I think one could easily get that information.

Dr. VARMUS. Could I interject a note of caution here? Many people are interested in the idea of assembling all the people and information available regarding any specific research area. I think one has to be very careful about the purpose of such an aggregation of information. Because it's very expensive to put it together, very hard to keep it updated. One also has to be very careful about the purpose of such a data base. If it's simply to identify the investigators around the country who are working on diabetes in order to send out newsletters, that's fine. If it's an attempt to keep up the complete repertoire of ongoing projects and results, it would become extremely burdensome to investigators. It's very difficult to coordinate centrally and, frankly, not as useful as having national meetings on diabetes to which investigators go.

WOMEN'S HEALTH

Mrs. LOWEY. Thank you, Dr. Varmus and Dr. Gorden.

I'm also interested in an update on the status of your research collaboration with the Office of Research on Women's Health, which is looking at cardiovascular disease in women with Type I diabetes. I understand that this is a long-term study, but can you tell us what progress has been made thus far, and what you hope to accomplish in the coming year.

Dr. GORDEN. Yes. we were talking about our Diabetes Control and Complications Trial just a moment ago. And we have a program in which we are following all of those patients. And one of the important things that this particular project is involved in is

studying what we refer to as macrovascular disease. And one of the initial thrusts of this project was to get a baseline measurement of this population that we continue to follow, that we call carotid ultrasound, to get some idea of the vessel status of those individuals as they have been treated with these different regimens. That initial measurement has been made. It has been made with the resources that we received from the Office of Research on Women's Health. And we plan to continue that, both the collaboration with them and this project. And it is a very active, ongoing project in which we have many other things to do. And it's one that we're pursuing with some vigor.

ARTIFICIAL PANCREAS

Mrs. LOWEY. I thank you. And lastly, what is the status of efforts to perfect a biomedical pancreas, which would enable people with insulin-dependent diabetes to make their own glucose, in medical terminology, to achieve——

Dr. GORDEN. Euglycemia.

Mrs. LOWEY. Okay, euglycemia.

Dr. GORDEN. Good.

Mrs. LOWEY. Thank you.

Dr. GORDEN. This is an area that relates to finding ways to take cells that make insulin, islet cells that make insulin, and do two things. One is to find ways to protect them from the immune system, so that when they're put into an individual, they will not be recognized as foreign. And the second goal of this research is to find ways to get these cells to grow in a sustained way over a long period of time.

And these are two areas, there are a variety of techniques, some very basic, that are very interesting, that are being used for immune protection. Some have to do with the co-expression of cells that can serve as sort of "policemen" in a sense, and guard these transplanted cells from the immune system. Some involve mechanical encapsulation devices. And some involve still other types of technology. So this is an area that is actively being explored. But at the present time, it only has a relatively limited clinical application with respect to long-term results. So we're continuing to try, and we're continuing to press this area. But we are not able to present it as a therapy that would be available to someone tomorrow.

Mrs. LOWEY. Thank you, Dr. Gorden.

Thank you, Mr. Chairman.

Mr. PORTER. The gentlelady returns one minute of her time.

Mrs. LOWEY. Oh, I'll take it. [Laughter.]

COSTS OF TREATING DIABETES

Mrs. LOWEY. Actually, I remember a few years ago, one of my constituents testified before this committee and talked about the extraordinary expense that she faced with her daughter in being diagnosed for juvenile diabetes. And I was thinking about that this morning, wondering, with the impact of managed care, how has that affected this process? She was talking about something like $25,000, it still rings in my head, because it was so amazing to me.

But I assume this included a whole battery of tests and the other procedures that had to be taken. And she said that she retired from her job to take care of her young child, but thank goodness, she had that insurance while this battery of tests was being done.

Do you have any first-hand information on that? Have the tests gotten cheaper? Or how has one fared under managed care with this, based upon your information?

Dr. GORDEN. Well, we would certainly hope that the message that managed care would receive is that this treatment works, and this treatment reduces the complications of the disease. And if a managed care company plans to have an individual as one of its clients for a number of years, it would be cost-effective for the managed care company to permit that patient to use the most modern facilities, and resources that are available. And we have actually some quantitative data to show the cost-effectiveness of that approach. And looking at the difference in cost of say, equipment, for more conventional treatment versus what we would call intensive treatment.

And we have data to show that the increase in initial costs is more than offset by the savings that one has in the morbidity of the complications of the disease. That's the message that we're giving managed care. And I have the sense that that's being heard. We certainly have seemed to have gotten the message into the Medicare system. And I think that there are a variety of efforts that are being made to do that.

And the feedback that we're getting suggests to us that this is really having an effect. So I can't answer your question completely, certainly, for every managed care orgainzation. But, I think the message is clear, and I think we will continue to press that message. And I'm very optimistic that that's going to be heard, and that they will understand that.

Mrs. LOWEY. Are the costs still so high? I was amazed at that initial diagnostic work and treatment.

Dr. GORDEN. It would depend to some extent on what you're actually including. If you were to truly take the measures that were used in this trial, it may approach those costs. Our estimates are something under $5,000 for intensive treatment. But then it would depend to some extent on the numbers of people who were involved. Is there a dietician; is there a nurse practitioner; is there another trial coordinator of some kind helping manage your care?

So one could imagine that this could, and also depending on where you are in the country, costs could range up to perhaps what you say. But it depends on this constellation of things.

Mrs. LOWEY. Thank you.

Thank you, Mr. Chairman, for that additional minute.

Mr. PORTER. It ended up being an additional four minutes. [Laughter.]

INTRAMURAL RESEARCH

Mr. PORTER. Mr. Miller.

Mr. MILLER. I'd like to take a few minutes to get a better understanding, in a more generalized question, but using your Institute to understand better intramural versus extramural, and the role of

the small business setaside. And again, I'm just trying to get a grasp of the issue. Dr. Varmus may want to chime in here.

A little bit over 10 percent goes to intramural research?

Dr. GORDEN. Eleven point four percent, yes.

Mr. MILLER. For your Institute?

Dr. GORDEN. For our Institute.

Mr. MILLER. What is the average for the entire NIH?

Dr. VARMUS. Well, it was 11.3 percent when I came on board, and now it's about 10.5 percent.

Mr. MILLER. Is it basically all in Bethesda, or is that nationwide?

Dr. GORDEN. We have two components. Our major component is in Bethesda, and we have another very significant component in Phoenix, Arizona, a study in diabetes. This is located at the Phoenix Indian Hospital, and is involved in a longitudinal study and clinical studies of the Pima Indians, that have the highest prevalence of diabetes in the world.

And so this has been an extremely productive study in which we can follow the population of patients and follow them over time, and also study genetic factors and what we call pathophysiology, the sequence of events that develop in the individual before they develop diabetes, during the intermediate phase and, finally, what happens when they develop the full-blown disease.

So this has been an extremely valuable resource. We have done this in collaboration with the Indian Health Service. And it's worked out extremely well for us over a long time. It's extremely highly regarded internationally.

Mr. MILLER. How much money do you spend in that program, for example?

Dr. GORDEN. Let's see if we could give you a reasonably accurate number. It's about $7.5 million a year.

Mr. MILLER. Okay, out of your $90 million.

In making intramural decisions, do you start new programs versus phasing out current studies? And have you phased out any to conclusion and say, we really want to start a new program? How do you go about making that decision and have you made any such decisions?

INTRAMURAL DECISION-MAKING

Dr. GORDEN. Yes. We make those decisions all the time. It's a continuous process. It works in several ways. In our Institute, and in I think most NIH Institutes, we have a division of intramural research, and we have a director of that division. And we depend very much on that individual to help guide and advise about how that ought to be and where resources should be put. Should we put more resources here and less resources there? This is a continuous process. We have a Board of Scientific Counselors that meets on a regular basis to review all of our laboratories in a continuous way. We take their review and their advice and we put it together with our own sense and assessments.

I meet on a very regular basis, having been part of the intramural program for many years myself, with the Director of Intramural Research. And we forge a program collectively with the advice of the Board of Scientific Counselors, and with the advice of a number of other people, including our National Advisory Council,

who are briefed on a regular basis about the activities in the intramural program.

So that we will make a major commitment to enhance promising areas. As an example, we have perhaps one of the leading structural biology programs in the world. We have garnered a group of people who are world class, and they are using the most advanced technology that is available.

For us to support that, it means that that has to be a very high priority, because this is very expensive. We have to really know that this is productive. And so that this facility has a major trans-NIH presence, everyone, not only just on the NIH campus, but essentially nationally and internationally, knows about this group and what they do. That's a kind of a fundamental commitment that we will make to enhance a particular area.

We also make it a point to keep abreast of our clinical activities. We have clinical activities in diabetes, digestive and kidney diseases, and nutrition and areas that represent the sort of fundamental mission of the Institute.

And we're constantly looking at ways to enhance those. We're very much a part of the new NIH Clinical Research Center. We're very active participants in the Clinical Center, so our Institute should be one that has a very strong clinical presence. We have done a number of pilot studies or sort of inventive types of clinical studies that have come out of our intramural program, a number of which I could discuss.

Mr. MILLER. So that you'll start them there and then——

Dr. GORDEN. Absolutely. A very good example would be, in sickle cell disease, in which we started a program to use a particular compound to enhance hemoglobin concentration in individuals with sickle cell disease. We have a very talented investigator who began those programs as part of a clinical pilot study. That was so successful that it then translated into a multi-institution study that was primarily sponsored by the Heart, Lung and Blood Institute.

We've done this with the treatment of hepatitis, where we made pivotal observations about the use of certain drugs like interferon. Then multicenter clinical trials have been sponsored by the National Institute of Allergy and Infectious Diseases.

So the intramural program has been a resource in which we can rapidly move into clinical and fundamental areas, and then we can exploit those either ourselves, or with our colleagues in other Institutes.

Mr. MILLER. You have the same job as Dr. Varmus has, you have to allocate limited resources and make those tough choices, as we do up here, too.

Dr. GORDEN. Absolutely.

SMALL BUSINESS RESEARCH

Mr. MILLER. So I respect that.

May I ask one more little set of questions, and that is the small business set-aside. I'm just trying to get a better understanding of it, rather than questioning everything you're doing. How much is there in that area? What is the total amount of money in your budget that's in effect a small business setaside? Dr. Varmus, we talked about it briefly on the telephone before these hearings.

Dr. GORDEN. The percentage in the 1997 budget is 2.5 percent. That is the official percentage. The actual dollar amount for NIDDK is $17,878,000.

Mr. MILLER. Okay, because I was just looking at the—on this book here for the 1997 fiscal year SBIR is $15,878,000 under research projects.

Dr. GORDEN. Right.

Mr. MILLER. And then you drop farther down and I see the $23 million. I'm trying to figure the difference.

Dr. GORDEN. It falls into two categories, which to some extent get a little bit blurred. But we do categorize them as grants and contracts. In our case, we have $15.8 million in grants and $2 million in contracts, which is the total that I gave you for fiscal year 1997. That's the $17,878,000 of the total of those two.

And just as an example, Mr. Miller, of what we were just talking about in answering Mrs. Lowey's question about devices for treatment of diabetes, we would like very much to see the encapsulation devices, how we grow cells, how we use this sort of resource, we would like very much to see this go into industry. We would like to stimulate industry to do this in the whole glucose monitoring area, where we're trying to develop devices to measure glucose.

We have devices now that are somewhat detached from the person that we use, strips and things to measure glucose control. This type of device development we would very much like to steer towards small business. And we make a very big effort.

The recent work with the obesity gene has had an explosion in the biotechnology industry. We would like to see more of our small business resources go into those really promising areas. And we make a great attempt to see that happen.

Mr. MILLER. Has the quality of your small business applicants improved in recent years? There's been a concern that they don't rate as high. You have a difficult time because your demand for grants is far greater than the money you have available. Have you seen an improvement?

In addition to that question, answer this and then I'll conclude. Basically, the small business all goes to the private sector, I assume?

Dr. GORDEN. Yes.

Mr. MILLER. The rest of extramural, what percentage of that goes to the private sector versus the non-profit academic sector?

Dr. GORDEN. 100 percent of this goes into industry, small business.

Mr. MILLER. Right.

Dr. GORDEN. In the area of the non-small business funds, the vast majority goes to either research institutions that are either academically affiliated, but are generally non-profit institutions, or to academic institutions. I can't give you an exact number. I could try to get that for you. I don't have an exact number. All I could do is give you a qualitative answer. Clearly, the vast majority goes to research institutes, or to academic institutions.

Mr. MILLER. Do the big pharmaceutical companies get NIH grants, like a Merck or somebody?

Dr. VARMUS. Extremely small. Not Merck, as far as I know. It's almost all small business.

Mr. MILLER. So the remainder of extramural basically goes to the non-profit sector, or research institutes and all that?

Dr. GORDEN. Yes.

Mr. MILLER. So there's a very small amount that would fall in that area.

Dr. GORDEN. Right.

Mr. MILLER. Thank you.

Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Miller.

We're delighted our ranking member, Mr. Obey, can join us. He is ranking on the entire Appropriations Committee, and it means he has responsibility for 13 subcommittees, and his time is very, very dear. So you're recognized.

Mr. OBEY. Thank you, Mr. Chairman.

I apologize for not being here. We've got three Cabinet Secretaries up here today, and we have a Democratic caucus, which was absolutely fruitless to attend, but I did anyway. [Laughter.]

Mr. OBEY. I hope you are not going any better. [Laughter.]

ULCERS

Mr. OBEY. Let me just ask one question about ulcers. Can you tell us, what is the status of our knowledge now with respect to ulcer causation and treatment? I know in the old days, people used to think, they used to try to reduce tension, take plenty of Maalox, all the rest. Now we've discovered that the significant portion of the problem is bacterial.

How would you sum up what we now understand about that problem?

Dr. GORDEN. I would say first, Mr. Obey, it's really one of the seminal events in medical research, to make a discovery of the real cause of a disease. With respect to duodenal and gastric ulcer, we believe that there is a very, very strong correlation with this bacterium, H. pylori, and that it is the etiologic or causative base of most ulcers with perhaps two exceptions. Those exceptions are the ulcers that occur in the context of the so-called non-steroidal anti-inflammatory drugs that people take for arthritis or pains. The Motrin type of drugs or that general nature, or aspirin. Those drugs lead to ulcers in a certain proportion of patients.

There's another relatively uncommon but very important tumor that produces a substance, gastrin, which causes the gastric acid to go very high. And that is another important cause, although relatively rare.

So those two, with those two exceptions, we believe most or all peptic ulcers are associated with helicobactor. And the most remarkable thing about it is that this has been a chronic disease, that is, we could treat it and we had, as you pointed out, Maalox, and we even had better things than that. We had drugs, such as Zantac, we had acid blocking drugs that were actually very good.

But what those drugs did was control a chronic disease. Now what we've done is taken a chronic disease and converted it to an acute disease. That's really something we'd like to do with a lot of things. Because now, we can treat ulcers for two weeks as an acute illness, and we believe we can completely eradicate peptic ulcer disease.

Mr. OBEY. What percentages are you talking about?

Dr. GORDEN. We believe we can eradicate——

Mr. OBEY. No, I mean the percentage of ulcers that are caused by that problem.

Dr. GORDEN. I would say that the percentage is about 85 percent is caused by the H. pylori process, and about 15 to 20 percent are this other category, which are associated with non-steroidals and aspirin and other drugs of that nature. And this syndrome called Zollinger-Ellison syndrome. Those ulcers will not be affected by the H pylori treatment.

NUTRITION

Mr. OBEY. Mr. Chairman, just one other question. And maybe Dr. Varmus would like to comment on this, because it goes beyond your Institute.

I often have constituents express confusion, and my wife, who's interested in nutrition, also expresses it. The confusion people have with respect to dietary recommendations, because they often seem to be conflicting in terms of what reduces the chance or what increases the chance of cancer, versus what increases the chance of other diseases, including heart disease.

What can you say with respect to those tradeoffs, and what we know about them and what wise people would do?

Dr. VARMUS. I'll just make one brief, general comment and then turn it over to Dr. Gorden, whose Institute has a coordinating office on nutrition that is overseeing a lot of these activities.

Attempting to correlate diet with disease has been traditionally one of the trickier areas in epidemiology. That is so in part because the attempts to assign a pathological effect to a certain kind of diet tends to be based on fairly small effects. And such effects are very difficult to substantiate unless you use very large populations in multiple studies, because many other variables affect the population: where they're living, other aspects of lifestyle, genetic composition of the population, and so forth.

That being said, there are nevertheless some clear indicators that have developed with respect to the role of fat in the causation of coronary artery disease, especially in the generation of late onset diabetes, and perhaps in the causation of certain cancers, particularly cancer of the colon.

Do you want to comment?

Dr. GORDEN. I think that it is a complicated area, and I think that, with respect to the Federal Government, there's been an attempt to try to channel what is usually referred to as "a single voice," that is, between the Department of Agriculture, that has a major input, and the Department of Health and Human Services, including the NIH, which has a major input.

So that as Dr. Varmus says, there are certain fundamental things that can be recommended. That issue I think is the clearest one. The weight issue is very clear. In other words, dietary guidelines that would help people maintain a normal weight, that's a very clear guideline.

We have supported in the past something called the RDA, the Recommended Dietary Allowances. And the recommended dietary allowance is the amount of a nutrient, either a vitamin or other nu-

trient, that is consistent with a healthy lifestyle, so that there are a variety of things that are there, but there are also a variety of opinions about different things.

And sometimes it has to do with food additives and whether we should be adding things. And sometimes, as Dr. Varmus mentions, the epidemiologic studies with food suggest certain kinds of things that don't turn out to be true when you purify a particular substance. Beta carotene would be an example.

These are the things I think that lead to tremendous confusion. And of course, there's a lot of advertising and things that people are constantly being barraged with. It is a very difficult area. I think we need to constantly try to produce the very best science we can, and then we need to basically find ways to translate that in a meaningful way. And I think it continues to be an ongoing struggle. You're absolutely correct in pointing out the confusion.

EFFECTS OF ALCOHOL

Mr. OBEY. I swear to God, any time that there's any study at all that relates to alcohol, the networks have it and trumpet it. What do we know about the "beneficial" versus negative effects of alcohol, example, wine?

Dr. GORDEN. Well, of course, there was always tremendous reluctance to add alcohol into the Federal dietary guidelines.

Mr. OBEY. I'm not suggesting that. [Laughter.]

Dr. GORDEN. Well, no, in fact it actually has been added into the Federal dietary guidelines. But of course, the major concern is that when you recommend something at a given level, it gets exaggerated, and then all of a sudden, it becomes something that, if you take a little bit, and that is good, then if you take a lot of it, it must really be good. This is really a problem.

There does appear to be some basis for a benefit of alcohol with respect to say, cardiovascular disease. We do have some evidence to support the notion that there's a so-called good and bad cholesterol. The so-called LDL, which is referred to as bad cholesterol, and HDL is referred to as good cholesterol. Alcohol actually has a component of stimulating the good cholesterol.

Now, that ought to be good, and there have been some studies to demonstrate that a modest intake of alcohol actually will improve cardiovascular outcome. And this is the basis for this sort of recommendation. And of course, as you say, it is very easy to get confused.

Mr. OBEY. What about counterbalancing that with the concerns that alcohol causes cancer?

Dr. GORDEN. This is the real concern, because we certainly know the morbidity that alcohol can cause in so many ways, in terms of morbidity of liver disease, accidents, on and on. This is the problem with this sort of recommendation and this is why there's been so much reluctance to make this kind of recommendation.

Dr. VARMUS. One of the difficulties here is defining what's meant by moderate alcohol use. That was sometimes considered to be one or two drinks a day. Dr. Gordis informs me that there is increasing evidence that as few as one or two drinks a week may have beneficial effects. It's obviously important to determine what is actually required to get the modest beneficial cardiovascular effects.

Mr. OBEY. Are there any studies that compare the benefits that accrue from that with the negatives on the cancer side?

Dr. GORDEN. I don't think most of the studies have been done to do exactly what you say, but have been done to actually try to show the efficacy of what we refer to as moderate alcohol intake. They have not been done to try to show the other side, that is, what if you exceed what we call moderate.

I don't know of studies that would actually point to that. I think people have just simply accepted that excess alcohol has a major risk and have not really gone into the comparative studies.

Dr. VARMUS. The problem here, as elsewhere, is defining very low risk levels. When the dose is very low, it's very hard to say whether there's no effect or a small effect on cancer incidence.

H. PYLORI APPLICATIONS

Mr. OBEY. Thank you, Mr. Chairman.

Mr. PORTER. Thank you, Mr. Obey.

Going back to *H. pylori,* some in the clinical research communities cite the *H. pylori* case as an example of what they see as NIH's reluctance to fund clinical research, because the researcher involved was repeatedly turned down for NIH funding. Why do you think this research didn't fare well in peer review?

Dr. GORDEN. It's a little bit difficult to answer that question. I can give you certain, I guess, conventional answers. We're talking about basically Dr. Barry Marshall, who did apply for several NIH grants and did not receive them.

Dr. Marshall, of course, is responsible for a major discovery, that the bacterium *H. pylori* causes most ulcers. The fact that the grants were not awarded has to do with the fact that we depend largely for advice from expert panels on how we make awards. The fact that they weren't awarded means that we did not get promising reports from these expert panels.

But I'd like to say, Mr. Chairman, that this is something that is a fact and something that we're not very proud of, and I hope that this would not convey the idea that this is representative. This is clearly an aberration. It's a major aberration. And we can point to many other areas in which we as an organization or as an institution should be wiser than our expert panels. I don't for one minute accept that as an excuse. But it did happen.

And I believe that we have to learn from that example, and hope that we can do better in the future.

I think that many of the things that this related to were sort of fundamental observations. And I'm not really sure that this would be an example of any sort of negative aspect of the peer review system on clinical research. Because I think this was a failure of both the study section, the expert panel; council, which is the second level of peer review; and the Institute, including myself, to recognize this sort of thing.

All of us basically can serve as a checkpoint. And we all are responsible for being certain of support for clinical research. So this is clearly an aberration. It is certainly an embarrassment, and we have to accept that and accept responsibility for it.

Mr. PORTER. I didn't mean to suggest otherwise. I just meant to suggest that it probably is a learning process for everyone.

Dr. GORDEN. Yes, absolutely.

The conventional answer is that the grant was really not well constructed. It may very well be that the way the grant was constructed that it really wouldn't lead to any practical significance, and that one could argue that.

On the other hand, I think we have to be a little wiser than that, and we are many times, when we look at something, we say, this is really a grant that's not constructed well, but we have a responsibility to try to get this reconstructed in some way that will be more acceptable. So I think that we do this all the time.

Mr. PORTER. I believe that Dr. Varmus has told me a major effort is underway to do exactly that.

Dr. VARMUS. Well, let me comment about the notion that this might be indicative of a general pattern of not funding clinical research. As you know, I've been very responsive to the claims by the clinical research community that we're undervaluing their efforts. And the NIH clinical research panel, headed by David Nathan, has been looking carefully at the extent to which we support clinical research.

There clearly are difficulties and things that need to be repaired in that area. But one of the surprises, I think, to everybody is the very large segment of our research portfolio that is in the clinical arena. The number is something on the order of 30 percent.

Dr. GORDEN. And certainly, that's quite representative of NIDDK where we have 30 to 35 percent. So it wasn't in any way a deviation from our clinical research that had to do with this. This is clearly an aberration.

ULCER DIAGNOSIS AND TREATMENT

Mr. PORTER. Do you expect to see an increase in *H. pylori* diagnosis with the availability of the new breath test, which is cheaper and less invasive than the current diagnostic methods?

Dr. GORDEN. Yes, we certainly think that this would be a valuable tool. The other advantage of the breath test, there are really three ways to detect *H. pylori.* One is by an antibody test. The other is by endoscopy and actually biopsy. And the third is the breath test. And the breath test actually detects active infection. It's simple and straightforward, it's non-invasive.

And we think that it will have an extremely positive effect on detection and just working out what we need to do about *H. pylori* in general. We have a considerable discussion going on about the whole issue of *H. pylori*'s role in ulcer disease.

Mr. PORTER. Today many of the things that were previously used as treatments for peptic ulcer are now on the market as non-prescription drugs like Pepcid AC and Zantac and there are so many of them, they advertise so heavily you can hardly keep up with them. Do you think that has given a kind of a alternate message as to the cause of peptic ulcer, and what's your sense of how widely known the *H. pylori* finding is by both practitioners and patients?

Dr. GORDEN. Well, Mr. Porter, one of the things that we did when we all began to recognize the importance of *H. pylori,* I think Dr. Varmus mentioned this in his opening statement, is we held a consensus conference. And one of the purposes of this consensus

conference was to really put a national imprimatur on the importance of this discovery and how ulcer can be treated.

And I think it had an enormous effect. The feedback we get suggests that it was perhaps the timing, whatever reason, it had an extremely positive effect. We think throughout the digestive disease community that this is part of the culture of the physician. We believe that this is permeating very much the entire medical practice community in a very significant way.

Now, there are other issues here that are under intense discussion. Now, many of the reasons that people take the kinds of drugs that you mentioned are really not due to peptic ulcer. They are due to conditions that we call non-ulcer dyspepsia. We don't know exactly what that is. But we know it is a syndrome that simulates the symptoms of an ulcer. It may be pain, it may be bloating, it may be a variety of symptoms. And that this is the reason that people are taking this.

We're looking into the question of now if individuals come in with this sort of a general diagnosis, should they be screened for helicobactor, and if there's evidence, say, from the breath test, should all these people be treated? These are things that are being actively discussed now.

But it's not the issue of ulcer. I think that knowledge really has penetrated very much into the community. It is the ancillary, other conditions that we're not certain, about the effect of the relationship of *H. pylori* to these conditions in which they simulate the same symptoms. And I think we'll come out with a sensible kind of recommendation that will take a little bit longer to percolate through the community Because it won't be quite as straightforward as the ulcer recommendation, which I think has really penetrated to a very significant extent.

Mr. PORTER. I was thinking more of the patient community and people taking these kinds of readily available drugs, which provide them some relief from a peptic ulcer, but never allow them to get to a physician and receive a real cure.

Dr. GORDEN. I think there is a risk of that. And what we're encouraging is, if someone has something that's sustained for several weeks to several months, that that is the time they really should stop the self-medication and actually see a physician, and that we would hope then to have the broad practice community sort of channeled into this whole notion of the possible relationship of *H. pylori* to that condition.

But I think it's a little bit tricky, and there are some problems related to the over-the-counter medication. But we believe that the more people become aware, the better this will work itself out.

DRUGS THAT WORK SELECTIVELY

Mr. PORTER. The science section of yesterday's *New York Times* described interesting work underway to produce custom designed drugs that would offer many of the benefits of estrogen, without the risks that dissuade many women from taking it. We discussed yesterday the dilemma women face in deciding whether to take estrogen to prevent osteoporosis and heart disease, but risk breast and uterine cancer. When will these new designer drugs be available to relieve women of this difficult decision?

Dr. GORDEN. This is again one of these really modern kinds of miracles of science. Our endocrine program has been involved in the study of how steroid hormones work for a number of years. Estrogen falls into the class of steroid hormones. And previously, it was thought that estrogen and the receptor for estrogen bind each other and you give a signal and that's sort of an all or none signal, that you don't modify that signal.

It's becoming clear through a number of studies that it's not quite that simple, that there's a whole constellation of things that go on when that signal in these two proteins come together. And they have to do with things that are called co-factors and co-stimulators and repressors and certain other terminology that's used.

So it turns out that this receptor, this estrogen receptor, has a certain kind of plasticity. And the conformation of this receptor seems to be able to communicate different things, and we might then be able to make this much more tissue-specific. That is, what we would like is to generate positive effects in the cardiovascular system and in bone, and actually to not have those effects occur in, say, uterus and breast, which is the major concern.

And it would certainly appear that we have the wherewithal to do that, there are a variety of either agonists or antagonists or other kinds of reagents that are being looked at now. And this is really, I think, an extremely active area of research that we're involved in and several other Institutes are involved in. And it goes beyond estrogen. It certainly goes to the whole cascade of steroidal hormones, so that one could begin to see implications for prostate cancer and other cancers, which we know are hormone—responsive types of cancer. So I think the ramifications of this are enormous.

DIGESTIVE DISEASES

Mr. PORTER. Research indicates that a group of peptides known as trefoil proteins act to repair various forms of gastrointestinal tract injury. They are being studied for possible use in preventing the ulcers that are sometimes the result of prolonged use of anti-inflammatory drugs. Would these drugs also potentially treat other gastrointestinal inflammations, like the inflammatory bowel disease?

Dr. GORDEN. We certainly have a lot of preliminary evidence that that may be true. These are natural products that are stimulated when the intestine needs to repair itself. They seem to be involved in both the protection and reparative processes. And as I mentioned earlier, this technology involves so-called "knockout genes," where you could actually eliminate this particular protein. It has several different forms. If you eliminate one form it does one thing, another form, it does another.

It seems that, when you eliminate it and don't allow it to be expressed, certain types of intestinal injury take place in terms of inflammation. When you eliminate another form of this trefoil peptide, neoplasia or cancer seems to occur.

So we think that this is an extremely promising clue to the mediation of gastrointestinal injury. You allude to the non-steroidal anti-inflammatory drugs and how they injure or have the potential

to injure mucosal linings. We think that this is, we would say it is in sort of a pre-clinical stage, that is, pre-clinical testing.

But we would imagine that this kind of approach would very rapidly move into some sort of drug development program in the near future. This is being primarily spearheaded from our Digestive Diseases Center in Boston, among other places. But we have indications from them that this is likely to be the case.

UROLOGY

Mr. PORTER. Dr. Gorden, you and NIH have been under pressure for some time from the advocacy groups to establish a new study section dedicated to urology or to increase the number of urologists in existing study sections. An innovative pilot study is underway to address these concerns. Can you describe this effort, and give us your impression of how it is working?

Dr. GORDEN. Yes. There's been considerable discussion with the Division of Research Grants. We had the new Director of the Division of Research Grants, Dr. Ehrenfeld, meet with our National Advisory Council the last time we met. And I think we're making a considerable amount of progress. One of the possible solutions for the concerns of urologists that they're not being totally represented within the context of these review groups is to have what we call a "special emphasis panel," in which we might, say, take a set or subset of grants that are generally related to urology and have specific time receipt for them, so that they would be reviewed perhaps somewhat less frequently than in the routine study sections.

But this would permit a larger aggregation of these grants to be reviewed at one time. And this has been piloted, and we have seen the result of it. And my impression is that the urology community is very pleased, it is very excited about this approach. And when discussing it with Dr. Ehrenfeld, she felt that this was something that we probably ought to encourage.

And so we've been involved in trying to help relate the urology community to the Division of Research Grants. We're very pleased to see some resolution of this. There are other ways that we have of dealing with this. We've dealt with it in our own review process to review special aspects of urologic research.

And in fact, urologic research has been one of the fastest growing areas of the Institute. So that clearly it's thriving, it's becoming a very scientifically competitive research group. And I think all those things are going to bode well for this process, which I am pleased with.

PROSTATITIS

Mr. PORTER. This is a related question. The prostatitis community is very anxious for your Institute to support research in this area. An NIDDK workshop concluded that several preliminary steps must first be taken, including an agreement on diagnostic criteria and the development of treatment outcome measures. How long do you think it will take to complete this preliminary work so that prostatitis research can productively be supported?

Dr. GORDEN. This is again one of the areas that we really haven't gotten a research handle on, Mr. Porter. We convened this workshop to try to give us a focus on this. We do a lot of work that re-

lates in an indirect way, for instance, in our longitudinal prostate study, the prostate biopsies, we have a lot of information on this kind of thing.

But to kind of energize what I think this community is asking us to do, we're proposing a set of grants that would help us define diagnostic criteria so that we can develop a research focus. We have what we call an RFA, or a Request for Applications, out right now. We expect to have applications back in the near future and fund those this fiscal year. And this will give us an entree into how we might better conduct research in this area. It's one of the important things that we need to deal with, but we need to find our way before we can really expand this area.

HEPATITIS

Mr. PORTER. Hepatitis seems to be an expanding target for research. As soon as a vaccine is developed for one type of hepatitis, scientists identify yet another variant. Can you describe the universe of hepatitis infections and the state of knowledge about the various forms?

Dr. GORDEN. Well, certainly it's been a very exciting area of discovery in the last several years. Hepatitis has sort of grown a little bit like the alphabet. And we used to use the term infectious hepatitis, and that refers to what we now call hepatitis A, which is the type of hepatitis that one gets from eating contaminated foods. Fortunately, now we have a vaccine against that hepatitis. It usually is a self-limiting illness and doesn't usually lead to chronic disease, although rarely it causes a very acute fulminant type of hepatitis.

Hepatitis B is a type of hepatitis that approximately 10 percent of people develop a chronic form, and when they develop the chronic form of this disease, it can result in one of two things. It can result in scarring or cirrhosis of the liver, or it can result in liver cancer. There have been some important inroads in the treatment of hepatitis B. It basically has been eliminated from the blood supply, because there are clear-cut tests. And now fortunately, we have a vaccine against hepatitis B. So two of the forms of hepatitis we have vaccines for.

The third very important form of hepatitis, we used to refer to the terminology, non-A, non-B. But then in the last several years, there's been a new form defined called hepatitis C, which is probably the most prevalent form of chronic hepatitis. And it was the type of hepatitis that people who were getting multiple blood transfusions were receiving. And we're still seeing that reservoir of patients who got hepatitis from blood transfusions. It's still a very important part of hepatitis. Although the transmission through the blood supply has decreased virtually to zero.

In approximately 40 to 45 percent of the cases, we really don't know how it's transmitted. And this is an important area of scientific investigation now.

We do have some treatments for it. They are not ideal. We're having a consensus conference this month to talk about the treatment of hepatitis C and the sort of impact of hepatitis C on liver disease. Unfortunately, we do not have a vaccine. But we do have a very accurate way of testing for it.

Now, beyond that, there are several other forms. There's a new form, something called Delta hepatitis, which is a variant of hepatitis B, and there's a new hepatitis virus, which we call hepatitis G. And at the present time, we really don't know the exact significance of hepatitis G. But it is an area that is under active investigation.

POLYCYSTIC KIDNEY DISEASE

Mr. PORTER. The past year has been a fruitful one in research on polycystic kidney disease. How does your Institute plan to capitalize on the new scientific opportunities?

Dr. GORDEN. Mr. Porter, this is an example of what we really call scientific opportunity. For many years, we knew that there was a genetic form of cystic kidney disease, referred to as polycystic kidney disease. The early chromosomal methods to localize the genetic defect, because it ran in families in a way that we knew was familial, gave us an idea that there was more than one form, in other words, we knew that more than one type of gene was involved.

And then a very pivotal discovery was made, and that was what that gene is, or what we call "polycystic kidney disease 1." And that has led to the discovery of the protein that's abnormal. We supported two years ago a group of research applications to exploit what the function of this protein is. And in the last several months, we've seen enormous fruits of those grant applications, and we've seen some really important findings come out about the mechanism by which this genetic defect possibly leads to this cyst formation.

And it really has a lot of ramifications that relate to the concepts that are being investigated in cancer and tumor suppressors and other types of things. Very interesting phenomenon.

Almost on the heels of that discovery, our investigators at Albert Einstein discovered the cause of the so-called second form, "polycystic kidney disease 2." And we now have two separate proteins that we feel might in some way interact with each other, but might have sort of a separate etiologic track of their own.

We know that there are other rare forms of cystic disease, but now we know the fundamental cause. And so we think it's incumbent that we vigorously pursue this to understand completely what this genetic defect causes in terms of the protein that's abnormal, what this protein does and how it leads to cyst formation. We even have some clues about some therapeutic manipulations that might be actually instituted for this disease. But these are in a very, very preliminary stage.

So I think it's really an extremely promising area, one that we plan to vigorously pursue and I look for some really important things to come from that in the near future.

Mr. PORTER. Dr. Gorden, last year you indicated that you did not favor the development of research centers specifically for polycystic kidney disease. Is PKD a research focus for any of your existing George O'Brien Kidney Research Centers, or the Pediatric Nephrology Centers?

Dr. GORDEN. Well, it certainly is a venue for those centers. And we welcome and openly encourage people with that interest to apply for these centers. So it's a completely open field in either of those two areas, either the George O'Brien or the pediatric centers.

The fundamental reason, and so that that venue is open to individuals who have an interest in polycystic kidney disease, the reason that we have not encouraged yet another set of centers is because we believe we have more versatility in pursuing this through the research project grant mechanism, since we already have these centers which are available to individuals. And the important thing is for investigators to put together a real consortium that really constitutes a center.

If that isn't possible or isn't necessarily one that is the most fruitful approach, it's best done by project grants, which we can control in a much more rapid sort of way. And we have much more versatility with the project grant mechanism.

COOLEY'S ANEMIA

Mr. PORTER. Dr. Gorden, the committee has encouraged for some time the development of oral chelator drugs for Cooley's anemia patients, to spare them the painful daily 12-hour administration of the only currently approved drug. Are you close to initiating clinical trials for alternative therapies?

Dr. GORDEN. We have actually had under study several compounds, Mr. Porter. As you mentioned, this is a very devastating disease, particularly for children and young adults who develop this iron overload syndrome, because of the severe hemolytic process, that is, the breakdown of blood cells and the accumulation of iron.

We have an excellent treatment that can be given parenterally, that is by injection, and it works very well. But it's very difficult, and it's very hard to get people to do this over a very long period of time. And that's why there's been this interest.

We have tried to get pharmaceutical companies to develop these compounds, but without much success. So we've taken it upon ourselves, and we've investigated at least three or four compounds. Unfortunately, what seems to happen is that, when we get a compound that has some reasonable efficacy, we have two kinds of problems. One is that the sheer amount of the drug that patients have to take to accomplish what we're trying to accomplish is large. And it's sometimes more debilitating than actually the parenteral injection.

And the second problem we've had is toxicity. We've been unable to develop a compound so far that we really feel is safe. It's an area that we're continuing to pursue. We just had a group of experts come in and advise us in this area. It's one that we're totally open to in terms of pursuing. We truly understand the need for it. And we're going to have to either continue this, if we can find some other promising compounds to pursue, or try to steer the course of research in a little bit different direction.

But it's certainly an area that we will aggressively pursue.

DIABETES REGIMEN

Mr. PORTER. Dr. Gorden, you mentioned your diabetes control and complications trial, which indicated that diabetes can be managed through a precise program. Have there been any follow-up studies to determine if the regimen can actually be maintained in everyday settings by ordinary families?

Dr. GORDEN. There have been no formal studies, Mr. Porter. But one thing that we do have is the population itself, that is, the population that participated in the Diabetes Control and Complications Trial. When they were involved in the study, we had the so-called conventional arm of the study, and we had the intensive arm of the study. We were able to maintain the level of what we call hemoglobin A1C, which is a chronic measure of blood glucose concentration, about in the range of about seven for the intensively controlled group, and around nine for the conventional group.

At the end of the study, the patients were basically taken care of by their own private doctor. Now, these are people who have had a lot of experience in treatment. Now, what's happened over the last two years? What's happened over the last two years is that both groups have tended to come together. Our very latest analysis suggests that the conventional group is no longer nine, they're eight, and the intensive group is no longer seven, but they're eight.

And one of the most important things that we found is that this beneficial effect that I have told you about in terms of protection, let's say, from retinopathy of the eye, is remembered. That is, there is a memory for the fact that they were in the intensive group. So they continue to do much better, continue to maintain the benefit that they received at an earlier time.

Something that we know from other sorts of pharmacologic interventions, is that, when you intervene over a period of time, that effect will be sustained over a longer period of time. We believe that the trend for diabetes control is getting better. And we believe we're seeing this in this sort of microcosm of patients.

But we really do not believe that we have in a national sense the facilities to maintain this level of control that was maintained. This is why it's so important that we try to develop alternative treatment strategies. We've got to find ways that can make this possible for people in the real world and real time. And that's really a goal that we have. And it's one that has been rather resistant to our achieving, but we're committed to that area, and we plan to pursue it vigorously.

IMPACT OF DIABETES TRIAL

Mr. PORTER. I think you just answered this, but let me ask it in any case. We've heard the concern voiced that an unintended consequence of the control and complications trial may be an impression that diabetes is a manageable disease and that this may discourage further research. I think you just said it will not.

Dr. GORDEN. I'd like to comment on that, if I could, Mr. Porter. I think that's a slightly different issue.

Unfortunately, this really doesn't relate so much to the insulin-dependent form of diabetes, but it relates more to the non-insulin dependent form of diabetes. There was a kind of view that if your blood sugar was just kind of moderately elevated and you really didn't have any symptoms——

Mr. PORTER. What would that be?

Dr. GORDEN. Well, let's say 150 to 200. And you had no symptoms, because that level of blood sugar elevation, say anywhere from 50 to 100 percent elevation, usually does not cause symptoms. So everyone felt fine.

And unfortunately, the community of physicians and so forth was somewhat content with that, because no one really complained. Well, this is really one of the major points of our prevention trial in Type 2 diabetes. Because we clearly know now that the complications of diabetes are related to two things: the chronicity of blood sugar elevation and the intensity. So it is both the magnitude and the intensity. So that if you have mild elevation over a very long period of time, it clearly is doing you harm.

So what we're trying to do is to say that we can interdict that process while it's still mild and prevent the occurrence of actual hyperglycemia for a period of time. We'd like to believe we could do it forever. But even if we could do it for five to ten years, that would be extremely important in this chronicity effect.

So one would be exposed to hyperglycemia for a shorter period of time. And this would create a healthier patient population. We can't completely eliminate diabetes, but it would create a healthier population of patients with diabetes. And this is the goal.

So we're really focused on two things. One, prevention. And treatment of mild diabetes. Because the more severe form, that I think is abundantly clear what we have to do about that. We've got to focus and get people to understand that we've also got to treat the mild form of diabetes as well as the more severe form. So I think that's a little bit different twist to the question that you asked.

Mr. PORTER. But the question was, is this going to discourage research. And I think you said no.

Dr. GORDEN. It absolutely should not. Because the problem still remains. In other words, why is this true? We're desperate to find alternative approaches to controlling the blood sugar.

For instance, we're looking at inhibitors of so-called "advanced glycosylation products." We're looking at certain kinds of inhibitors of chemicals, enzymes that we believe might be related to the complications of diabetes. If we could find ways to control this tertiary effect of the elevated blood sugar at the cell level, then the need for control would be somewhat diminished, if we could add those two things together.

This would be a tremendously additive effect in trying to achieve our goal of less intense effect of the blood sugar and less intensity of the elevation of blood sugar. So we're working at both fronts to try to achieve that.

Another example of that kind of thing is the recent clinical trial showing that certain types of blood pressure controlling agents, so-called "ACE inhibitors," have an effect in ameliorating the progression of kidney disease of diabetes independent of their blood pressure controlling effect. So there's something else that these drugs do, probably related to the microvascular circulation of the kidney. It's that kind of thing that we're trying to achieve. We can show that we can decrease the deterioration of renal function in those patients by 50 percent with these drugs.

OBESITY

Mr. PORTER. Last December, your Institute's Task Force on the Treatment and Prevention of Obesity published the results of its literature review on the effect of prescription weight loss drugs.

The Task Force concluded that the drugs may help patients lose weight and maintain weight loss in the short term, but that very little is known about the effects past one year. The Task Force did report that most patients regained weight when they stopped taking the drugs. Should obesity be treated as a chronic disease like diabetes where patients will be medicated for their entire lives? And what research is your Institute supporting to address some of the questions identified in the Task Force's report?

Dr. GORDEN. First of all, I'd like to say that we put together this task force of experts on obesity to address this very important problem of both the dissemination of information and the direction of research. And it's been extremely successful.

The issue of pharmacologic treatment of obesity is a very important issue. I think what you've said is essentially what we know about it, that is, there are drugs that have been approved and can be used, we believe, over a relatively short period of time. We're uncertain about the effects of these drugs over a very long period of time, in terms of either their efficacy or potentially, their toxicity.

Now, to kind of amplify the point is that here's an area that there's been an absolute explosion in the science of understanding weight control and the mechanisms of weight control. There's been an explosion that has really kind of penetrated the entire biomedical research community and had a tremendous impact on the biotechnology and pharmaceutical industry.

And we believe that this is going to have tremendous ramifications. I mean, just in the last two years, we've had more of a molecular understanding of the events involved in weight maintenance, weight gain, or weight loss than perhaps we've had in the last 2,000 or 3,000 years.

It's really been dramatic, and it's something we could amplify on. But we've talked about this before, the concept of this newly discovered hormone, leptin. But it's not just that. It's the ramifications that that had on other discoveries, which have been so rapid over the last two years, it's been incredible.

Mr. PORTER. I have two questions on leptin. We've talked in previous years about the complex relationship between the hormone leptin and obesity. How do researchers explain the fact that despite the evidence implicating leptin and its receptor in weight control, mutations of their genes do not seem to be at fault in human obesity?

Dr. GORDEN. Well, at the present time, we can't totally explain that. There is an attempt to find mutations in human obesity. And they of course could occur either in the leptin system or some other place.

But we have to sort of fall back on analogies that we understand a little bit better, say, non-insulin dependent diabetes, where we understand and have studied the relationship of insulin to so-called "insulin resistance" over the years. So that even normal or elevated amounts of insulin are typical of non-insulin dependent diabetes, just like normal or elevated amounts of leptin are typical of most patients who are obese.

So the concept of leptin "resistance" has grown. And this is an area that is being pursued. But what I think is going to be impor-

tant is to understand in a much more complete way the connections that this leptin system is involved in. Very recently, our Phoenix group that I mentioned earlier, that studies the Pima Indians, found that in fact, those individuals who were prone to gain weight over a period of, say, two to three years, were individuals who had relatively low leptin levels.

So there's a lot we clearly don't understand yet about the role of leptin in this sort of biology and the potential role of leptin, either as a therapeutic model or something that's going to lead us to a more appropriate therapy for this condition.

The answer to your question, should it be treated as a chronic condition, absolutely.

Mr. PORTER. And what role might leptin have in controlling diabetes?

Dr. GORDEN. Well, that's a very interesting question also. We have two different kinds of approaches here. In one approach, a recent paper suggests that perhaps leptin could in fact increase the resistance of diabetic cells to insulin. But that type of study has been conducted largely in isolated cell systems, and we don't really understand what that means in the whole body context, which may have a completely different context.

Certainly there is a very strong link between non-insulin dependent diabetes and obesity. At least 80 percent of patients are obese. We know that weight reduction ameliorates the hyperglycemia; we know that weight reduction can prevent the onset of disease, from a variety of epidemiologic studies, so that anything that relates to obesity is going to have clear implications in diabetes.

So here's an area that has really literally just opened up for investigators who are interested in obesity and diabetes, just in the last two years.

Mr. PORTER. Dr. Gorden, we were hoping that Mr. Bonilla of Texas would be able to join us. We had an indication that he would be here. And I've kept asking you questions not only because I wanted the answers to them, but because I wanted to give Mr. Bonilla a chance to arrive. He has not arrived. I have a meeting with the Speaker right at this moment.

So let me end by complimenting you on the fine work you do at your Institute. You also are well known for controlling administrative costs better than most of your colleagues, and we admire that as well. We thank you for your tremendous knowledge and ability to speak in such a way that we can understand what it is that the answers are meant to convey. That has been very, very helpful to all of us, and we very much appreciate the wonderful job that you're doing there.

Thank you so much.

Dr. GORDEN. Thank you very much, Mr. Porter. I appreciate it.

Mr. PORTER. The subcommittee will stand in recess until 1:30.

[The following questions were submitted to be answered for the record.]

HEPATITIS C

Mr. Porter: Has CDC updated its estimate of the number of hepatitis C cases in this country?

Dr. Gorden: Yes, the CDC has revised its estimate of the prevalence of hepatitis C in the United States upward from 3.5 million to 3.9 million.

Mr. Porter: Pending development of better interventions, what are the best current treatment and prevention strategies for containing the spread of hepatitis C?

Dr. Gorden: The only currently approved treatment for hepatitis C is alpha-interferon. This treatment improves serum aminotransferase levels in approximately 50 percent of patients during treatment. However, once interferon therapy is discontinued in these patients, 50 to 80 percent relapse. Only 10 to 15 percent of patients sustain a long-term response. In regard to prevention strategies, screening the blood supply, encouraging health professionals to take blood and body fluid precautions, and informing people about high-risk behaviors remain the only means of preventing the spread of hepatitis C.

DISEASE FUNDING

Mr. Porter: Identify 1996-1998 spending on the following: diabetes, interstitial cystitis, obesity, prostate, inflammatory bowel disease, celiac disease, osteoporosis, nutrition, cystic fibrosis, polycystic kidney disease, Cooley's anemia, sickle cell anemia, liver disease, prostatitis, and IgA nephropathy.

Dr. Gorden: The following identifies funding by the National Institute of Diabetes and Digestive and Kidney Diseases for the disease areas listed below in fiscal years 1996-1998:

	1996	1997	1998
Diabetes	$197,542,000	$209,100,000	$213,200,000
Interstitial Cystitis	9,081,000	9,100,000	9,300,000
Obesity	32,400,000	34,300,000	34,900,000
Prostate	13,776,000	14,500,000	14,700,000
Inflammatory Bowel Disease	15,459,000	16,300,000	16,600,000
Celiac Disease	2,244,000	2,370,000	2,400,000
Osteoporosis	23,700,000	25,000,000	25,500,000
Nutrition	79,500,000	84,200,000	85,800,000
Cystic Fibrosis	22,991,000	24,300,000	24,700,000
Polycystic Kidney Disease	7,497,000	7,900,000	8,050,000
Cooley's Anemia	6,900,000	7,300,000	7,400,000
Sickle Cell Anemia	4,216,000	4,460,000	4,560,000
Liver Disease	46,600,000	49,300,000	50,200,000
Prostatitis	183,000	1,300,000	1,330,000
IgA Nephropathy	14,400,000	15,200,000	15,500,000

RESEARCH CENTERS

Mr. Porter: Identify the number and subject matter of research centers supported in FY 1997.

Dr. Gorden: The NIDDK supports a total of 59 research centers:

(1) Twelve diabetes research centers -- six Diabetes Research and Training Centers (DRTC), and six Diabetes-Endocrinology Research Centers (DERC). The essential difference between the two types of centers is that the DERCs focus entirely on biomedical research, while the DRTCs have an additional Demonstration and Education component. Examples of research that is being conducted at these centers include investigations of the genetic basis of insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM); clinical physiology of insulin secretory alterations in subjects with different genetic forms of NIDDM; pancreatic islet physiology, chemistry, and molecular biology; carbohydrate metabolism; diabetes complications; analysis of insulin action on gene expression; and inhibition of fat breakdown by insulin in abdominal obesity.

(2) Five Cystic Fibrosis (CF) Research Centers, which focus on areas such as inflammation and host defense in the lung, clinical studies, epithelial cell biology, various aspects of the cystic fibrosis transmembrane regulator mutation and protein, and development of new treatments for CF.

(3) Three Gene Therapy Centers for Cystic Fibrosis and Other Genetic Diseases, which are investigating such areas of fundamental research as the development of safer and more efficient gene therapy vectors, development of animal models, and basic mechanisms of gene transfer.

(4) Twelve digestive diseases research centers, which focus on liver diseases and disorders, inflammatory bowel disease, ulcer disease, gastrointestinal (GI) biology and hormones, and fundamental studies of the structure and function relationships in the digestive tract.

(5) Six Clinical Nutrition Research Units (CNRUs), which provide shared facilities and research services for studies in perinatal nutrition, nutrient transport, energy expenditure, hypertension, obesity, trace elements in nutrition, nutrient absorption, vitamin D metabolism, food intake, impact of alcohol on GI function, diabetes, hypertension and fish oil.

(6) Four Obesity/Nutrition Research Centers, which concentrate on the study of the natural history of obesity, energy metabolism and diabetes, education and training programs for health care professionals, the impact of neuropeptides on behavior, eating disorders, and epidemiology, behavior modification and relapse in the treatment and prevention of obesity.

(7) Twelve George M. O'Brien Kidney and Urological Research Centers, which support interdisciplinary basic, clinical, and applied aspects of research in renal physiology and pathophysiology, nephrology, and urology. The goal of these centers is to reduce the incidence of mortality and morbidity from kidney and urologic diseases such as end-stage renal disease, kidney disease of diabetes mellitus, and benign prostatic hyperplasia.

(8) Two Research Centers of Excellence in Pediatric Nephrology and Urology, which support research on the basic cellular and molecular pathogenesis of pediatric nephrologic and urologic diseases and disorders. The goal of these centers is to foster and extend the development of new approaches into the causes, early diagnoses, improved treatment, and where possible, the prevention of urological and kidney diseases such as polycystic kidney disease, IgA nephropathy, and the hemolytic uremic syndrome in the pediatric population.

(9) Three Centers of Excellence in Molecular Hematology, which are intended to promote the development of the broad range of scientific expertise and technologies needed for the investigation of genetic diseases and genetic therapy and emphasize the study of gene structure and function, the structural biology of proteins, and the mechanisms of hematopoietic cell maturation and differentiation. The goal of the Centers is the development of preventative, curative, or intervention strategies in the treatment of genetic diseases.

PUBLIC EDUCATION ACTIVITIES

Mr. Porter: How much is included in your 1998 budget for public education activities?

Dr. Gorden: In FY 1998, the NIDDK will spend approximately $1.2 million on the National Diabetes Education Program, our only formal public education program. We do however, have other public information and outreach programs to disseminate information about research results to health professionals, patients and the public, and these other programs represent an additional estimated amount of $4.5 million in FY 1998. The NIDDK develops and disseminates health-related fact sheets, newsletters, brochures, and posters. The Institute supports media outreach activities in diabetes, and a long-term community-based health campaign, "Sisters Together," a prototype established to raise awareness of the importance of healthful eating and exercise in obesity-prone minority communities. We disseminate information through the National Diabetes Information Clearinghouse, the National Digestive Diseases Information Clearinghouse, the National Kidney and Urologic Diseases Information Clearinghouse, the National Diabetes Outreach Program, and the Weight-control Information Network.

FUNDING FOR DIABETES RESEARCH

Mr. Porter: In coordination with the NIH budget office, provide for the record a ten-year history of both NIDDK and trans-NIH funding levels for diabetes-related research.

Dr. Gorden: The following provides a ten-year history of both NIDDK and trans-NIH funding levels for diabetes-related research:

	NIDDK	NIH
FY 1989	$160,532,000	$258,819,000
FY 1990	163,276,000	249,233,000
FY 1991	175,114,000	261,519,000
FY 1992	184,500,000	278,412,000
FY 1993	187,100,000	285,894,000
FY 1994	191,409,000	293,615,000
FY 1995	193,597,000	295,185,000
FY 1996	197,542,000	298,920,000
FY 1997	209,100,000	316,292,000
FY 1998	213,200,000	322,683,000

POLYCYSTIC KIDNEY DISEASE

Mr. Porter: Are there opportunities for collaborative PKD research with other NIH Institutes? If so, what is being done?

Dr. Gorden: Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of cysts in the kidney. PKD can also cause cysts in the liver and pancreas and problems in other organs such as the heart and blood vessels in the brain. Another important symptom is hypertension. PKD may occur at any point in life, including in utero. These various manifestations provide opportunities for collaborative PKD research with other NIH Institutes. For example, the NIDDK plans to issue a Program Announcement in fiscal year 1997 to solicit high-quality research grant applications. We are currently exploring the possibility of collaborating with other Institutes in the issuance of this solicitation.

Mr. Porter: You are planning an international PKD workshop in September. What outcomes are expected from this meeting? Will you be announcing an RFA or similar research mechanism?

Dr. Gorden: The NIDDK will support both a polycystic kidney disease (PKD) scientific workshop and a Program Announcement (PA) in FY 1997. The workshop will provide a useful forum for the exchange of scientific information among investigators working on PKD, with particular emphasis on the possible functional role

of the PKD protein, polycystin. If we can learn about the functions of polycystin, it may be possible to design strategies to ameliorate or possibly even eradicate this disease. The PA will solicit high-quality research grant applications from both established PKD researchers and investigators new to the study of PKD. This announcement will encourage research to capitalize on the discovery and sequencing of the genes for PKD1 and PKD2, and the identification of the protein which these genes may regulate.

UROLOGY

Mr. Porter: What has been the NIDDK funding level for urology research in FY '94-96? What are the estimated funding levels for FY 97-98?

Dr. Gorden: The following provides expenditures for urology research by the NIDDK for fiscal years 1994-1996 and estimated funding levels for urology research for fiscal years 1997-1998.

FY 1994	$39,353,000
FY 1995	44,517,000
FY 1996	42,981,000
FY 1997	45,500,000
FY 1998	46,400,000

ADMINISTRATIVE ISSUES

Mr. Porter: The share of your budget going to the RMS category - administrative costs - is lower than at most institutes. What techniques do you use to limit the size of your RMS budget?

Dr. Gorden: The NIDDK has for many years sought to reduce its administrative costs in favor of spending money directly on research. We have achieved a large part of this goal by keeping employment levels low in many of our offices, and maintaining a high workload of grants for each member of our scientific programs staff and our grants management staff. An aggressive program to utilize personal computer equipment has resulted in a steady drop in the employment of secretaries and clerks. We have also entirely eliminated some functions such as the scientific coding of grants and moved those employees into other offices.

We decided several years ago, in holding with OMB's efforts to contract out programs in order to reduce Federal costs for salaries and pensions, that all three of our Clearinghouses could be performed under contract, thereby allowing reassignment of staff who had been performing those functions directly. As we completed the scientific design of our most recent large multi-center clinical trials, we determined that they could be performed either through contracts, requiring extensive staffing, or through cooperative agreements, which can be administered with more limited staffing. We have chosen to use cooperative agreements for all of our current large trials, and some savings of staff resources has been possible without compromising the quality or safety of the trials.

We are looking forward to the conclusion of the Congressionally-mandated study of the structure of the RMS function at the NIH, which seeks to rationalize the category and achieve some comparability across institutes.

Mr. Porter: Are the costs of your public education efforts and clearinghouses included in the RMS category, as they are in the Heart Institute?

Dr. Gorden: Most of those costs are not in the RMS category. We decided several years ago, in holding with the OMB's efforts to contract out programs in order to reduce Federal costs for salaries and pensions, that all three of our Clearinghouse functions could be performed quite well under contract. Our recently initiated National Diabetes Education Program is also being performed under contract.

The contractors utilize pamphlets and booklets addressing diseases in our purview which are written, designed, and periodically updated by our own expert staff. They also utilize procedures designed by our staff for satisfying the inquiries from the public. Overall, about nine tenths of the costs are paid in the Research and Development Contracts category.

DIABETES REGIMEN

Mr. Porter: Dr. Gorden, while much progress has been made in diabetes management, how much have we learned about the root cause of the disease? For example, have viruses or bacteria been ruled out as etiological agents?

Dr. Gorden: Mr. Porter, we have learned a great deal about diabetes management as the result of the NIDDK-supported Diabetes Control and Complications Trial, and other basic and clinical research on pharmacologic approaches to diabetes control. We also have gained substantial knowledge of the risk factors for diabetes, some of which cannot be easily controlled--such as family history and genetic predisposition to diabetes--but others which can--such as excessive weight gain and sedentary lifestyle, to name two. There is also some evidence that viruses may play a causative role in the development of Type I diabetes, but this relationship is still under investigation.

LIVER DISEASE INFORMATION

Mr. Porter: In view of the fact that 12 NIH institutes conduct liver disease research, what is NIDDK doing to develop a centralized coordination and information program that would be useful to both the research community and the patient community?

Dr. Gorden: The statuatory National Digestive Diseases Interagency Coordinating Committee chaired by the NIDDK is the institutional mechanism for involving and coordinating the NIH and Federal community with respect to research efforts in liver diseases. The Committee meets four times a year to discuss current and planned efforts of each of its member institutes relative to the conduct of liver disease research. With

the goal of developing a scientifically appropriate plan for addressing areas outlined in the research agenda prepared by the American Liver Foundation, the Committee will conduct an overview of the agenda at a mini-symposium in June 1997. Later in the year, the Committee plans to discuss research directions in gallstone and biliary tract diseases. Initiatives undertaken in the past year by the NIDDK include publication of Program Announcements on cellular ontogeny and differentiation of the liver and biliary tree, and the etiology of biliary atresia. The Institute has also funded two large multicenter trials in liver disease on the use of transjugular intrahepatic porto-systemic shunts (TIPS) in the management of variceal hemorrhage and ascites related to chronic liver disease. Meetings on "Liver Transplantation for Alcoholic Liver Disease," co-sponsored by NIDDK and NIAAA, and an international meeting on "Targeting of Novel Therapeutics to the Liver and GI Tract, were held during the past year. In March 1997, NIDDK will co-sponsor with NIAID a Consensus Development Conference on "Management of Hepatitis C."

A guide to health information can be found on the NIH Home Page of the Internet. This guide includes an NIH Health Information Index which is a source for information on major research areas, important health-related topics, and diseases currently under investigation by NIH or NIH-supported scientists. Also on the NIH Home Page is a list of information clearinghouses operated by NIH and their phone numbers, as well as Health Information Resources. Included among these resources are: the CancerNet, the Combined Health Information DataBase, the National Library of Medicine's online database of health-related organizations operating toll-free telephone services, the full text of consensus statements developed through the NIH Consensus Development Program, and information about currently active research studies conducted by the Intramural Programs of the NIH.

Mr. Porter: What is NIDDK doing along with other appropriate institutes to conduct outreach to the liver disease research community to make them aware of priorities and funding availability?

Dr. Gorden: The NIDDK, along with other institutes, jointly sponsors program initiatives, such as Program Announcements, which are advertised in the *NIH Guide for Grants and Contracts.* These initiatives address research questions on the various aspects of liver disease that fall within the research missions of each of the NIH Institutes supporting research in liver disease. National and international meetings and workshops on topics such as hepatitis C, alcoholic liver disease, and gene therapy approaches to liver disease are often co-sponsored by two or more institutes and offer an ideal forum for identifying areas that need to be targeted with respect to research in liver disease.

LIVER DISEASE IN CHILDREN

Mr. Porter: The Committee understands that research in the field of liver disease in children has been very limited and has frequently taken a lesser priority to adult disease. Within the amounts requested what is proposed to be spent on liver disease in children? What are the most promising areas of research in liver disease in children?

Dr. Gorden: It is estimated that approximately $4.8 million will be committed to pediatric liver disease research by the Liver Program of NIDDK in fiscal year 1998. Among the most promising areas of research in liver disease in children is biliary atresia, for which a paucity of information exists on the etiology of disease, predictors of natural history and risk factors, or optimal use and timing of medical intervention versus surgical intervention. Biliary atresia is a very serious condition that leads to end-stage liver disease within 6 to 18 months after birth and is a major reason for liver transplantation in children. The NIDDK published a program announcement requesting grants in pediatric disease last year and plans to publish this announcement again next year. Other efforts would focus on the development of animal models to better understand the genetic basis of liver disease and the pathogenesis and therapy of these diseases.

OBESITY

Mr. Bonilla: On March 4, 1997, the Coalition for Excess Weight Risk Education released a 33-city study that ranked my hometown of San Antonio as the "third-fattest city." Medical experts in San Antonio said that local research has confirmed a high incidence of obesity in the Alamo City.

There is no doubt that we have great food in San Antonio. Obesity, however, is becoming a serious problem as your budget justification points out on page 9, "obesity is a major risk factor for numerous chronic diseases, such as diabetes, cardiovascular diseases and high blood pressure. The cost of obesity to society is close to $100 billion, including nearly $70 billion in direct and indirect medical costs, and about $30 billion associated with weight-loss programs and products."

It is my understanding that last November researchers found that leptin, a protein once thought to be used as a weight-reducing agent, causes adult diabetes. Researchers suggested that is was a "big jump to conclude from this study that leptin is a cause of diabetes." Has NIDDK confirmed these results?

Dr. Gorden: The story of leptin and the other hormones and neuropeptides that interact to regulate energy balance is a very complex one. The discovery you are referring to was reported late last year, and indicates that, in a line of cells derived from a human liver cancer, leptin decreases some of the signals that insulin sends in these cells. In addition, in many obese individuals, leptin levels are elevated. These two observations have been linked to suggest that leptin may be one of the factors involved in insulin resistance. It is likely only a part of a very complicated story, however. Leptin's role also may vary somewhat in different individuals and ethnic or racial populations.

I think the important point to draw from this is that we are closing in on understanding all the different molecular details that influence and interfere with insulin action in healthy individuals and in diabetic patients. In addition to the different roles leptin may play in different tissues, there are an increasing number of other factors that help to regulate energy balance. Just this month a new protein called UCP2 was discovered that appears to cause fat cells to simply burn off excess calories, rather than storing them as fat. Strains of mice that produce a lot of UCP2 after being fed a high fat diet gain much less weight than strains that produce less of the protein. Since humans also make UCP2 in many cells, this clearly points to a whole new pathway affecting energy regulation, and hence diabetes. This is one of the fastest moving areas of research today, so I can predict that we will have many more surprises ahead as we work toward solving the puzzle of obesity and diabetes.

TREATING AND PREVENTING DIABETES

Mr. Bonilla: You state in your testimony that almost immediately after the leptin link to diabetes was discovered, a host of related fundamental discoveries were made and this research has had an enormous positive impact on U.S. pharmaceutical and biotechnology industries. Do any of them pertain to treating and preventing diabetes?

Dr. Gorden: At this point, none of the discoveries of the past two years have been developed to the point where we can say they are definitely going to result in a new treatment for obesity or diabetes. However, pharmaceutical companies are very active in pursuing the potential uses of these newly discovered biologic factors that control energy balance. Many of the newly discovered hormones, neuropeptides, and proteins have the potential to play a role in treating or preventing diabetes, especially through weight control.

FUNDING FOR DIABETES RESEARCH

Mr. Bonilla: As I explained to Dr. Varmus when he testified, recent breakthroughs of a University of Chicago research team made in finding two new genes linked to causing diabetes opens the door for more research and understanding of the disease. I am concerned that this significant momentum will be lost, because of the low 2.3 percent increase NIH has assigned to NIDDK. This percentage does not keep pace with biomedical inflation, which is expected to be at least 3 percent for the next two years.

In light of the fact that 27 percent of the entire Medicare budget is spent on caring for persons with diabetes, my concern is that if it is not given higher priority, we will lose the momentum needed to prevent and cure the disease, which would also significantly reduce the economic burdens of this disease on society. Do you agree with my assessment?

Dr. Gorden: We are of course, eager that opportunities in diabetes research, and particularly in the genetics of diabetes, be pursued to the fullest extent possible. It is truly amazing to consider that this relatively new field has already made considerable strides in understanding the genetic components that play a role in diabetes. This progress is due, in part, to two NIDDK initiatives implemented within the past few years to encourage research on the genetics of Type I and Type II diabetes. We realized that technological advances had positioned diabetes genes research to begin to make real progress, and the identification of the two genes you mentioned is a direct result of these initiatives. We are very aware that this area needs continued support, and will make every effort to fund new research opportunities as they arise.

Mr. Bonilla: Dr. Varmus very eloquently stated his belief that NIDDK is given sufficient priority at NIH. I also believe science , not politics, should dictate increases in funding. However, I have a chart (see enclosure) that shows the growth in funding of NIH's individual institutes from FY 88-97. The institutes which support the largest amount of diabetes research, NIDDK, NICHD, NHLBI, and NEI, have a much lower percentage increase than the other institutes.

In your opinion, at the rate NIDDK is increased in this budget, is it sufficiently funded to find a cure which will not only prevent life loss and hardship, but also reduce the economic burdens is poses to society?

Dr. Gorden: Mr. Bonilla, opportunities in diabetes research exist at virtually all budget levels, not just for the NIDDK, but for all institutes you cited. In this regard, annually the NIDDK identifies areas that may be explored or expanded within a certain framework of resources. Having said that, I want to assure you that we believe we use our allocation of resources in the most efficient and effective ways possible. We have built a diabetes research portfolio that emphasizes extramural basic research--which underpins our prevention and treatment efforts--and also includes substantial investments in clinical studies and trials, and in a world class intramural research program.

DIABETES EDUCATION AND RESEARCH

Mr. Bonilla: Dr. Varmus also commented that a large problem related to diabetes morbidity is a result of physicians and patients not taking the discoveries made through NIH and making them apply in the clinical aspect. What activities does NIDDK engage in to educate and encourage physicians and patients to apply discoveries in hospitals and doctor's offices?

Dr. Gorden: The NIDDK has several education and outreach programs for diabetes. For example, the National Diabetes Outreach Program (NDOP) disseminates the results of the ten-year NIDDK-sponsored Diabetes Control and Complications Trial (DCCT) to the public through the "Do Your Level Best" campaign, which emphasizes control of blood glucose levels in order to prevent complications, including amputations. In addition, in collaboration with nine other public and private agencies, the NDOP's "Feet Can Last a Lifetime" outreach campaign was implemented. This foot-care awareness program is designed to reduce the number of amputations among people with diabetes. The campaign includes public service announcements, workshops for patients and health professionals, and the dissemination of foot care information kits.

The NDOP is now evolving into a much larger effort, the National Diabetes Education Program, led by the NIDDK and the Centers for Disease Control and Prevention. The NDEP will provide a framework for organizations involved in diabetes to develop effective partnerships at the national, state, and community levels to reduce the burden of diabetes as a public health problem, especially among minority populations.

Lastly, the NIDDK's National Weight-Control Information Network (WIN) is an outreach initiative designed to bring greater awareness about the health risks and problems associated with being overweight, a major risk factor for Type II diabetes. The WIN provides health professionals and the public with practical information on obesity, weight control, and nutritional disorders. The WIN's pilot program, called "Sisters Together: Move More, Eat Better," targets African American females. Nearly one-half of African American women over the age of 20 are overweight.

COLLABORATIVE EFFORTS

Mr. Bonilla: How is diabetes research supported by the Office of Research on Minority Health, as well as other Institutes, coordinated with NIDDK? In your view, is this collaboration working well? Are there adequate resources available in this area?

Dr. Gorden: We have an outstanding relationship with the Office of Research on Minority Health in a number of areas, with diabetes being one of the most important. In general, ORMH asks the institute for proposals for research to address important minority health research and training issues. In response, we try to let ORMH know our most promising ideas. Frequently Dr. Ruffin will ask me or the institute staff for additional information on one or more of the proposals. ORMH then reviews our concepts and, in conjunction with its advisors, identifies the areas that are of highest priority to both organizations. I am pleased to say that the ORMH has been supportive of most of the proposals we have advanced.

In terms of coordination with the other ICDs, one major mechanism is through the Diabetes Mellitus Interagency Coordinating Committee (DMICC). This group, which meets at least three times a year, includes not only the other NIH institutes with diabetes interests, but also all other agencies in the Federal government that sponsor diabetes research. In addition, the NIDDK diabetes program directors work with staff in other institutes to sponsor workshops and conferences that stimulate research, to develop cofunding for efforts of joint interest, and to ensure that resources are used as efficiently as possible. To this end we also have encouraged partnerships with outside organizations such as the Juvenile Diabetes Foundation International and with pharmaceutical firms. Overall, I believe that we are addressing a multitude of important diabetes research questions in a highly effective manner. However, many additional opportunities remain, as have been identified in recent workshops and conferences, as well as in our program initiatives planning document.

DIABETES PREVENTION TRIALS

Mr. Bonilla: Dr. Gorden, what is the current status of the Diabetes Prevention Trials, known as DPT1 and DPT2? How much are those trial likely to cost?

Dr. Gorden: Both trials are recruiting and enrolling patients. The Federal government will expend approximately $38.3 million for the DPT-I over nine years (FY 1993-FY 2001). The DPT2, which is now called the Diabetes Prevention Program (DPP), will cost an estimated $120.6 million in Federal funds over seven years (FY 1994-FY 2000).

OUTSIDE INPUT FOR DIABETES RESEARCH

Mr. Bonilla: Dr. Gorden, now that the National Diabetes Advisory Board has ceased to exist, what forums exist through which you can integrate lay and scientific input from the diabetes research community into a vision for future directions for diabetes research? What alternative modes of input can you now rely upon to fill the void left by elimination of the NDAB?

Dr. Gorden: Mr, Bonilla, the NIDDK has in place several mechanisms for receiving input from the lay and scientific communities with regard to research. The first is our National Diabetes and Digestive and Kidney Disease Advisory Council, which I chair and which consists of lay and scientific members, and ex officio members representing federal government agencies. Another mechanism is the National Diabetes Mellitus Interagency Coordinating Committee, which is led by the NIDDK. NIDDK-sponsored scientific workshops are another vehicle used to bring federal and non-federal scientists together to discuss the latest advances in research and to share ideas about future research opportunities. Apart from these formal mechanisms, Institute staff communicate regularly with the scientific community to discuss various aspects of diabetes research and related activities. Finally, this year the NIH and NIDDK will cosponsor a conference on diabetes research. The conference will involve all institutes having a scientific interest in diabetes research, and will focus on special opportunities and directions that this broad interdisciplinary approach brings to diabetes research.

REVIEW PROCESS FOR CLINICAL STUDIES

Mr. Bonilla: Do you think that early-stage clinical studies receive proper consideration in the review process at NIDDK and the NIH in general?

Dr. Gorden: We are acutely aware of the importance of early-stage clinical studies in the transfer of basic research findings to the clinical level. Within the limits of available resources, we try to emphasize such investigations; as a result, NIDDK devotes more of its resources to clinical (physician) studies than any other NIH component, according to data published by the NIH Office of Extramural Research. Within NIH as a whole, the Director has been working with a panel devoted to strengthening clinical research. In addition, the peer review study section process for clinical studies is under examination for ways to facilitate the adequate evaluation of clinical proposals.

NEWLY DIAGNOSED DIABETICS/EARLY INTERVENTION

Mr. Bonilla: As I read your Diabetes Statistics from your web site, I am amazed but not surprised to see that 1,700 new cases of diabetes are diagnosed every day, amounting to 625,000 a year. A drug developed in Japan and being tested at the University of Arkansas for Medical Sciences could let many of these newly diagnosed diabetics reduce or stop insulin injections. In addition, is NIDDK using this drug to prevent the onset of diabetes? How far are we away from reaping the benefits of this new drug?

Dr. Gorden: I believe, but am not certain, that the drug you are referring to is a thiazolidine dione, a class of compounds that includes troglitazone, one of the drugs that is being tested for prevention of Type II diabetes in our Diabetes Prevention Program (DPP) clinical trial. Since the NIDDK is not funding the research you describe at the University of Arkansas, I do not know the details of this study. I can tell you, however, that we are very hopeful that oral troglitazone, which was recently approved by the FDA for treatment of Type II diabetes, also will be useful for preventing or delaying the onset of Type II diabetes. The DPP is scheduled to be completed in FY 2000. Parenthetically, I understand that troglitazone originally was developed by a Japanese company.

ULCERS

Mr. Istook: Dr. Gorden, you testified today that the discovery that *Helicobacter pylori* is the cause of 85% of all ulcers patients are treated for, had moved from a chronic disease, treated through a maintenance program, to a disease treated over a two week period as an acute problem, just like many other bacterial infections. Please describe, in detail, the efforts being made by your Institute to get the word out to medical practitioners.

Dr. Gorden: We fully appreciate the importance of communicating information to physicians regarding optimal treatments to eradicate *H. pylori*, which is the major cause of ulcers and linked to gastric cancer. The NIH has distributed broadly the summary of the 1994 Consensus Development Conference, to clinicians through publication in medical journals and over the Internet. The consensus panel concluded that combination drug therapy effectively eradicates the bacterium associated with peptic ulcer disease and reduces the rate of ulcer recurrence in up to 90 percent of patients. A fact sheet on "Stomach and Duodenal Ulcers" describing the *H. pylori* discovery continues to be distributed to health professionals by the National Digestive Diseases Information Clearinghouse, funded by the NIDDK. The NIDDK also worked closely with the American Digestive Health Foundation, a cooperative effort of the American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy, to develop its plans to enhance communication to consumers, physicians, and managed care organizations in launching a major educational campaign to convey this message.

Mr. Istook: What other federal agencies or entities are sharing this effort to let family practitioners know about this treatment?

Dr. Gorden: In the Conference Report on the FY 1997 budget for DHHS, the Conference Committee concurred in the recommendation of the Senate report that CDC initiate a trans-department public education campaign to foster more effective communication between consumers and physicians on *H. pylori* and its link to ulcer disease.

DIABETES RESEARCH

Mr. Istook: You testified that your Institute has primary responsibility for research into diabetes. According to Dr. Varmus' testimony, there is diabetes related research going on at a variety of the Institutes, from the National Eye Institute to the National Heart, Lung, and Blood Institute. Does your institute have primary responsibility for research into the metabolic causes of diabetes?

Dr. Gorden: Yes, Mr. Istook, the NIDDK has primary responsibility for research in this area. Out of the $298.9 million expended throughout the NIH on diabetes research in FY 1996, the NIDDK spent $197.5 million, or 66 percent.

Mr. Istook: The Centers for Disease Control study that showed that in 1992, Medicare spent 26.5% of its budget, or $28.6 billion, treating diabetes and its complications. In 1995, that number is estimated to be $42.5 billion. I know that you are aware of the crisis we are facing in the Medicare Trust fund. If we could solve the complications of diabetes, and save $42.5 billion a year, it would make that crisis disappear. The Speaker of the House, Newt Gingrich, has been publicly discussing this since September of 1995. Do you have promising research into the metabolic causes of the disease that is underfunded because of budget constraints?

Dr. Gorden: Mr. Istook, scientific opportunities exist at virtually all budget levels, not just for the NIDDK, but for all institutes. In this regard, annually the NIDDK identifies areas that may be explored or expanded within a certain framework of resources. Certainly, much of the research we support is examining the precise mechanisms involved in the complications caused by diabetes, and also the ways that complications can be ameliorated. For example, our recently completed Diabetes Control and Complications clinical trial, a ten-year landmark study, demonstrated that a significant reduction in diabetes complications can be achieved by intensive control of blood glucose levels.

Mr. Istook: Please describe those research opportunities.

Dr. Gorden: Perhaps the most far-reaching and comprehensive of the diabetes-related opportunities we have identified is what we call the Diabetes Prevention and Treatment Initiative (DPTI). This major activity was spawned by the results of the Diabetes Control and Complications Trial (DCCT) which, again, demonstrated conclusively that intensive management of diabetes delays the onset and slows the progression of many complications brought on by the disease. This multi-faceted initiative encompasses investigator-initiated fundamental and applied research, clinical studies and trials, and national multicenter trials conducted by the NIDDK. Our national clinical trials to prevent Type I and Type II diabetes are part of the DPTI. Other aspects include research on beta cell replacement therapies and approaches to achieving normal blood glucose levels in diabetics; the Epidemiology of Diabetes Intervention and Complications (EDIC) program, which is a long-term follow-up study to ascertain clinical microvascular and macrovascular disease endpoints in the DCCT cohort; diabetes prevention studies in minority populations; the genetics of diabetes, including the search for the diabetes genes; metabolic staging of Type II diabetes; the relationship between obesity and diabetes; and the kidney disease of diabetes.

Mr. Istook: Please describe how much your Institute's budget would have to be increased to enable you to take advantage of these opportunities?

Dr. Gorden: Many promising diabetes research projects will be funded through the President's FY 1998 Budget request for NIDDK.

PEER REVIEW

Mr. Istook: Dr. Gorden, you testified today that the NIH peer review process had, frankly, missed the research opportunity and failed to fund several grants into the research done that has lead to a cure of 85% of all ulcers. Has there been any discussion of cross-fertilizing NIH peer review panels with practitioners from related disciplines, like veterinarians, biochemists, or others that deal with human or animal diseases?

Dr. Gorden: It is common practice at the NIH to design the membership of review committees so that varying expertises are brought to bear on the portfolio of applications reviewed. For example, in a DRG study section that would likely review applications on H. pylori, there is expertise in gastrointestinal disorders, nutrition, membrane biochemistry, molecular biology, immunology, bacteriology, surgery, muscle physiology, pathology, infectious diseases, and inflammatory diseases, in animals as well as humans.

Mr. Istook: Are most of the panels made up of specialists within a specific research area?

Dr. Gorden: As noted above, expertise can vary widely within a review committee. These committees normally are designed with a degree of breadth so that the review of a number of related applications can appropriately be accommodated. However, when applications are reviewed within the Institutes in response to an RFA, the review groups tend to be somewhat more specialized in expertise.

Mr. Istook: You have testified that you do not believe there is a flaw in the basic peer review system, that failing to fund the ulcer research was an unfortunate happenstance. There was a presentation given by Dr. Richard Anderson of the U.S. Department of Agriculture entitled, "Beneficial Effects of Chromium for People with Type II Diabetes," presented to the American Diabetes Association's 56th Annual Scientific Sessions conference on June 8-11, 1996. This was a human trial conducted on 180 Chinese subjects, in which Dr. Anderson gave chromium picolinate supplements in 100 microgram (mcg) or 500 mcg doses twice a day for four months. Dr. Anderson and his colleagues measured hemoglobin each day for four months. They found those who received no chromium measured 8.5 percent, and those who received supplementation at 100 mcgs per day were at 6.6 percent. For the record, please describe the range for glycated hemoglobin in each of the following:

i. Diabetics who require insulin injections.
ii. Diabetics who receive oral medications.
iii. The chronic elevated levels you mentioned at today's hearing.
iv. The non-diabetic person.

Dr. Gorden: For the non-diabetic person, normal levels of glycated hemoglobin and hemoglobin A_{1c} are any levels below 7 percent and 6 percent, respectively. Type I diabetics, who require insulin injections, have glycated hemoglobin levels between 10

and 11 percent and above, and hemoglobin A_{1c} levels between 8 and 9 percent and above, though more intensive insulin treatment can keep these levels closer to the lower ends of the ranges. Type II diabetics should receive oral medications, in combination with dietary intervention, at hemoglobin A_{1c} levels of 7.5 percent and above. While people who have "chronic elevated" hemoglobin A_{1c} levels of, say, 7.5 to 9.0 percent, should be treated as I have noted, they often are not because these levels do not produce obvious symptoms--perhaps for years--to indicate there is a health problem or risk. Thus, people who have chronic elevated blood glucose and hemoglobin A_{1c} levels are often are unaware that they even have diabetes. This points up the insidious nature of Type II diabetes. In fact, undiagnosed Type II diabetes is extremely problematic because fully one half of the people who have the disease do not know it. They only know it after their uncontrolled diabetes has begun to do serious irreversible damage to multiple organ systems.

Mr. Istook: Please describe efforts planned by your institute to examine Dr. Anderson's research.

Dr. Gorden: Mr. Istook, while Dr. Anderson's research spurred great interest at the time, we believe that further basic research, animal studies, small clinical studies, and randomized, controlled, double-masked clinical trials are needed to confirm--or disprove--the findings he reported.

Mr. Istook: How much money would be required to put together a definitive clinical trial to verify Dr. Anderson's findings? Please describe how such a trial might be constructed and conducted.

Dr. Gorden: Before the NIDDK determines that a given clinical trial is warranted, a critical body of scientific evidence must be established to justify the trial. In the case of chromium supplementation for diabetes, we do not believe that such evidence is in place. Beyond this, a team of researchers charged with conducting the clinical trial would consider many factors in the design and conduct of the trial, and the cost of the trial would reflect its scope, complexity, and duration.

DIABETES RESEARCH

Mr. Istook: Can you give examples of the scientific evidence that is needed in order to justify a clinical trial? Based on your experience with clinical trials, once an appropriate knowledge base is established, what is the estimated time frame and resource commitment that would be involved in a diabetes clinical trial involving chromium?

Dr. Gorden: Studies of dietary supplements such as chromium have been sponsored by NIH, USDA, and others, and there is now an NIH Office of Dietary Supplements which is responsible for promoting and advancing research on dietary supplements by exploring their role and helping to develop good research efforts; these goals require coordination and joint planning with other offices and agencies. That Office works

together with the NIH Division of Nutrition Research Coordination, under the leadership of NIDDK's Dr. Van Hubbard, and with the NIH Office of Alternative Medicine, and with other Federal agencies such as the USDA and the FDA.

These studies have suggested that trivalent chromium, a trace metal for a broad range of organisms including humans, may play a role in the treatment of diabetes; however, the problem at the present time is that there are not sufficient scientific data to relate chromium to the host of other variables influencing carbohydrate metabolism or to devote a major clinical trial to it.

Research on laboratory animals has shown that chromium is a cofactor for insulin action, and is required for maintaining normal glucose metabolism, though its precise mechanism in carbohydrate metabolism is not clear. In humans, early reports noted that three patients with pronounced chromium deficiency also had impaired glucose tolerance, a condition that often precedes the onset of non-insulin-dependent, or Type II, diabetes. Data from some clinical studies, including the one conducted by Dr. Richard Anderson of the USDA's Beltsville Human Nutrition Research Center, suggest that Type II diabetics treated with chromium picolinate showed improvement in blood measures associated with diabetes. In Dr. Anderson's study, a higher dose (1000μg per day) produced the beneficial effects after two months of treatment, whereas a lower dose (200μg per day) produced less marked effects, which appeared after four months of treatment. However, we do not know whether the subjects in that study were deficient in chromium, or what their baseline levels of chromium were. It is possible that chromium supplementation might have different effects in a population nutritionally deficient in chromium compared to a population that has adequate dietary chromium. For example, iodine is useful in preventing hypothyroidism in countries where iodine is deficient, but not in the U.S., where dietary iodine is adequate. Thus, although Dr. Anderson's study may indicate a relationship between chromium supplementation and Type II diabetes, the results are not definitive.

The randomized, controlled, double-blinded prospective clinical trial is the gold standard in clinical research. As it turns out, NIH has conducted at least three such trials on the use of chromium in diabetes therapy, but the findings differed and the answers are still equivocal.

The NIDDK supported a randomized, double blinded, crossover placebo-controlled clinical trial, published in 1983 by Rabinowitz and colleagues, on the use in diabetic patients of inorganic trivalent chromium versus brewers' yeast in two forms, with and without "glucose tolerance factor", or GTF, an organic complex of chromium. All treatments raised chromium levels in the body by about 25 percent, but none of the treatments affected levels of glucose or lipids or the glucose response to a standard test meal or to tolbutamide. Of the 43 subjects, only those resistant to ketosis (15 obese men) showed a significant increase in insulin response to meals; this was with the GTF yeast treatment.

One of the Institute's investigators, Xavier Pi-Sunyer, conducted a randomized, controlled clinical trial of chromium-poor and chromium-rich yeasts in 24 elderly subjects (mean age 78), including eight with mild diabetes and the rest without diabetes, in 1980. Compared to baseline data, both the total group and the two subgroups, with and without diabetes, showed significant improvement in glucose tolerance, and in levels of cholesterol and total lipids. The control group, receiving chromium-poor yeast, did not.

The third NIH-supported clinical trial was published in 1994, and was a prospective randomized, double-blind, placebo-controlled, crossover study of Hispanic groups, 14 men and 16 women, with non-insulin dependent diabetes. Each subject received either 200 micrograms of chromium picolinate or a placebo for two months, then was switched over to the other after a washout period. In the 28 who completed the study, there were no adverse effects, and there was a significant reduction in triglyceride levels, but no effect on cholesterol levels or on hemoglobin A_{1c} levels.

Numbers of subjects in the Anderson study and in the three NIH studies were apparently too small to control for unidentified variables affecting the results. If NIH were to replicate the scope of the Anderson study, which the USDA estimates to have cost close to a million dollars, it would likely be viewed as another in the inconsistent series of trials, unless it includes a very large population sample with many well-defined subgroups. It seems clear that chromium is one of many elements and compounds that can influence carbohydrate metabolism; only some of these many other compounds have been studied to the point of clinical testing. Vanadium is an example of another mineral for which effects in diabetics are under study.

Additional studies of chromium have been conducted, and these extend the record of inconsistent results. A 1992 study of 26 patients with impaired glucose tolerance treated with 160μg of chromium per day for up to six months showed no improvement in glucose tolerance in these patients. A 1993 scientific review summarizing the results of 15 controlled clinical studies of chromium supplementation in individuals with impaired glucose tolerance concluded that three of the studies showed no beneficial effects on blood glucose and insulin levels, while 12 studies showed improvement in "insulin efficiency."

We need to determine more precisely the variables which contribute to the effect of chromium in carbohydrate metabolism, and ultimately to the effectiveness and dosage requirement of chromium treatment for patients with Type II diabetes. It appears that short-term toxicity of chromium picolinate is very low, though the long-term safety in humans of chromium supplements above 200μg per day remains untested. Another research challenge is to develop and validate a procedure to diagnose chromium status. Because chromium status cannot be accurately determined at present, neither can the human chromium requirement. Thus, the tentative Recommended Dietary Allowance for this element is between 50μg and 200μg per day for adults. The chromium intake in a typical Western diet is estimated to be about 50μg per day.

While the NIDDK has supported a number of clinical studies on the effect of dietary interventions on the course of disease, we have funded only one major, formal clinical trial of this type to date. This trial, the Modification of Diet in Renal Disease trial, was the first large-scale, randomized, multicenter clinical trial to test the effects of different levels of protein and phosphorus intake and blood pressure control on the decline of kidney function among individuals with chronic kidney disease. This seven-year study of 840 patients was completed in 1993 at a total cost of $63 million.

The cost of NIDDK clinical trials in general has ranged from as little as half a million dollars for a very small study to as much as $169 million total for a ten-year multi-center trial in over 1400 patients. The costs depend on numbers of patients, complexity, and duration. Clinical trials last from about three years to ten years or more before definitive results are possible.

To estimate the cost of a formal clinical trial of chromium in diabetes, we would assume a procedure along the following lines. The study population would have to include representative subpopulations of major chromium-associated demographic areas. These would be divided between a group given a fixed amount of chromium each day, at two or more dose levels, and a group given a placebo. While the number of patients studied would need to be sufficiently large to obtain meaningful results, it should also be based on the number necessary to establish with reasonable certainty that the expected effect of the treatment being tested is a real one. The trial itself would be designed by a planning committee of experts, and carried out by a consortium of qualified research institutions. This implementation would be done by investigators in medical schools and other research institutions who would compete through the NIH peer review system, on the basis of scientific merit and technical feasibility, for the award of funds to participate in the conduct of the trial. The investigators would determine the parameters of the study, including baseline data. For example, should individuals with impaired glucose tolerance or overt Type II diabetes be studied? How would chromium status be determined? What level of chromium supplementation would be used? How and on what schedule would responsiveness to chromium be measured and evaluated? What would be the endpoint(s) of the study? The investigators would consider many other variables in developing the protocol for the trial, an effort that could take a year or more. Then, patients would be recruited, evaluated, and enrolled in the study. It could take three years or more for all the patients to complete the specified course of treatment. The data would be analyzed in the final year of the trial. We believe this example describes a general time frame and vision for a clinical trial evaluating the usefulness of chromium in treating glucose intolerant or Type II diabetic individuals.

In the absence of the necessary data on which to base a cost estimate, the best we can do is to provide a rough "guesstimate" for such a five year clinical trial, on the order of three to five million dollars per year. Please note, however, that we consider it scientifically premature to undertake a large scale clinical trial without additional pilot

studies to identify who might benefit, and to determine the appropriate dosages of chromium to test, and the sample size (number of subjects to be studied) and duration of the study. Thus, we would not recommend such a clinical trial at this time as the best use of diabetes resources.

ADDITIONAL MATERIAL SUBMITTED BY MR. ISTOOK

CHROMIUM DIABETES STUDY

Study would involve recruitment, medical evaluation, testing and chromium supplementation of 250 subjects with the expectation of having 180 people finish the 8 month study. Subjects would be divided into 3 groups taking 2 capsules/day containing placebo, 100 µg of chromium as chromium picolinate or 500 µg of Cr as chromium picolinate.

The most expensive variables in running the study in the US would be medical fees, testing for insurance purposes, paying of the subjects for coming in for testing and for completing glucose tolerance tests. Study should be completed at three centers and involve subjects with uncomplicated type II diabetes that have not taken nutrient supplements during the preceding three months. No nutrient supplements other than those provided by study personnel would be permitted during the study.

Medical fees for subjects:		
Office visits:		
250 people, testing at preliminary, 0, 2, 4, 6, 8 months:		
$200/ visit (6 visits)	$1200 x 250 x 6	$300,000
Medical Profile	$48 x 250 x 6	72,000
Liver and kidney profile	$44 x 250 x 6	66,000
Payment for glucose tolerance tests	$100 x 250 x 6	150,000
Expenses to Medical Center	$ 50 x 250 x 6	75,000
Two graduate students to help with recruitment, testing and analyses:		
$20,000/year/student 3 years		120,000
Supplies to do testing for the following:		150,000

Hemoglobin A1c, fasting and 2 hour glucose and insulin, insulin binding and receptor number, cholesterol, triglycerides, HDL cholesterol, cortisol, dehydroepiendosterone sulphate, dietary chromium intake, chromium excretion (and if possible red cell chromium), and apolipoproteins. (Body composition measurements should also be made but expenses for these have not been included in the budget).

Study would be completed over three years with recruitment, testing etc. during years one and two with analyses and compilation of the data and writing of manuscripts during the third year.

Expenses for 3 government employees would be paid out of normal operating funds.

Total Outside Funds to Complete Study: $933,000
(This does not include overhead costs)

Richard A. Anderson, Ph.D., C.N.S.
Nutrient Requirements and Functions Laboratory

United States Department of Agriculture | Agricultural Research Service | Beltsville Area Beltsville Human Nutrition Research Center | Beltsville, Maryland 20705

April 2. 1997

NEW METHODS FOR TREATING DIABETES

Mr. Wicker: A recent New York Times article discusses an innovative new method for treating diabetic patients who depend on insulin. This method uses an electronic pump, surgically implanted under the skin, to release insulin into the abdominal cavity. In the article, Dr. Joan Harmon, chief of Diabetes Research at NIDDK, pointed out the significance of the advance. I was wondering if you could elaborate on the findings of this study. In understand that primary beneficiaries of such a method are adult diabetics. What involvement did the Institute have, in terms of funding or research, in the development of the new method? Will it save money in comparison to other methods?

Dr. Gorden: Mr. Wicker, this study was conducted by the Department of Veterans Affairs and thus focused on Type II diabetics, one third of whom require insulin. From the published report, it appears that this device produced more satisfactory blood glucose control than did insulin injections. It has the additional advantage of being internally implanted, as opposed to the currently available pumps, which must be worn externally. External insulin pumps, along with multiple insulin injections, were the two methods used in our Diabetes Control and Complications Trial. Both methods produced excellent results.

The internal pump would have to be tested in children, and approved by the Food and Drug Administration for this use, in order to be available to children. Though the internal pump works quite differently from the external one, older children with Type I diabetes should not have problems using it; younger children probably would require adult assistance, primarily at meal times. With the internal pump, there is the cost of the device and the surgery to implant it. However, if the pump achieves the desired result--tight blood glucose control--it will be cost-effective in terms of reducing the health and economic burden of complications caused by poorly controlled diabetes.

DIABETES PREVENTION

Mr. Wicker: Last year, this subcommittee's report asked NIDDK to focus on prevention through education programs. Could you elaborate on your efforts in these areas, in terms of the programs and their effects?

Dr. Gorden: The National Diabetes Outreach Program was developed by NIDDK to promote the message that improved blood sugar control in people with insulin-dependent diabetes reduces eye, kidney, and nerve damage associated with the disease. Patients calling a toll-free recording can obtain a free information kit with a variety of material about diabetes. To date, over 30 million people have received mass media messages in this campaign, and over 200,000 booklets have been distributed. We also are involved in a collaborative effort with the American Diabetes Association, the Juvenile Diabetes Foundation, the Centers for Disease Control, and other government and private organizations to help inform diabetic patients of the importance of foot care. Because of poor circulation and nerve damage, people with diabetes are more likely to

develop infections from even a minor injury, too often leading to severe damage and amputation. The campaign is called "Feet Can Last a Lifetime." The NIDDK and the Centers for Disease Control and Prevention currently are planning an expanded diabetes education initiative, the National Diabetes Education Program. The NDEP will provide a framework for organizations involved in diabetes to develop effective partnerships at the national, state, and community levels to reduce the burden of diabetes as a public health problem.

RISK FOR DIABETES

Ms. Northup: How do you determine whether a person is at high or moderate risk for diabetes?

Dr. Gorden: In the NIDDK's clinical trial for the prevention of insulin-dependent diabetes, called the Diabetes Prevention Trial--Type I (DPT-I) , patients are being treated based on whether they are at moderate or at high risk for developing Type I diabetes over the next five years. After individuals are recruited, the "staging" process determines the person's risk for diabetes. People with a positive islet-cell antibody (ICA) test, and additional correlative tests, are classified as high risk. Islet cell antibodies progressively destroy the islet cells of the pancreas, resulting in Type I diabetes. These patients are projected to have a greater than 50 percent chance of developing Type I diabetes, and subsequently are assigned to the DPT-I's Insulin Injection Trial. Patients who test negative for ICA, and whose correlative tests do not suggest high risk, are considered to be at moderate risk. That is, they have a 25 to 50 percent chance of developing Type I diabetes in the next five years. These patients are assigned to the Oral Insulin Trial.

Ms. Northup: What percentage of the U.S. population would be in this category?

Dr. Gorden: It is hard to say. I can tell you that the ten DPT-I centers and 350 satellite affiliates will have to screen between 60,000 and 80,000 people, who suspect they may be at risk for diabetes, to be able to enroll the 830 patients necessary for this study. It is estimated that about 13,000 new cases of Type I diabetes arise each year in persons 19 years of age and younger, and that about 16,500 cases arise in persons 20 years of age and older. These 29,500 new cases annually represent a rate of over 27 cases for every 100,000 Americans. What we don't know is what portion of the newly diagnosed patients were at high or moderate risk in the fifth year preceding their diagnosis of diabetes.

Ms. Northup: Why are minority populations disproportionately affected?

Dr. Gorden: Ms. Northup, several studies have shown that minority populations are not disproportionately affected by Type I diabetes. However, it is very likely that the development of non-insulin-dependent (Type II) diabetes depends both on genetic and environmental factors. This is a very active area of investigation supported by our Institute. For example, researchers already have identified several genes that are associated with Type II diabetes and, because diabetes is a complex genetic disease, it is likely that many more genes will be found. We also know that external factors, such as obesity and a sedentary lifestyle, place a person at increased risk for diabetes. Thus, it is possible that minority populations may be genetically predisposed to Type II diabetes and, in addition, that external factors may play a role in the progression of this predisposition to diabetes.

DIABETES INITIATIVE

Ms. Northup: How is your Institute working with other agencies to promote the diabetes initiative which was included in the President's budget?

Dr. Gorden: In addition to the DPT-1, the NIDDK currently is conducting another major clinical trial for the prevention of Type II diabetes. This trial, called the Diabetes Prevention Program, is being conducted with the support of the National Institute of Child Health and Human Development, the National Institute on Aging, the NIH Office of Research on Minority Health, the NIH Office of Behavioral and Social Science Research, the Centers for Disease Control and Prevention, and the Indian Health Service. The DPT-I is a collaborative trial between the NIDDK, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Center for Research Resources (through the General Clinical Research Centers) and the NIH Office of Research on Women's Health.

Ms. Northup: What level of funding will be used in your Institute for this program?

Dr. Gorden: The Federal government will expend approximately $38.3 million for the DPT-I over nine years (FY 1993-FY 2001). The Diabetes Prevention Program will cost an estimated $120.6 million in Federal funds over seven years (FY 1994-FY 2000). The NIDDK's contributions to the DPT-1 and DPP will be approximately $37.8 million and $116.4 million, respectively. We are aware that there is also a proposal in the President's budget to expand Medicare coverage for diabetes self-management training programs in outpatient settings and coverage of glucose monitoring strips. This initiative is within the purview of the Health Care and Financing Administration and does not involve the NIH and NIDDK biomedical research budgets.

Ms. Northup: Are you able to identify F508 in potential parents and if so, what does this mean to reducing the incidence of cystic fibrosis?

Dr. Gorden: Over 500 different mutation in the cystic fibrosis (CF) gene have now been identified which can cause CF. Everyone inherits two copies of each gene, one from each parent, and people with CF have mutations in both copies of the CF gene. One half of CF patients carry the most common mutation, ΔF508, in both copies of the CF gene, and 90 percent have his mutation in one of their two copies of this gene. Thus, interventions to identify ΔF508 have the potential to identify 90 percent of CF carriers. In 1992, the Office of Technology Assessment published a report on CF carrier screening, and concluded that screening tests are likely to become routine within the decade (i.e., by 2002). CF carrier screening will be the subject of an NIH Consensus Development Conference to be held April 14-16, 1997, in Bethesda.

OBESITY

Ms. Northup: How do you test for high levels of leptin in a patient?

Dr. Gorden: Most often a blood test is used to determine the levels. Currently, this test is only available in a research setting.

Ms. Northup: Do you believe that drugs and diet programs which provide drugs are more helpful or harmful to those people who are not obese, but need to lose weight?

Dr. Gorden: Right now we have very limited evidence about the benefits and risks of long term use of drug therapies for obesity. The National Task Force on Prevention and Treatment of Obesity recently published a review article discussing this topic. Their conclusion was that long term use of pharmacotherapy cannot be routinely recommended even for obese patients, but needs a careful case-by-case consideration of the health of the individual concerned. Certainly for those who are only slightly overweight, we cannot recommend pharmacotherapy until we have more information about long-term risks and benefits. The NIDDK is sponsoring a meeting this spring to look at the feasibility and design of a clinical trial that would examine the long-term health consequences of weight loss.

Ms. Northup: Are you fearful that the public will want a drug cure-all for overweight problems, and do you believe such a drug would replace exercise which is so important to reducing the risk of heart disease, stroke, etc.?

Dr. Gorden: Obesity is a complex condition that has environmental and behavioral contributors, as well as metabolic underpinnings. All of these aspects must be addressed in order to help patients lose weight and maintain weight loss. Therefore, medications to treat obesity should not be used alone, but should be used in conjunction with a long-term program to change lifestyle behavior in terms of eating and exercise. Certainly the drugs available now can help only if used this way. In fact, what may happen is that weight loss medications may make it easier for an individual to change food intake and to increase exercise by regulating the metabolic factors that tend to oppose these changes.

END-STAGE RENAL DISEASE

Ms. Northup: Last year the Committee encouraged your research and prevention in kidney diseases, especially in children, yet your justification did not reflect this work. What is your Institute doing in regard to children with end-stage renal disease and kidney disease?

Dr. Gorden: The NIDDK now supports pediatric nephrology research centers and projects related to hemolytic uremic syndrome, IgA nephropathy, and polycystic kidney disease. Among the important basic and clinical research in these areas are clinical trials on HUS and IgA nephropathy. We are also pleased to support research training of

pediatric nephrologists under the National Research Service Award Program. In addition, the NIDDK recently released a Request for Applications (RFA) entitled "Exploratory Grants in Chronic Renal Failure in Children." The NIDDK invites Exploratory Research Project Grant Applications to encourage and facilitate studies designed to develop and/or apply new promising experimental tools to the understanding of the pathophysiology and pathogenesis of events resulting in chronic renal failure and its complications, in children.

DIABETES GENE

Mr. Stokes: An estimated 16 million Americans have diabetes and about half of these individuals are not aware that they have the disease. What specific steps has the Institute taken to expand its efforts on the search for diabetes genes, and what are the major implications of this research for improvements in diabetes treatment, early detection, and prevention?

Dr. Gorden: Research on the genetics of diabetes continues to receive emphasis in the portfolio of NIDDK diabetes research. Though still a relatively young program, this area has generated considerable interest and excitement, and also has spawned numerous collaborative efforts within the research community. Two initiatives the NIDDK implemented in FY 1992 and FY 1993 are at least partly responsible for this surge in research activity. Reports of new diabetes genes now are being published on a regular basis, particularly within the past year.

The genetics of diabetes is complex. Understanding the genetic transmission of Type I diabetes from parent to offspring may offer ideas as to what genetic information causes diabetes and why there is an increasing incidence of Type I diabetes in genetically predisposed populations. In addition, there is some evidence that environmental factors may protect a genetically predisposed individual from developing diabetes. Understanding the role of these environmental factors is critically important.

Identification of genes underlying the more common Type II diabetes is urgently needed so that screening, and then appropriate treatment, of patients can be undertaken before they exhibit full-blown diabetes. It appears that there is significant heterogeneity in the underlying genetic basis of this form of diabetes, and to date only a small fraction of Type II patients exhibit mutations in the genes examined. Thus, considerable effort must still be directed at genetic analysis of patients and their families at risk for developing Type II diabetes.

Efforts to understand the genetic factors involved in diabetes are rapidly progressing. Continued application of genetic approaches may guide researchers to particular areas of the human genome in their quest to ascertain other genes responsible for Type II diabetes. As mutations of these genes are identified, it is likely that investigators will employ transgenic and homologous recombination ("knockout") genetic technologies in order to create animal models for examining the roles of these genes in the development of diabetes. It may further be possible to develop diagnostic tests, based on knowledge of these susceptibility genes, that can be used to identify prediabetic individuals. Such individuals might then take advantage of appropriate interventions to prevent diabetes.

DIABETES IN MINORITIES

Mr. Stokes: As you know, African Americans, Hispanics, and other minority groups continue to suffer a disproportionately higher rate of diabetes as compared with the general population. Do we know what the actual extent of the problem is in minorities? What is the status of the Institute's research agenda as it relates to diabetes in minority populations?

Dr. Gorden: Mr. Stokes, the disproportionate impact of diabetes on minority populations is relatively clear. Consequently, our research agenda continues to incorporate activities that hopefully will lead to a solution to this problem. For example, minorities will comprise at least 50 percent of the patients enrolled in our largest current diabetes clinical trial, the Diabetes Prevention Program, which is studying various pharmacologic and lifestyle interventions to delay or prevent Type II diabetes. We also are supporting a portfolio of smaller prevention studies in minority populations, as well as grants investigating diabetes genes in minorities. We support collaborative diabetes research efforts with the NIH Office of Research on Minority Health, and have implemented a "pilot" outreach program targeting obesity in African American women. As you know, obesity is a major risk factor for Type II diabetes, so efforts that succeed in preventing or reducing obesity will have a favorable impact on reducing diabetes.

OBESITY

Mr. Stokes: Obesity continues to take an enormous toll on the health of the American people, and it is a key risk factor for a number of diseases and disorders. What is the extent of obesity in adults, the elderly, and children, across genders, and across racial and ethnic groups?

Dr. Gorden: Our best recent data have come from the National Health and Nutrition Examination Study III (NHANES III), which looked at 40,000 randomly selected individuals in careful detail. According to data gathered in the period from 1988-1994, almost 35 percent of adults are now overweight. The definition of overweight for this purpose is a body mass index, or BMI, of greater than or equal to 27.8 kilograms/meter^2 for adult men and a BMI for 27.3 or greater for adult women. For white adults, 34 percent of men and 34 percent of women are overweight. For African-Americans, 52 percent of adult women and 33 percent of adult men are overweight. For Mexican-American adults, 50 percent of women and 36 percent of men are overweight. Fourteen percent of children aged 6 to 11 years, and 12 percent of adolescents aged 12 to 17 are overweight. In the elderly aged 75 and older, the prevalence of overweight tends to be somewhat lower than in younger adults. These numbers have increased dramatically over the previous data-gathering period from 1976 to 1980, when comparing the same definitions for obesity. This represents a major public health problem whose consequences will get more severe in the future as these obese individuals suffer the long-term medical effects of their weight.

Mr. Stokes: As you know, progress in obesity research continues to be prominent in the news. What practical effect does this research have on the prevention and treatment of obesity, particularly with regard to Type II diabetes?

Dr. Gorden: As far as treatment is concerned, it is clear that for individuals with Type II diabetes, even modest weight loss can be beneficial. In many cases, weight loss can result in reduction or even elimination of the need for medications. So any progress we make in obesity research may lead to help for those individuals struggling to reduce or control their weight because of diabetes. We also are trying to find out what the benefits are of long-term modifications in diet and exercise as compared with drug treatments in preventing or delaying the onset of Type II diabetes in individuals who are at risk for the disease. The Diabetes Prevention Program clinical trial is enrolling patients to examine this question over the next few years. Fifty percent of patients in the trial will be recruited from a wide range of minority populations, because of the high prevalence of diabetes in these groups.

HEALTH STATUS OF WOMEN AND MINORITIES

Mr. Stokes: Doctor, in your professional opinion, what is the overall status of minority and women's health in this country, and especially, as it relates to the diseases and disorders that are studied by your institute?

Dr. Gorden: As you know, minorities suffer disproportionately from a whole range of serious chronic diseases. While we have a long way to go to remedy this situation, we are making some progress in addressing some of the problems. A few examples of areas where we hope to have a major impact are diabetes, obesity and hypertensive kidney disease. I have already mentioned the Diabetes Prevention Program, which is enrolling 50 percent of its patients from a wide range of minority populations. This trial could have a tremendous impact on minority health if it can demonstrate an effective intervention to delay or prevent the onset of Type II diabetes in individuals at risk for the disease. We also are studying the efficacy of antihypertensive medications on kidney disease associated with hypertension in African Americans in a major clinical trial that involves centers across the country. Preventing progression to end-stage renal disease in these patients would be a tremendous benefit. Finally, the obesity research progress we have been making may have particular importance to minority women, because over 50 percent of African-American and Mexican-American women are overweight, and are subject to all the serious complications associated with obesity. Over the past five years, our Institute has developed an effective and extensive collaboration with the Office of Research on Minority Health (ORMH), which is assisting us in these and other major endeavors.

We also have a number of women's health research problems within the mission of the NIDDK. Many of these conditions are serious and have resulted in a substantial chronic health burden to women. Again, we have a long way to go, but I believe we are making progress. In particular, I'd like to highlight women's urologic disease, an area in which we have made extensive efforts. As the result of several Requests for

Applications (RFAs) and Program Announcements (PAs), we have developed a substantial portfolio of research on disorders of the urinary bladder, including interstitial cystitis, urinary tract infections, and incontinence. Women are at greater risk of heart disease due to diabetes than men, and women who have experienced gestational diabetes have a high risk of progressing to Type II diabetes. Thus, our two major clinical trials in diabetes, which aim at preventing or delaying onset of both types of diabetes, may result in interventions that have great importance for women's health. We also are unraveling the genetics and molecular biology of diabetes, including the effects of gender. I have already mentioned the problem of obesity and our hopes that the breakthrough research of the past two years may lead to dramatic strides in this area. We have a very productive collaboration with the Office of Research on Women's Health (ORWH), which helps us in forming initiatives and provides research support in many of these areas.

COLLABORATIVE EFFORTS

Mr. Stokes: As I am sure you would agree, enhanced collaborative efforts across the institutes offer tremendous opportunities to accelerate research advances, and thereby, increase opportunities for improving the health of the American people. It is for these key reasons that increased collaborative efforts are strongly encouraged. What major collaborative activities are underway and/or planned between your institute and the other institutes of the NIH? Are there projects that are co-funded between your institute and the other institutes?

Dr. Gorden: Our institute has responsibility for a number of diseases that are related to aspects of the missions of other institutes. As a result, we have developed many collaborative initiatives; and we also lead a number of coordinating activities, including the Nutrition Coordinating Committee, and the statutory Diabetes Mellitus Interagency Coordinating Committee, Digestive Diseases Interagency Coordinating Committee, and Kidney, Urologic, and Hematologic Interagency Coordinating Committee. The NIDDK program directors maintain contacts with their counterparts in other institutes and are alert to possibilities for collaboration in new initiatives. As a result of such contacts, in the past year, NIDDK participated in a large number of RFAs and PAs issued jointly with institutes or offices including: NCI, NIAID, NHLBI, NIAMS, NINDS, NIDR, NIA, NIGMS, NINR, NICHD, NIGMS, and ORWH. These initiatives covered a wide range of topics, such as: diabetes interdisciplinary research, gender in autoimmunity, skeletal aging, chronic fatigue syndrome, anabolic hormones in bone, metabolic engineering, steroid receptor structure, eating disorders, osteoporosis and fractures in men, pancreatitis and pancreatic cancer, hematologic abnormalities of AIDS, hematopoietic stem cells, HIV infection in the genitourinary tract, biliary atresia, and *Helicobacter pylori*. The NIDDK took the leadership role in orchestrating a trans-NIH RFA on "Bionutrition" that was very successful.

Where appropriate, the NIDDK provides cofunding to support specific aspects of studies funded by other institutes, and we also receive cofunding for our activities. For example, NICHD, NIA and NIAID each contribute to fund parts of one or both of our

two large diabetes trials. As another example, NIDDK will be contributing this year to NIA's Health ABC study to examine free-living energy expenditure in the elderly as it relates to body composition, health status, and minority status.

Mr. Stokes: What major collaborative activities are underway and/or planned between your institute and the Office of Research on Minority Health? Are there major projects that are cofunded, and if so, which are they and what progress are we making in those areas of research?

Dr. Gorden: I have spoken a number of times of the very effective collaborative relationship that we have established with the ORMH. Almost all of our initiatives with the ORMH are cofunded. For several years, the ORMH has provided substantive support for our Diabetes Prevention Program trial, for the African-American Study of Kidney Disease and Hypertension, for an initiative on diabetes genes and treatment in minorities, for our clinical trial in benign prostatic hyperplasia, and for a clinical study of obesity in minority women. We were recently informed that ORMH intends to continue cofunding for these studies in FY 1997. In addition, ORMH has provided major cofunding to our various programs to train minority researchers at all levels, and to a number of individual grants looking at diverse areas such as: pathogenesis of diabetes in Mexican-American women, a center for hepatitis C research that involves Alaska Natives, and the pathogenesis of *H. pylori*. For most of these projects, it is too early to have a published outcome, but the clinical studies have been making good progress, and we have had some very intriguing results suggesting that the genetics of obesity may vary in different populations.

PROSTATE CANCER

Mr. Stokes: As you know, African American men have the highest rate of prostate cancer than any other segment of the world's population. Could you update the Subcommittee regarding the Institute's research agenda as it relates to prostate cancer in minority populations?

Dr. Gorden: The Urology Subcommittee of the statutory Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee chaired by the NIDDK is developing a plan to expand research on prostate diseases in minority populations, mainly prostate cancer. The first step in this process is a workshop, currently in the planning stages. This workshop will examine generally epidemiologic, clinical, basic, and cost data available on prostate disease.

Also relevant is the NIDDK-supported clinical trial on benign prostatic hyperplasia (BPH) comparing the effects of different medications on the prevention of progression of symptoms of benign prostate disease. The clinical trial is expected to provide insights about the natural history, effective treatment, and interrelationships of the various prostate diseases. In addition, special funding has been provided to selected clinical centers specifically for African American recruitment and enrollment. The National Kidney and Urologic Diseases Information Clearinghouse--an information and

referral service of the NIDDK and a recognized resource for health care professionals, patients, and patient and professional organizations--distributes information on BPH and other urologic diseases and disorders.

Mr. Stokes: I understand that the "Medical Treatment of Prostate Disease" clinical trial appears to offer significant opportunity to address the devastating impact of the disease in minorities. Are there any specific plans being developed to utilize this trial to address this issue, please be specific?

Dr. Gorden: The NIDDK-funded Medical Therapy of Prostatic Symptoms (MTOPS) clinical trial has undertaken special recruitment efforts to encourage enrollment of minority populations. MTOPS is a multicenter randomized clinical trial studying the effects of two drugs, alone, or in combination, on the progression of benign prostatic hyperplasia (BPH) in men 50 years of age or older. Recruitment of nearly 3,000 men is ongoing and is expected to be completed by the end of 1997. A special effort to recruit minority participants into the trial was initiated by the NIDDK in 1996. A workshop, which included experts in minority recruitment and community outreach, was held to identify barriers to minority recruitment and to evaluate minority recruitment techniques that have been used successfully in other clinical trials. Based on the proceedings of that meeting, MTOPS investigators developed minority recruitment plans specific to their locale. Eleven of the 17 participating clinical centers were funded for this activity for a total expenditure of approximately $500,000. Three sites are seeking to enhance recruitment of Hispanic men whereas the remainder are focused on recruiting African Americans. Recruitment techniques include community outreach, recruitment from clinics located at hospitals and medical centers serving large minority populations, and use of mass media, including public service announcements. These special minority recruitment techniques are now being implemented across the country. National publicity about the need for minority participants is being coordinated by a women and minority-owned public relations firm located in Washington, D.C. The goal of this effort is to double the proportion of African American men enrolled in the trial (from nearly 8 to 16 percent) and to include at least 10 percent Hispanic men.

Mr. Stokes: To what extent does your Institute collaborate with NCI in the study of prostate cancer?

Dr. Gorden: The National Cancer Institute (NCI) and the NIDDK have a formalized working agreement under which the NCI assumes primary research responsibility for all aspects of carcinoma of the prostate, and the NIDDK assumes primary research responsibility for non-cancerous conditions. Under this agreement, many areas of mutual interest important to prostate cancer research require collaboration. They include the cofunding of three NIDDK George M. O'Brien Urologic Research Centers; the co-funding of grants that examine factors associated with benign prostatic hyperplasia and prostate cancer risk; the planning of a co-sponsored workshop on prostate disease, mainly prostate cancer, in minority populations; and the possible co-funding of grant applications related to the molecular

biology of normal and abnormal prostate growth that are currently under review. We also collaborate on conferences, such as the recent "International Conference on the Biology of Prostate Growth."

HELICOBACTER PYLORI

Mr. Stokes: Last year, we discussed the higher prevalence of infection with H. pylori in minorities. During that discussion the institute indicated that the disease may be related to several health problems. Specifically, what is the institute doing to advance research in this area?

Dr. Gorden: *Helicobacter* is a cause of chronic gastritis and peptic ulcer disease, and a strong cofactor in development of gastric cancer. Many gaps still remain in our knowledge, including: information about modes of transmission in different populations, the identification of cofactors that lead to cancer, insight into virulence factors in different populations, determination of genetic markers that may relate to disease, and identification of the mechanism of infection and how resistance to antibiotics occurs. I am pleased to tell you that NIDDK and ORMH jointly led in developing a trans-NIH RFA that targets "*Helicobacter Pylori* and Its Relationship to Digestive Diseases and Cancer," with special emphasis on minority populations. This RFA, which was issued in January, is cosponsored by NIDDK, ORMH, NCI, NIAID, and the American Digestive Health Foundation. Grants arising from the RFA should be funded this fall.

CLINICAL TRIALS -- PARTICIPATION

Mr. Stokes: I understand that the institute is supporting major clinical trials in diabetes and kidney disease that include large numbers of minority participants. Can you tell us how these trials are progressing and precisely what benefit they will have for minority populations?

Dr. Gorden: The Diabetes Prevention Program (DPP), is a multicenter clinical trial that is investigating intervention strategies to prevent or delay the onset of Type II diabetes in people with impaired glucose tolerance, or with gestational diabetes mellitus, who are at high risk for developing diabetes. Since Type II diabetes disproportionately affects minorities, the DPP will include approximately 50 percent minority enrollment. Lifestyle and pharmacologic interventions will be studied. The trial is a collaborative effort between the NIDDK and other components of the Public Health Service and the private sector. Successful efforts on a national level to prevent Type II diabetes would have major health and economic consequences.

The African American Study of Kidney Disease and Hypertension (AASK) is a clinical trial designed to evaluate whether lower than usual blood pressure control alone, or in combination with certain classes of antihypertensive drugs, can slow the progression of hypertension-related kidney disease in African Americans. The study is a seven-year, randomized, double-masked, prospective clinical trial. Randomization of

patients into the trial began in the Spring of 1995. As of February 12, 1997 a total of 651 participants were randomized into the trial. This is 62.4 percent of goal. Approximately one-third of the participants are women. The current recruitment goal is approximately 1,100 participants. While the rate of recruitment (randomization) is less than expected, we are encouraged that we have maintained about 60 percent of the goal recruitment rate for over one year. We anticipate continuing recruitment an additional 6 months beyond the originally expected date of completion of May 1997. Thus, we anticipate completing recruitment by the end of 1997. The major source of study participants is identification of patients with high blood pressure from established medical sources such as hypertension clinics, renal clinics, internal medicine clinics and physician offices. Retention of the trial cohort is very good. Ninety four percent of the scheduled follow-up visits have been completed. Unique features of this cohort that provide challenges to retention and adherence include: nearly one-third are unemployed, nearly one-third are divorced or separated, nearly one-half have an annual household income less than $15,000, and about 40 percent have a high school education or less.

More than 20 centers, including most Historically Black Colleges and Universities and most major metropolitan hospitals with a large African American patient population, are participating in this study. The National Institutes of Health Office of Research on Minority Health is also supporting this work. This trial should tell us whether we need to treat blood pressure to a lower level than what is usually practiced, whether a specific class of blood pressure drug is required, or whether both are needed to slow or stop the progression of hypertension-related kidney disease in African Americans.

ORGAN DONATIONS

Mr. Stokes: I understand that African Americans have a higher transplant rejection rate as compared to the general population. Could you elaborate on the rate of rejection. For example, is it across all organs and tissues, explain? To what extent have researchers been able to unravel the cause of this rejection? Are there collaborative efforts underway and/or planned with the NIAID to expand research in this area?

Dr. Gorden: According to data provided to us by the United Network for Organ Sharing (UNOS), African Americans have a higher rate of rejection for most types of organ transplants, and rejection becomes more marked with increasing time post-transplantation. No one knows the exact reason behind this. Postulated causes include differences in health status of the patients; differences in immunological competence and hyperactivity; deficiencies in the human leukocyte antigen (HLA) matching process such that many antigens in black populations are not tested; differences in cytokine production and cytokine levels; and socioeconomic factors. At this time, there are no collaborative efforts underway with the NIAID.

IMPROVING THE HEALTH OF MINORITIES

Mr. Stokes: African Americans and other minorities continue to suffer disproportionately from a tremendous number of diseases and disorders--from cancer to cardiovascular diseases to AIDS to diabetes. It is thought that fuller participation of minorities in the biomedical research enterprise--from the conduct of research to research training to research decision-making on the front-end, would help to dramatically close this long standing gap in health status. What is the institute doing to increase minority representation in basic research and research training?

Dr. Gorden: The NIDDK has reserved training positions to provide research training opportunities to underrepresented minority research trainees. Highly qualified minority investigators are assigned training positions to receive their research training under the guidance of nationally recognized researchers. The intent of this research training activity is to prepare these individuals to compete favorably for NIH research grant support and to fill leadership roles in the biomedical sciences and academic medicine.

NIDDK small grant activity supports recently trained minority investigators with a doctoral degree (M.D., Ph.D., D.O., D.D.S., D.V.M.), to enable the minority individual to accept a tenure-earning position, gain additional research experience and obtain preliminary data on which to base a subsequent research grant application in an area of diabetes, endocrinology, metabolism, digestive diseases and nutrition, kidney, urology and hematology.

CLINICAL RESEARCH

Mr. Stokes: Clinical research is a critical component of the research continuum, as its findings are one of the most important means of determining what constitutes appropriate medical care or treatment. What portion of the Institute's budget is invested in clinical research and how does this compare with the basic research investment?

Dr. Gorden: According to data published by the NIH Office of Extramural Research, the proportion of first-time research grant awardees who are physicians was 58 percent for NIDDK, in FY 1994, which was the highest level among all NIH institutes. This includes more than formal clinical trials, which represented only 8 percent of our budget in FY 1995. An internal NIDDK study of this question determined that physician-patient studies made up 31 percent of our FY 1995 budget. The NIDDK Division of Intramural Research has a direct focus on application of basic research to clinical studies, and devoted about the same percentage of its budget to such studies. The NIH Director's Panel on Clinical Research is now collecting data on NIH support of clinical research, and is using a definition somewhat broader than physician-patient studies as such. Because we consider basic medical research as the foundation for clinical applications, we have not tried to tabulate the two separately.

Mr. Stokes: Obviously, the relevance of clinical research findings is greatly enhanced when the study group is representative of the nation's population as a whole. What is the Institute doing to ensure minority representation in its clinical research programs?

Dr. Gorden: A full-scale clinical trial entitled "African American Study of Kidney Disease and Hypertension (AASK)," is underway to define the most appropriate antihypertensive regimen, as well as the appropriate level at which blood pressure should be controlled. The AASK study is a multicenter clinical trial evaluating whether lower than usual blood pressure control and/or certain classes of antihypertensive drugs can slow progression of kidney disease, and testing interventions to slow the progression of kidney disease associated with hypertension in African Americans. From its inception, the AASK trial has been committed to the participation of minority medical research institutions in collaborations with majority research institutions. The AASK trial is providing support for four Historically Black Colleges and Universities, plus Charles R. Drew University of Medicine and Science, in the full-scale trial.

A major clinical trial, the Diabetes Prevention Program, is underway to determine whether non-insulin-dependent (Type II) diabetes can be prevented or delayed. The interventions tested in this clinical trial are lifestyle changes in diet, exercise, and diet and exercise in combination; and two different pharmacological agents. This national prevention trial involves a number of institutions around the country, including the Washington Hospital Center/Medlantic Research Institute and the Howard University Medical School, that are collaborating in identifying and enrolling African American patients at risk for the development of impaired glucose tolerance and Type II diabetes.

The Medical Therapy of Prostatic Symptoms (MTOPS) trial is a multicenter randomized clinical trial studying the effects of two drugs alone (finasteride and doxazosin) on the progression of benign prostatic hyperplasia in men 50 years of age or older. Recruitment of nearly 3,000 men is ongoing and is expected to be completed by the end of 1997. A special effort to recruit minority participants into the trial began in 1996.

KNOWLEDGE "BOTTLENECK"

Mr. Stokes: The Director of NIEHS, Dr. Olden, spoke about a "bottleneck" when referring to the problems of identifying environmental hazards that contribute to human disease and illness. With regard to the diseases and disorders under the purview of your Institute, what are the most significant "bottlenecks in the Institute's knowledge base," and what are the health implications?

Dr. Gorden: Your question asks about bottlenecks to application and expansion of NIDDK knowledge bases. Fortunately, we have had success in arranging funding participation from non-Federal and commercial organizations as well as other Federal

health agencies interested in the diseases we cover. We have funded what we consider to be a balanced portfolio which attempts to meet the needs of the full range of programs and medical areas that we cover, with particular attention to disease mechanisms, prevention, and therapy.

Mr. Stokes: To what extent will the FY 1997 appropriations allow the Institute to address the "knowledge bottleneck" problem, and how much is included in the FY 1998 budget request for such? In your professional judgement, is the proposed funding level adequate to address the "knowledge bottleneck," Explain?

Dr. Gorden: Most of the reasons for research slow-downs or impediments that one can identify are not under our direct control, making it difficult to tie them to specific budget amounts. The FY 1997 appropriations and FY 1998 request will enable NIDDK to pursue many of the promising new research opportunities that lie before it.

CLONING

Mr. Stokes: All the leading newspapers, television, and science journals just recently reported on the Scottish scientists cloning of adult sheep, and Oregon researchers cloning monkeys. These articles expressed excitement with regard for opportunities for advances in medical treatments, and concern with regard to misuse of the technology and the possibility of human cloning. This is another area where we must now be certain to examine and address the ethical, legal, and social issues of research on the front-end. As a leading researcher and as an institute director, what is you professional opinion of this technology, and what are your most serious concerns?

Dr. Gorden: I support the President's moratorium on the use of federal funds for human cloning research until the scientific, legal, ethical, and regulatory aspects of this issue can be sorted out. In this regard, I look forward to the report of the President's National Bioethics Advisory Commission on this subject. As a scientist, I believe the technologies employed in these experiments may have non-human applications in the laboratory in areas such as developmental biology and gene targeting research. I think we have to be careful to protect the research applications of cloning technologies.

Mr. Stokes: With regard to the diseases and disorders studied by your institute, what are the most significant benefits that the cloning technology would yield?

Dr. Gorden: The NIDDK would be interested in non-human research to examine aspects of cloning technology that may be applied to understanding disease. For example, applications of cloning research to gene targeting may eventually lead to a better understanding of genetic diseases, including diabetes and cystic fibrosis, and help pave the way to the development of methods to repair or replace defective genes that cause these diseases.

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are currently underway, and what are the expected benefits to be achieved from this investment?

Dr. Gorden: Two major examples among current NIDDK clinical trials are the Diabetes Prevention Program (DPP) and the African-American Study of Kidney Disease and Hypertension (AASK). In the DPP, the important questions are "Can the development of non-insulin dependent diabetes (NIDDM) be prevented," and "Can the rate of development of NIDDM be slowed?" Particular attention is being given to the control of blood sugar levels in those with impaired glucose tolerance, a precursor state to NIDDM, in order to reduce the risk for cardiovascular disease and reduce cardiovascular risk factors, and to decrease atherosclerosis. This trial has drawn additional support from the NIH Office of Research on Women's Health and from the NIH Office of Research on Minority Health, and includes special populations as part of its multi-institutional scope. In the multi-center AASK trial, the goal is to slow down the decline in kidney function in African-Americans which occurs with clinically diagnosed hypertensive kidney disease. Treatment approaches include both new and established anti-hypertensive agents in order to maintain a lower than usual level of blood pressure. These two NIDDK trials should make a significant contribution to the prevention and reduction of the burden of two common and important diseases, in populations seriously affected by them. Other major ongoing clinical trials include a series of trials on NIDDM in special populations, the diabetes prevention trial for insulin-dependent diabetes, a trial on long-term outcome of obesity treatment in minority women, the Hemodialysis Study, and a trial on the Treatment of Benign Prostatic Hyperplasia (BPH). Altogether, there are 25 NIDDK-funded clinical trials in progress on diabetes, ten in endocrine and metabolic diseases and gene therapy, six on cystic fibrosis, seven on AIDS, twelve on digestive diseases, seven on nutrition and obesity (some obesity trials are in diabetes), ten on kidney and urological diseases, and eleven intramural trials (in digestive diseases, diabetes and endocrinology, and metabolic diseases). In each of these other trials, similar questions to those mentioned above are being addressed. Our total investment in clinical trials in FY 1996 was almost $60 million.

Mr. Stokes: What major clinical trials that are ready to be implemented will the FY 1998 budget request allow the Institute to pursue, and what are the expected benefits to be achieved?

Dr. Gorden: The 1998 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases represents an increase of 2.3 percent over the FY 1997 level. This level of support will not allow the institute to initiate any new major clinical trials in FY 1998.

POLYCYSTIC KIDNEY DISEASE

Ms. Delauro: Polycystic kidney disease affects 600,000 Americans and 12.5 million people around the world. Great progress has been made toward treatment and a cure for the disease. Could you please update the Committee on how your institute has contributed to this research?

Dr. Gorden: Recent advances in polycystic kidney disease (PKD) are impressive and encouraging. We are proud of our role in supporting much of the research that has formed the foundation for these discoveries. Funding for PKD research through the NIDDK grew from $1.4 million in FY 1986 to $7.5 million in FY 1996. This growth was fueled scientifically by the discovery and sequencing of two genes, *ADPKD1* and *ADPKD2*, and by the identification of the protein regulated by these genes. Most recently, investigators have directed their efforts to gaining insights into the functions of the protein polycystin. If we can learn about its functions, it may be possible to design strategies to ameliorate or possibly even eradicate this disease. To capitalize on this progress, we plan to hold a scientific workshop in September and to solicit additional research grant applications through a Program Announcement.

PUBLIC/PRIVATE RESEARCH PARTNERSHIPS

Ms. DeLauro: I noticed that your institute has developed public/private research partnerships. How do these partnerships work? What kinds of research have you been able to accomplish that might have been achieved more slowly without public/private partnerships? Have other institutes developed similar partnerships?

Dr. Gorden: The NIDDK is very proud of these partnership arrangements, which essentially allow our private sector partners to enhance funding of research in areas we believe hold great promise. The NIH peer review system and traditional grant mechanisms are used for these activities in order to ensure that research applications are evaluated objectively and that only the very best applications are considered for funding support. Our private sector partners often will fund projects that, while scientifically meritorious, are not able to be funded by the NIDDK. We and our partners have found this to be a very productive way to augment the federal research effort. I know of several institutes that have developed similar partnerships.

NUTRITION AND DIABETES

Ms. DeLauro: Nutrition plays a large role in diabetes management. How does your institute address the role of nutrition and diabetes?

Dr. Gorden: Nutrition and diabetes are closely related, especially overnutrition leading to obesity. For Type II diabetes, obesity is one of the major risk factors relating both to onset and to severity of disease. For some Type II patients, even a modest weight loss can lead to reduced use of medications or to even freedom from medications altogether. One of the important questions we now are trying to answer in

diabetes is whether the onset of Type II can be prevented or delayed in patients at risk for the disease. Both diet and exercise modification programs and the use of two different drugs are being tested in our major clinical trial, the Diabetes Prevention Program, to find the answer to this question. A number of small studies also examine the roles of various culturally specific interventions for diabetes in different populations. We also have a large portfolio of investigator-initiated research grants that are looking at the underlying molecular biology of obesity and its relation to diabetes.

DIABETES IN AFRICAN AMERICANS

Ms. DeLauro: A recent study by the Pittsburgh Diabetes Epidemiology Research International Mortality Study Group found that African Americans die at twice the rate of white individuals. What is your institute doing to address this disparity?

Dr. Gorden: According to this study, African Americans appear to be genetically predisposed to Type II diabetes, and obesity or other lifestyle habits may trigger this predisposition, resulting in diabetes. We have known that African Americans, as well as many other minority populations, are disproportionately affected by Type II diabetes. In addition, more than one half of African Americans who have diabetes, and who therefore should be receiving treatment, do not even know they have the disease. Chronic, undiagnosed diabetes causes very serious and irreversible problems to the eyes, kidneys, and peripheral nervous system, and is a risk factor for cardiovascular disease and stroke. The sooner a diagnosis of diabetes is made, the sooner the disease can be controlled. In addition, preventing or delaying the onset of diabetes would reduce morbidity, mortality, and economic burden caused by the disease.

The NIDDK has taken steps to address this problem. I will mention two of the programs we have initiated. The first is the National Diabetes Education Program. A strategic plan for this program is being developed under the leadership of the NIDDK and the Centers for Disease Control and Prevention. The program will provide a framework for organizations involved in diabetes to develop effective partnerships at the national, state, and community levels to reduce the burden of diabetes as a public health problem, especially among minority populations. Representatives of minority organizations and communities are and will be actively involved in the development, implementation, and evaluation of this program.

The second program, the Diabetes Prevention Program (DPP) is a recently implemented multi-center clinical trial to determine whether Type II diabetes can be delayed or prevented in patients that are of high risk for developing diabetes. Patient screening and recruitment for this primary prevention, community-based study began in June 1996. Four thousand patients at high risk for developing diabetes (e.g., obesity or history of gestational diabetes) ultimately will be enrolled at 25 sites in the U.S. Because Type II diabetes disproportionately affects minority populations, approximately 50 percent of the people enrolled in the DPP will be from those populations. DPP patients will have been determined to have impaired glucose tolerance (IGT), which is a major risk factor for development of Type II diabetes. IGT

is a less severe stage of altered blood glucose control that often precedes Type II diabetes. Patients will be randomized into four treatment groups. One of the groups will be given the drug metformin, a second group will be given the drug troglitazone, a third group will receive an intensive diet and exercise intervention, and a fourth will receive healthful lifestyle information about how to prevent diabetes. All of these interventions are aimed at preventing or delaying the progression from the pre-diabetic, IGT state to diabetes, over a period of about 4½ years. All patients will be counseled on healthful diet and exercise habits, and all will be followed closely for their blood pressure, blood lipids, and diabetes status. The National Institute of Child Health and Human Development, the National Institute on Aging, the NIH Office of Research on Minority Health, the NIH Office of Behavioral and Social Science Research, the Centers for Disease Control and Prevention, the Indian Health Service, and the American Diabetes Association are contributing to the DPP. This clinical trial also is receiving major support from the private sector.

CROHN'S DISEASE

Ms. DeLauro: Crohn's disease is a very painful, chronic disease. I commend your institute on the good work you are doing in regards to clinical trials in this area. This past September I participated in a Walk-a-Thon organized by Ricky Slifkin, a courageous young Crohn's sufferer from my district. What strides have we made recently in finding a cure for the disease, particularly in children?

Dr. Gorden: Perhaps because the cause of Crohn's disease and ulcerative disease, the chronic inflammatory bowel diseases, remains illusive, therapies are still unsatisfactory. Though not specific to children, significant advances are being made in both the pre-clinical and clinical areas to better understand the immunologic processes, acute and chronic inflammation, and genetic susceptibility in IBD. Over the last several years, researchers have developed new and exciting animal models that promise to yield insights into the cause of these diseases and provide a means for testing medications and new approaches to therapy. Recent preliminary studies on a group of peptides known as trefoil proteins have shown that they can repair various forms of gastrointestinal tract injury in experimental animals and offer potential for use as orally administered therapy for IBD. Presently, steroid therapy is the primary therapy for treating active Crohn's disease. NIDDK grantees recently conducted a multicenter, randomized, double blind placebo controlled clinical trial using interleukin-10, an immune modifier, and demonstrated results of clinical remission of the disease process in more than 50 percent of the patients compared to placebo. The institute also continues to encourage investigations of treatment options in adults and children through its continuing Program Announcement for small grants for clinical trials in digestive diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

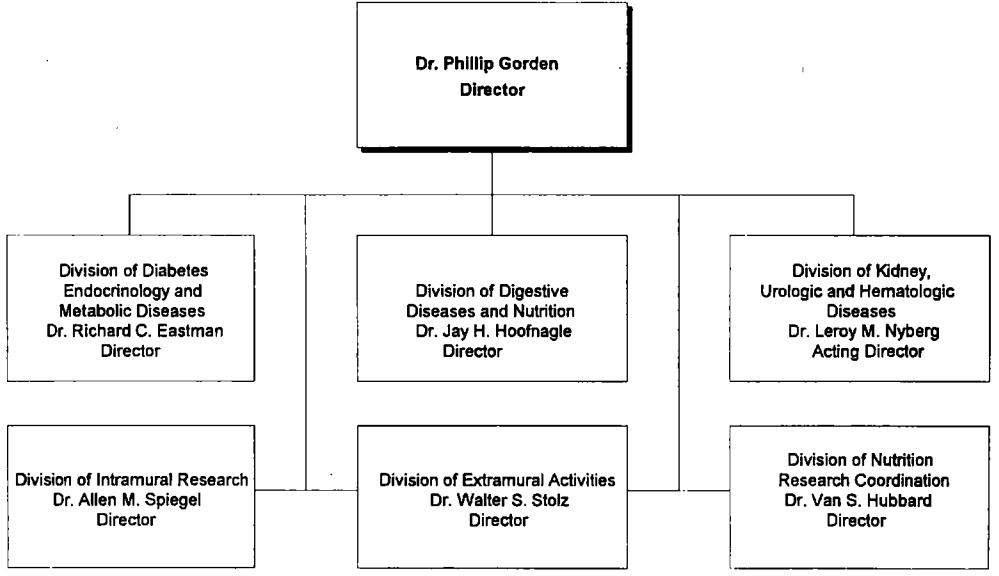
National Institute of Diabetes and Digestive and Kidney Diseases

FY 1998 Budget	Page No.
Organization Chart	2
Appropriation language	3
Amounts available for obligation	4
Justification narrative	5
Budget mechanism table	27
Budget activity table	28
Summary of changes	29
Budget authority by object	31
Administrative costs	32
Significant Items in House and Senate Appropriations Committee Reports	33
Authorizing legislation	47
Appropriation history	48
Detail of full-time equivalent employment (FTE)	49
Detail of positions	50

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases, [$815,982,000] *$821,164,000*.

(Department of Labor, Health and Human Services, Education, and Related Agencies Appropriation Act, 1997, P.L. 104-208)

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

	1996 Actual	1997 Estimate	1998 Estimate
Appropriation	$771,252,000	$815,982,000	$821,164,000
Rescission in accordance with P.L. 104-134	(670,000)	---	---
Reduction in accordance with P.L. 104-208		(375,000)	
Subtotal, Adjusted Appropriation	770,582,000	815,607,000	821,164,000
Real transfer to: Other NIH Institutes through the NIH Director's one percent transfer authority	(2,052,000)	0	0
Comparative transfer to: Office of AIDS Research, NIH for HIV activities	(11,735,000)	(12,718,000)	0
Subtotal, adjusted budget authority	756,795,000	802,889,000	821,164,000
Unobligated balance, lapsing	(177,000)	0	0
Total obligations	756,618,000	802,889,000	821,164,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 1996 - $13,110,000; FY 1997 - $14,000,000; FY 1998 - $14,500,000

Also excludes funding for HIV activities included in the NIH Office of AIDS Research:
FY 1998 - $12,638,000

Note: Excludes $203,205 in FY 1996 and $337,000 in FY 1997 for royalties.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation: Section 301 and 487 of the Public Health Service Act, as amended. Reauthorizing legislation will be proposed.

Budget Authority:

FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
545	$756,795,000	545	$802,889,000	545	$821,164,000	—	$18,275,000

This document provides justification for the FY 1998 Non-AIDS activities of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Justification of NIH-wide FY 1998 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

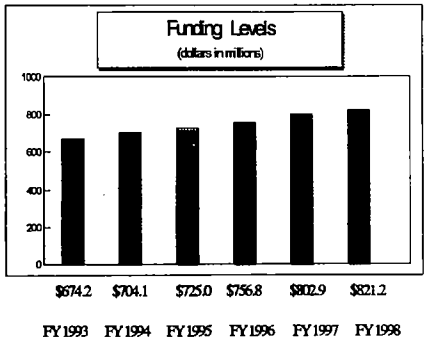
The NIDDK conducts and supports research on many serious and costly diseases affecting the public health. Several diseases studied by the NIDDK are among the leading causes of disability and death in the Nation; all seriously affect the quality of life of those suffering from them. The economic burden of these diseases exceeds $350 billion annually.[1]

A focus on basic research has traditionally guided the Institute's programs. It is grounded in the belief that a fundamental understanding of biologic systems will ultimately explain the abnormalities underlying each disease and thus is imperative for the development of the most effective strategies for prevention and therapy. In addition to basic research, however, the Institute has a strong commitment to expand advances in the understanding of disease processes into appropriate clinical studies and ultimately into efforts to transmit knowledge and effective technologies to practicing physicians.

The NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases is responsible for extramural research and research training related to diabetes mellitus; endocrinology, including osteoporosis; and metabolic diseases, including cystic fibrosis. The Division of Digestive Diseases and Nutrition has responsibility for managing research programs related to liver and biliary diseases, pancreatic diseases, gastrointestinal diseases, including neuroendocrinology, motility, immunology, and digestion in the gastrointestinal tract, nutrient metabolism, obesity, eating disorders, and energy regulation. The Division of Kidney, Urologic, and Hematologic Diseases supports research on the physiology, pathophysiology, and diseases of the kidney,

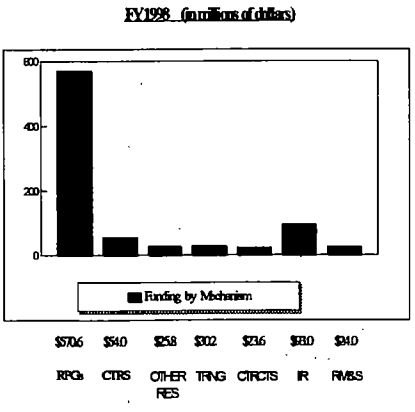
[1] NIH report "Disease-Specific Estimates of Direct and Indirect Costs of Illness and NIH Support," 1995.

genitourinary tract, and the blood-forming organs to improve or develop preventive, diagnostic, and treatment methods. The Division of Intramural Research conducts research and training within the Institute's laboratories and clinical facilities in Bethesda, Maryland, and Phoenix, Arizona. Shared interests in the biochemical and genetic processes underlying disease link the programs and divisions of the Institute, while close communication between the NIDDK and other NIH programs also fosters a confluence of fundamental knowledge in these vital areas of investigation.



Purpose and Method of Operation

The major program areas of the Institute foster basic, clinical, and applied and developmental research through investigator-initiated research grants, program project grants, research center grant awards, research career development awards, Small Business Innovation Research awards, research and development contracts, and intramural research. Training for research careers and/or teaching is accomplished through National Research Service Awards. Particular emphasis is placed on encouraging individuals from under represented minority populations to pursue careers in biomedical research.



Overall Budget Policy

The FY 1998 budget request for the NIDDK provides a 2.3 percent increase and totals $821,164,000, an increase of $18,275,000 over the FY 1997 level. The FY 1998 request will support 545 full time equivalent positions (FTEs), the same number as the FY 1997 estimate.

In the FY 1998 President's Budget Request, the NIDDK's support for research project grants (RPGs) would increase by 2.6 percent over the FY 1997 level. NIH policy links RPG average cost increases to total program budget

requests. The FY 1998 President's Budget requests a 2.6 percent increase for NIH. Thus, Cost Management Plan increases of two percent will be provided for research project grants (RPGs). In general, individual noncompeting RPGs will receive increases of two percent over FY 1997 levels. Average costs of competing RPGs will increase by up to two percent over FY 1997. These increases parallel current projections for FY 1998 inflation indices of 3.1 percent for the Biomedical Research and Development Price Index (BRDPI) and 2.6 percent for the Gross Domestic Product (GDP). Within these levels, the NIDDK will support 548 competing RPGs, a decrease of 56 competing RPGs below FY 1997, and 2,354 total RPGs, an increase of 40 total RPGs over FY 1997.

The FY 1998 request includes funding for 59 research centers, an increase of $1,059,000 and the same number of awards as in FY 1997. The FY 1998 level will fund 232 research career awards, an increase of 5 awards and $397,000 over FY 1997 and 37 other research grants, the same number of awards and an increase of $71,000 as compared to FY 1997. The FY 1998 request will fund 926 research trainees, the same level of awards and an increase of $591,000 and 56 R&D contracts, the same level of awards and an increase of $463,000 as compared to FY 1997. The FY 1998 request provides an increase of $1,365,000 for Intramural Research over FY 1997 and the same level of funding for Research Management and Support as compared to FY 1997.

Stories of Discovery

The Prevention of Diabetes and its Complications

An estimated 16 million have diabetes, a chronic disease that has enormous adverse impact on people who are afflicted, as well as a staggering economic cost to the nation--about $138 billion annually.[2] Basic research, much of it funded by the NIDDK, underpins many therapies developed for diabetes--insulin pumps, various forms of insulin, and strategies for treating insulin-dependent, or Type 1, diabetes; and a host of medications for non-insulin-dependent, or Type 2, diabetes. Even with these therapies, however, diabetes remains an exceedingly difficult disease to control. The health complications that result from uncontrolled or poorly controlled diabetes are largely responsible for the toll diabetes takes on human health and on the health care system. Thus, preventing diabetes and its complications are major goals of research.

The NIDDK is supporting a variety of large and small investigations on diabetes prevention. From many years of multidisciplinary basic research in genetics, immunology, and metabolism, scientists now have the ability to identify individuals at risk for developing Type 1 diabetes. Research, first in animals and then in small human studies, also has shown that low-dose insulin therapy may actually prevent or delay the clinical onset of diabetes. Coupling this knowledge, the NIDDK is conducting a multicenter clinical trial to investigate whether Type 1 diabetes can be prevented or delayed. The goal of the study, called the Diabetes Prevention Trial-1, is to identify individuals at high and moderate risk for diabetes and then to treat them with low-dose insulin. Patients will be followed for four years to determine whether insulin therapy can in fact reduce the risk of developing diabetes

[2] NIH report "Disease-Specific Estimates of Direct and Indirect Costs of Illness and NIH Support," 1995.

A second major diabetes clinical trial, the Diabetes Prevention Program (DPP), is a multicenter investigation of intervention strategies to prevent or delay the onset of Type 2 diabetes in people with impaired glucose tolerance, or with gestational diabetes mellitus, who are at high risk for developing diabetes. Since Type 2 diabetes disproportionately affects minorities, the DPP will include approximately 50 percent minority enrollment. Lifestyle and pharmacologic interventions will be studied. The trial is a collaborative effort between the NIDDK and other components of the Public Health Service and the private sector. Successful efforts on a national level to prevent Type 2 diabetes would have major health and economic consequences.

NIDDK-supported research has made important progress on the prevention of the devastating health complications of diabetes. The Institute's 10-year, landmark Diabetes Control and Complications Trial (DCCT) showed that very careful management of blood glucose levels dramatically reduces the risk of microvascular complications, such as eye, kidney, and nerve damage, due to diabetes. These findings, the first of which were released in 1993, have profound implications for the life-long health and quality of life for all diabetics. To facilitate implementation of the DCCT's recommendations, the NIDDK initiated a National Diabetes Outreach Program and a media campaign, "Do Your Level Best: Start Controlling Blood Sugar Today." The campaign encourages physicians and people with diabetes to adopt a treatment approach that greatly reduces the complications of diabetes. Most recently, the NIDDK, the Centers for Disease Control and Prevention, and private sector diabetes organizations are collaborating to design a National Diabetes Education Program. The program will incorporate research results, specifically those of the DCCT, in public messages about diabetes care.

New Therapeutic Approaches for Cystic Fibrosis

Cystic fibrosis (CF) is characterized by abnormal transport of water and salt by cells lining the lung, pancreatic ducts, intestines, sweat ducts and other tissues. The primary molecular defect lies in a protein called CFTR, which is the product of the gene that is defective in people with CF. CF causes the body to produce an abnormally thick, sticky mucus, which clogs the lungs and leads to fatal infections; and obstructs the pancreas, which prevents enzymes from reaching the intestines to digest food.

Just a few decades ago, parents of the one in three thousand American babies born with CF could expect these children to live less than five years. Research, however, has led to improved antibiotic therapy, aids for clearance of lung secretions, and improved nutritional support, so that the median survival of CF patients now is 30 years of age. Today, newborns with CF may have an even longer life expectancy because of the promise shown of recently introduced aerosolized antibiotic therapy, anti-inflammatory therapy with ibuprofen, and of other new treatments. Even as we have reaped the benefits of continued improvement in therapy directed at removing airway mucus, reducing infection and inflammation, and improving nutrition, researchers are striving to translate the identification of the CF gene discovered in 1989, and the ensuing explosion of information on the biologic basis of the disease, into new approaches to therapy.

Since 1989, basic research has identified an astonishing 500 gene mutations that cause CF. Most of these mutations are rare. The most common mutation, ΔF508, when inherited from both

parents, accounts for nearly 50 percent of CF. Another 40 percent of CF patients have one copy of ΔF508 and a second rarer mutation. Thus, a therapy that could improve function of ΔF508 CFTR has the potential to help 90 percent of patients with CF. Researchers presently are clarifying the different mechanisms by which mutations in the CF gene, particularly ΔF508, alter cell function. They have found that CFTR has several important roles in cell function, each of which could be the target of a therapeutic intervention. This knowledge will have important implications for the design of pharmacologic therapies directed at the basic defect.

Identification and cloning of the CF gene has provided an opportunity for exploring gene therapy approaches to CF. Most NIDDK-supported research in this area has focused on the development of safe and effective methods of transferring a corrected CFTR gene into appropriate cells. Although simple in concept, there are many impediments to targeting the gene to the appropriate cell types and achieving therapeutic levels of gene expression. The Institute is now supporting phase one clinical trials involving small numbers of CF patients to evaluate vectors based on adenovirus and adeno-associated virus as well as lipsome-mediated gene transfer. Substantial effort is also underway to develop new and improved vectors that will be useful for therapy of CF and other genetic diseases.

Cystic fibrosis research continues to be one of the most exciting and fertile areas of science the Institute supports. As new discoveries are made, new opportunities arise. Pursuit of these opportunities will bring us closer to a cure for CF.

Obesity Genes and Neuropeptides

Obesity is a major risk factor for numerous chronic diseases, such as diabetes, cardiovascular disease, hypertension, gallbladder disease, and certain cancers. The cost of obesity to society is close to $100 billion, including nearly $70 billion in direct and indirect medical costs[3], and about $30 billion associated with weight-loss programs and products.[4] This enormous public health impact is likely to be amplified in the future due to the epidemic of obesity in the U.S. that has developed over the past ten years. More than one third of all adults are now considered obese, and childhood obesity also is on the rise. Fortunately, we have never had greater opportunities to attack this problem, based on a true understanding of obesity at the molecular level.

For years, studies funded by the NIDDK hinted that obesity is a complex condition based partly on genetic factors affecting metabolism in obese individuals. We have been gradually gathering evidence about an intricate network of neuropeptide factors that carry signals between the brain and fat, muscle, liver and other cells to regulate intake of food and level of energy expended. This research was suddenly energized two years ago by the breakthrough discovery of the *obese* (ob) gene in mice. Within months, it was demonstrated that the *ob* gene product, leptin, could have dramatic effects on weight and energy expenditure.

[3] NIH report "Disease-Specific Estimates of Direct and Indirect Costs of Illness and NIH Support," 1995.

[4] Institute of Medicine report "Weighing The Options: Criteria for Evaluating Weight-Management Programs." National Academy Press, 1995.

In the past year, NIDDK-funded researchers have demonstrated that mutations in the gene for the leptin receptor also can cause obesity and diabetes in rats and mice. This is crucial evidence of the link between diabetes and obesity. Possible variations in the leptin receptor in human obesity and diabetes are being studied intensively. In Mexican-Americans, variations in the *ob* gene region itself have been shown to be associated with both insulin precursors and obesity-related traits, such as extremity skin-fold measurements, again reflecting the linkage of obesity and diabetes. Other studies have demonstrated that high levels of leptin can cause significant changes in many of the insulin-induced activities in human cells. This implies that leptin in obese individuals may act directly on liver cells to modulate glucose metabolism, and reinforces the idea of its potential as a contributing factor in the onset of non-insulin-dependent (Type 2) diabetes mellitus.

The leptin receptor is present in the brain, as well as other tissues, and presumably serves as a means for leptin to interact with other brain neuropeptide signals. Defective leptin signaling in mice has been demonstrated to lead to over expression of neuropeptide Y in the hypothalamus, which in turn is related to overeating. In another strain of genetically obese mouse, the *agouti* mouse, obesity appears related to blocking of melanocortin-4 receptors in the hypothalamus. Likewise, the newly discovered hormone, urocortin, appears to act through receptors in the hypothalamus to dramatically reduce food intake. All of these peptides and receptors present potential candidates for design of drugs to block or enhance their actions, with potential for improved interventions in obesity. Many such candidates are under development by the pharmaceutical industry, and offer great hope.

Eradication of *Helicobacter pylori:* A Bacterial Culprit in Ulcer and Gastrointestinal Disease

It is now widely accepted that *Helicobacter pylori* is the major cause of chronic gastritis and is strongly associated with duodenal and gastric ulcers. Infection with this bacterium is also a risk factor for gastric cancer. The 1994 recommendations of an NIH Consensus Development Conference confirmed that all patients with peptic ulcer disease should be treated with antibiotics and antisecretory agents once the bacterium is detected. Where formerly the prevailing dogmas were "no acid, no ulcer," and "once an ulcer, always an ulcer," clinical practice has been revolutionized by the discovery that eradication of the infection-causing bacterium with antimicrobial drugs and acid blockers heals ulcers and significantly reduces their recurrence. The recent FDA approval of several drug combinations that use antibiotics with acid blockers should impact in a major way on the health care costs of ulcer disease, which are estimated at between $400 and $800 million annually in the United States.

The means for detecting active ongoing infection has been made far easier with recent FDA approval of the urea breath test--a noninvasive and inexpensive test developed by NIDDK grantees. This safe and very effective diagnostic tool confirms the presence of H. Pylori and should help to eliminate unnecessary treatment sometimes prescribed by physicians to avoid the more expensive and invasive endoscopic diagnostic procedure.

In exploring specific virulence factors that may influence the outcome of infection, NIDDK-supported investigators discovered that persons infected with *H. pylori* strains of the CagA type

have increased risk of developing cancer or duodenal ulcer. They also learned that persons infected with strains of the vacA genotype S1 type are at increased risk of having duodenal ulceration. Other research has shown that the duodenal mucosa is protected by the interaction of several defensive factors such as blood flow, mucus secretion, and bicarbonate secretion. Now, researchers have found that duodenal ulcer patients infected with *H. pylori* have markedly decreased bicarbonate secretion in the duodenal bulb and that duodenal mucosal bicarbonate secretion returns to normal once the organism is eradicated, which may thereby reduce ulcer recurrence. In another development supported by the NIDDK, a family of proteins known as trefoil factors have been shown to protect the epithelium. Trefoil proteins may act as a defense against damage induced by *H. pylori*, which depletes the mucous layer and increases its vulnerability to damage after infection.

Understanding the causes of a disease and its pathogenic mechanisms is essential to effectively impacting on its incidence. It is estimated that a treatment strategy of antibiotics and antisecretory agents should eliminate 80 percent to 90 percent of *H. pylori*-related peptic ulcer disease in the United States. Outstanding questions remain regarding whether all patients with dyspepsia should be screened for *H. pylori* and treated with antibiotics, or even whether healthy people should be screened for *H. pylori* and treated to prevent possible future peptic ulcers or gastric cancer. These are subjects that invite further clinical and basic studies.

The Discovery of Genes for Polycystic Kidney Disease

Polycystic Kidney Disease (PKD), which is characterized by the growth of numerous cysts in the kidney, is one of the most common genetic diseases in humans, affecting approximately 1 in 1,000 individuals. PKD includes two genetically distinct conditions: autosomal recessive PKD (ARPKD) and autosomal dominant PKD (ADPKD). ARPKD constitutes a very serious renal illness in children, often leading to end-stage renal disease during childhood. ARPKD has recently been localized to a small interval on chromosome 6 and candidate gene isolation is likely to begin shortly. Studies suggest that this disease is genetically homogeneous.

ADPKD represents the most common form of PKD, responsible for approximately 85 percent of all PKD cases, and accounts for eight to ten percent of all end-stage renal disease world-wide. As well as renal disease, ADPKD is associated with hypertension and cystic growth in other organs, namely the liver. The nature of the primary defect which triggers cyst formation is unknown, and therefore a large effort has been devoted to identifying the causative agent by genetic means. In the last two years, dramatic progress has been witnessed in understanding the cause, pathogenesis, and clinical course of ADPKD. The genes that are mutated in PKD1 and PKD2, the two most common forms of ADPKD, have been cloned, sequenced, and the protein structures deduced. At least one more gene for ADPKD is known to exist and genetic linkage studies are presently underway to try to identify this gene. As a result of these findings, DNA testing may now be used to define the type of PKD that affects a family.

On another front, there has been steady progress to determine the natural history of both ARPKD and ADPKD. Risk factors that predispose an individual with PKD to end-stage renal disease, hepatic cysts, and intracranial aneurysms have been identified and a number of compounds have been shown to decrease the rate of cyst formation in animal models of PKD. Other studies in

animals with hereditary PKD have shown that administration of pharmacologic agents and dietary modifications substantially altered the clinical course of this disease. In addition, there is evidence of a role for modifying genes in both adult and pediatric forms of PKD.

These discoveries provide important insights for the diagnosis and therapeutic interventions designed to slow disease progression and attenuate PKD-associated morbidities. These landmark research accomplishments, from which new achievements will certainly flow, help move the field toward the ultimate long-range goal of gene therapy for PKD.

Extramural Research

Rationale for Budget Request

The FY 1998 budget request for the Extramural Program is $704,100,000, an increase of 2.5 percent over the FY 1997 appropriation of $687,190,000. With the FY 1998 extramural request, these funds will provide support for the following activities: Diabetes, Endocrinology, and Metabolic Diseases, $342,100,000, an increase of $7,736,000 or 2.3 percent over the FY 1997 estimate of $334,364,000; Digestive Diseases and Nutrition, $170,400,000, an increase of $4,200,000 or 2.5 percent over the FY 1997 estimate; Kidney, Urologic, and Hematologic Diseases, $191,600,000, an increase of $4,974,000 or 2.7 percent over the FY 1997 estimate of $186,626,000.

Research Highlights: Diabetes, Endocrinology, and Metabolic Diseases

Diabetes

The NIDDK is the lead agency of the Federal government for research efforts to combat diabetes mellitus and its complications. Diabetes is the sixth leading cause of death from disease in the U.S., afflicting an estimated 16 million people in FY 1997, one-half of whom are undiagnosed. This figure reflects a 50 percent increase in diabetes since 1983, which is believed to be due to several factors. More Americans are now in the older age ranges where the rates of non-insulin-dependent, or Type 2, diabetes are higher, and the rates of obesity and physical inactivity, both of which are risk factors for Type 2 diabetes, have increased. Diabetes is the leading cause of new adult blindness, kidney failure, and non-traumatic amputation, and is a major risk factor for increased, stroke, heart attack, and premature death. With an annual economic cost to the nation of approximately $138 billion, diabetes ranks near the top of the most costly illnesses and threats to health in America.

Type 1 (insulin-dependent) Diabetes Mellitus: Type 1 diabetes affects an estimated 800,000 Americans, with onset usually occurring in childhood or early adulthood. In this disease, the immune system, which is designed to protect against foreign agents such as bacteria and viruses, initiates a powerful attack to destroy the insulin-producing islet cells of the pancreas. Eventually, for survival, affected individuals require insulin from an external source to regulate blood glucose levels.

In the past year, investigators were able to markedly delay the onset of Type 1 diabetes in a strain of mice that spontaneously develop the disease. They did this through intranasal administration of an insulin peptide. Other investigators bioengineered rat pituitary cells to produce insulin, then transplanted the cells into diabetic mice. Normal blood glucose levels and reversal of diabetic symptoms were achieved in the host animals, and the foreign implanted cells were not destroyed by the host animal.

Islet transplantation holds promise for the treatment of diabetes. For this promise to be realized, however, it will be necessary to overcome immunological barriers to the survival of the transplants and the problem of disease recurrence. NIDDK grantees have demonstrated that islet graft rejection in mice can be prevented by co-transplantation with cells producing a protein that interacts with lymphocytes such that the lymphocytes themselves are destroyed before they destroy the islet graft Researchers are further examining this approach as a means of maintaining the long-term survival of islet transplants.

Type 2 (non-insulin-dependent) Diabetes Mellitus: Type 2 diabetes accounts for about 90 percent of all diabetes. What makes Type 2 diabetes so insidious is that it often is diagnosed only after it has begun to damage the heart, blood vessels, kidneys, eyes, teeth, and nerves. In addition, as diabetes develops it becomes increasingly difficult to treat.

One of the problems in type 2 diabetes often is not that pancreatic islets cannot produce insulin, as in Type 1 diabetes. Rather, it is the control of insulin production and distribution to the body that is defective. Recent research by NIDDK grantees has begun to unravel the molecular mechanisms that control insulin production and secretion in Type 2 diabetes. These studies, which are the result of over ten years of basic research, are critical to the development of new generations of pharmacologic therapy for Type 2 diabetes.

Other researchers examined cyclic changes in insulin sensitivity in Type 2 diabetic patients over a 24-hour period. They demonstrated that while insulin levels remained unchanged over 24 hours in diabetics (levels fluctuate in non-diabetics) insulin sensitivity decreased during the night and increased during the day. Cyclical changes in insulin sensitivity have clear implications for the diagnosis and treatment of patients with Type 2 diabetes.

Genetics of Diabetes: Genetics appears to be the common denominator underlying the various factors that lead to diabetes. Intensified genetic research offers great promise for understanding, controlling, and preventing diabetes. The role of genetics in the development of Type 1 diabetes was further elucidated this year. An examination of 9,500 offspring from 5,300 Finnish parents with Type 1 diabetes concluded that the risk for diabetes is higher in offspring of fathers than of mothers with diabetes. Also, if the offspring were of the same gender as the diabetic parent, male offspring had a higher risk of diabetes than female offspring. If the offspring were of a different gender, the risk in male offspring was lower. A separate analysis of transmission of a diabetes-specific antibody confirmed the validity of this predictive indicator.

During the past year, significant results were reported suggesting the chromosome locations of several Type 2 diabetes susceptibility genes. The first report identified a region of chromosome 2 as a susceptibility gene and called the yet-unidentified gene within this region, NIDDM 1. These

results were obtained by screening the genes of Mexican American siblings. In a second study, which also utilized genetic material from Mexican Americans, linkage of blood glucose concentration two hours after oral glucose administration was observed in two regions of chromosome 11. A third study utilized a population from western Finland and performed a genome-wide scan. The results demonstrated linkage between low insulin levels in affected individuals and a region on chromosome 12, which is referred to as NIDDM 2. This region also contains the gene causing the rare, dominant, early-onset form of diabetes, MODY3. The investigators suggest that MODY3 and NIDDM 2 may represent different forms of a single gene, with severe mutations causing MODY and milder mutations giving rise to Type 2 diabetes.

While only a small fraction of diabetes genes, particularly those associated with Type 2 diabetes, are now known, continued application of genetic approaches may guide researchers to particular areas of the human genome in their quest to ascertain other genes responsible for diabetes. As mutations in these genes are identified, it is likely that investigators will employ transgenic and homologous recombination ("knockout") genetic technologies to create animal models for examining the roles of these genes in the development of diabetes. It may further be possible to develop diagnostic tests that can be used to identify prediabetic individuals; such individuals might then take advantage of appropriate interventions to prevent diabetes.

Diabetes in Minority Populations: Minority populations, including African Americans, Hispanic Americans, Native Americans, Mexican Americans, Native Hawaiians, and Alaskan Natives, are disproportionately affected by Type 2 diabetes and its health complications, and by its enormous economic and health burden. Research has shown that the most prominent risk factors for Type 2 diabetes are a family history of diabetes, obesity, insulin resistance, hyperinsulinemia (increased insulin secretion), a history of gestational diabetes, and impaired glucose tolerance.

Minority populations will play a major role in the recently initiated Diabetes Prevention Program. This multi-center, seven-year clinical trial of preventive intervention strategies is targeted at individuals with impaired glucose tolerance, a history of gestational diabetes, and/or newly diagnosed NIDDM. Minorities will make up 50 percent of the study population. Interventions will include diet, exercise, and pharmacologic agents.

Recently, NIDDK grantees utilized intensified therapy (insulin and sulfonylurea administration) of newly diagnosed African American Type 2 diabetics to bring the blood glucose levels of these individuals to near normal. The therapy was then withdrawn, and was observed to be followed by near normal blood glucose remission for approximately 40 months. It is possible that remission may be prolonged by low-dose sulfonylurea treatment, thereby potentially reducing the frequency and/or severity of complications from diabetes in African Americans, and possibly in other groups yet to be studied.

Endocrinology

Hormonal Regulation of Bone and the Prevention of Osteoporosis: NIDDK support of endocrinology research has led to major advances in understanding the biologic roles of parathyroid hormone (PTH), the key hormone regulating bone and mineral balances; parathyroid hormone related peptide (PTHrP); and the common PTH/PTHrP receptor. These elements are

involved in normal and abnormal bone development and remodeling, with implications for the prevention and treatment of osteoporosis and related bone disorders. In recent years, NIDDK grantees have isolated, cloned, and characterized each of these elements.
In a major new advance, NIDDK-supported investigators have determined the underlying mechanism of action of PTHrP in regulating bone development and growth. The regulation of the proliferation and differentiation of embryonic tissues is regulated by a family of secreted proteins called "hedgehogs." These embryonic signaling molecules were found to be present in the developing cartilage of the long bones, but it was not clear what role they played.
Researchers now have discovered that one of the hedgehog proteins, "Indian hedgehog" (Ihh), is produced and released by cartilage cells and stimulates expression of PTHrP, which then further regulates the cartilage cells through the PTH/PTHrP receptor. PTHrP slows the conversion of dividing cartilage cells into mature cartilage cells, allowing for continued growth of the long bones. In this way, the rate of bone formation is regulated, as is the final length of the long bones. In the absence of Ihh, or of PTHrP, or the PTHrP receptor, defects in bone growth result because of the loss of normal control of the rate of development of the cartilage cells, with premature ossification causing shortened bones. When each factor is expressed appropriately, growth of the long bones is carefully controlled, and bone growth occurs at an appropriate rate. Bones do not grow too long, nor too short, nor too fast.

Reduction of estrogen levels at the menopause causes an initial rapid decline in adult peak bone mass, as bone loss exceeds the rate of bone formation. Subsequently, there is a gradual loss of bone mass and an increased risk of fracture. Postmenopausal women are particularly prone to fracture at the spine, the hip, and the wrist. In work supported by NIDDK, it has become clearer how estrogen works to maintain bone mass. This hormone shortens the lifespan of cells that cause bone loss (osteoclasts). It does so indirectly by stimulating production and release of a potent growth factor in bone, transforming growth factor-beta (TGF-β). The major role for TGF-β in bone appears to be to regulate the life cycle of osteoclasts, but only when stimulated by estrogen. In the absence of estrogen, such as in postmenopausal women, this level of control is lost, and osteoclasts are not regulated, resulting in excessive bone loss (osteoporosis) and increased risk of fracture. Hormone replacement therapy, which includes estrogen, would partially reverse this effect by restoring a more normal mix of hormones to the bone environment.

These major new advances now provide investigators with improved understanding of the underlying mechanism of action of bone regulating hormones and growth factors. This opens up the exciting possibility of designing drugs or other agents that can mimic the desired effects of PTHrP or estrogen on bone turnover to either preserve bone or stimulate the production of new bone. Since estrogen has many other effects on tissues, such as breast and uterus, which are not desired when considering its role in the prevention of osteoporosis, agents that have effects limited to specific target tissues would be very important.

Metabolic Diseases

Gene Therapy--Long-term Systemic Delivery of Proteins Expressed in Muscle: The ultimate goal for the treatment of genetic diseases is to replace the defective gene with a corrected gene. In theory, this is a simple concept; in reality, however, there are many impediments to targeting a gene to the appropriate cell types and achieving gene expression at physiologic levels. This year,

several laboratories have investigated the use of muscle cells to deliver serum proteins into the circulation. Investigators were able to achieve long-term physiologic affects using a variety of gene transfer approaches into muscle. NIDDK-supported researchers were able to express two different cytokine genes, erythropoieting and G-CSF, in mouse muscle, and observed physiologic changes for over a year. These approaches could ultimately be useful for the delivery of other serum factors such as factor IX, factor VIII, alpha-1-antitrypsin and insulin. However, the concentrations required for a physiologic effect by these factors will require technological advances to increase gene expression levels. An alternate approach to deliver recombinant proteins could have economic benefits. For example, the annual cost of recombinant erythropoietin for the treatment of anemia in renal disease has been estimated at $500 million.

New Animal Models for Studying Genetic Metabolic (Orphan) Diseases: Orphan diseases are defined as diseases which affect less than 200,000 people. There are many genetic metabolic diseases that are considerably rarer, affecting only 100 to 1,000 people. Although each individual disease is rare, in aggregate they represent a substantial health burden. For many genetic diseases, there is no effective treatment. The development of animal models for genetic diseases is essential for investigation of various treatments. For some diseases, bone marrow transplantation has shown beneficial results, but the risks of bone marrow transplantation for those with an unmatched donor has prevented this from becoming standard therapy. For diseases where the cause is known, specific treatments such as enzyme replacement therapy and gene therapy are being investigated.

NIDDK grantees reported the development of several new animal models for orphan diseases this year: tyrosinemia type 1 (mouse), APRT-deficiency (mouse), Fabry Disease (mouse), Krabbe disease (dog), and glycogen storage disease, type VII. These models will be critical to testing new treatment strategies, including enzyme replacement therapy, gene therapy, and bone marrow transplantation for these genetic diseases.

Research Highlights: Digestive Diseases and Nutrition

Digestive Diseases

Diseases of the digestive tract exact an enormous health burden in the United States as compared with other organ systems. Digestive diseases afflict 62 million persons, result in some 50 million office visits to physicians, 10 million hospitalizations, 230 million days of restricted activity, and nearly 200,000 deaths. Total costs for digestive diseases have been conservatively estimated at $56 billion a year.[5]

Inherited Diseases of the Liver and Pancreas: Hereditary hemochromatosis (HH) is one of the most common hereditary disorders among individuals of Northern European descent occurring in about 1 in 400 of the U.S. population. Despite its prevalence, it is widely under diagnosed. Hemochromatosis is marked by an excessive absorption of iron from the intestine which over years can gradually accumulate in various organs, such as the pancreas, liver and heart, and lead to diabetes, cirrhosis, liver cancer, and cardiac dysfunction. Most importantly, this disease is

[5] NIH report "Disease-Specific Estimates of Direct and Indirect Costs of Illness and NIH Support," 1995.

easily treated if detected early. Treatment merely requires donating blood every one to two weeks until the abnormal stores of iron are decreased to normal. If, however, HH is not detected until after there is tissue injury (heart or liver disease), morbidity and mortality are significant. In a collaborative effort between NIDDK-supported researchers and industry, a linkage mapping approach was used to identify a region adjacent to the major histocompatibility complex (MHC) which was identical in 85 percent of patients with HH, but only in 3.2 percent of controls. Within this region was a gene named HLA-H containing a missense mutation that predicts inaction of the HLA-H proteins and is homozygous in patients with HH. The proteins expressed by the HLA-H regions are found in the tissues of organs which exhibit dysfunction in HH. Discovery of a strong candidate gene for HH is a major breakthrough that will permit researchers to develop a genetic test to identify those persons at risk and allow them to further examine the mechanisms which involve the HLA-H protein in iron metabolism.

Scientists have taken important steps in another genetic digestive disease. Hereditary pancreatitis is an inherited form of pancreatitis characterized by recurring bouts of severe epigastric pain with onset in childhood. Progression to chronic hereditary pancreatitis can result in diabetes mellitus, and/or pancreatic cancer. Research involving a 500 member pedigree constructed from a U.S. kindred centered in eastern Kentucky and West Virginia has disclosed a single point mutation in a pancreatic enzyme gene in all individuals with hereditary pancreatitis that provides a genetic marker for this disabling condition. Thus, individuals at risk for hereditary pancreatitis can be identified before the onset of clinical symptoms.

Protective Role of Oral Trefoil Peptides in Gastrointestinal Disease: Estimates are that some 14 million persons in the United States take nonsteroidal anti-inflammatory drugs (NSAIDS) for relief of pain and joint symptoms. A limiting factor in the use of NSAIDS is their ability to cause gastrointestinal side effects, including symptomatic ulcers and potentially life-threatening ulcer complications which are reported in two to four percent of patients who take NSAIDS for a year. These rates are probably higher in the elderly. Though the side effects of NSAIDS are infrequent, they are potentially serious and have become a major health care problem because of the numbers of patients who use them. The role of a group of peptides known as trefoil proteins for their distinctive three-leafed chemical structure has now been defined in the maintenance and repair of the intestinal mucosa in experimental animals. The recent research of NIDDK grantees reveals that mucosal healing of epithelial injury was impaired in mice unable to express intestinal trefoil factor (ITF)--a protein secreted throughout the small intestine and colon. Trefoil factors offer potential for use as oral therapy for various forms of gastrointestinal tract injury.

Gallstones: Gallstone disease is present in 10 to 40 percent of individuals over the age of 60, and genetic factors appear to play an important role in its development. Though evidence to support the role of genetic factors in human gallstone disease is limited, it is known that in certain native populations of North and South America a high percentage of adults develop cholesterol gallstones, which suggests common genetic factors. Gallstone disease has also been shown to be familial. In recent studies a genetic analysis was performed of the difference in gallstone prevalence rates between inbred mouse strains--one resistant to gallstone formation and one with a high prevalence of gallstones. The mice that were resistant to gallstone formation were shown to down regulate an enzyme which is a rate-limiting enzyme in cholesterol biosynthesis. Mouse strains susceptible to gallstone formation did not down regulate this enzyme indicating a

mechanism for the hypersynthesis of cholesterol. A major gene, called *Lith1*, was mapped to mouse chromosome 2. These studies demonstrate that gallstone formation is genetically determined and that susceptibility to gallstones is a dominant trait. The better the genetics of gallstone formation in mice is understood, the easier it will be to clarify the genetic determinants of this disease in humans.

Inflammatory Bowel Disease (IBD): Crohn's disease and ulcerative colitis, the chronic inflammatory bowel diseases, are common causes of gastrointestinal disease in the Western world. In recently described animal models, it has been shown that active IBD is associated with increased proinflammatory cytokines. Important new findings demonstrate that the cytokine interleukin-10 (IL-10) decreases production of inflammatory cytokines in the intestines of patients with IBD, suggesting anti-inflammatory and immunosuppressive properties of IL-10. Based on this observation, NIDDK grantees conducted a multicenter clinical trial using intravenous doses of interleukin-10 for seven days in patients with active Crohn's disease who were unresponsive to steroid therapy--the primary therapy for treating active Crohn's disease. After careful follow up for four weeks, results demonstrated clinical remission of the disease process at all dose levels of interleukin-10 in more than 50 percent of the patients compared to placebo. Corticosteroids often cause undesirable side effects. Thus, support has increased for other forms of therapy that will be effective in steroid refractory patients with Crohn's disease. Larger controlled studies of IL-10 are now indicated that will further evaluate the route of administration and impact of other routes of administration on clinical response to this exciting new therapy.

Nutrition

The NIDDK supports a broad portfolio of basic nutrition research that seeks to understand the molecular role of nutrients in the maintenance of health and in the prevention and treatment of disease. The Institute also fosters clinical nutrition research in the many areas of the NIDDK mandate, including diabetes, obesity, and chronic renal disease.

Ongoing Obesity Initiative: Even as NIDDK-supported researchers continue to pursue the molecular details of obesity, they are also addressing the clinical possibilities of currently available interventions. The National Task on Prevention and Treatment of Obesity, an outside group of experts in the field, provides scientific assessment of research opportunities and appropriate scientific messages to be translated to the public. The Task Force includes representation from other NIH and DHHS components with an interest in obesity issues. A major issue confronting the Task Force is the lack of information about the benefits and risks associated with long-term weight loss. This is an important public health question, because of the widespread availability and use of new medications for this purpose. In the spring of 1997, the Task Force will sponsor a workshop to discuss the design and feasibility of a randomized clinical trial of long-term intentional weight loss and health outcomes.

To inform the public, the NIDDK is continuing to develop its Weight-Control Information Network as a major avenue for communication with the public, featuring a toll-free number for information, a range of fact sheets based on the current scientific knowledge in obesity, a central database of obesity literature, and an important pilot study of obesity prevention in a group of

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minority women in the Boston area. A newsletter and exhibits are used to advise health professionals of recent nutrition and obesity research advances.

Bionutrition: In the early days of nutrition research, focus was directed primarily to the deficiency diseases caused by severe nutrient deprivation. Now, bionutrition research is revealing that dietary nutrients also can influence health and disease through the molecular control of gene expression. Dietary fat in particular has been of great interest, because of its linkage to obesity, insulin resistance, hypertension, coronary artery disease, and some cancers. NIDDK-funded studies indicate that fatty acids have specific effects on gene expression, leading to altered metabolism, cell growth and differentiation. For example, NIDDK-funded investigators have gradually developed a large body of information about two regulatory systems in the liver through which fatty acids can suppress the formation of fat in the liver. In one case, fatty acids activate a family of transcription factors, which in turn can activate or suppress transcription of the genes for specific metabolic enzymes. By means of a different regulatory factor, polyunsaturated fatty acids suppress the transcription of genes for certain fat and sugar processing enzymes. Further understanding of the details of these systems for controlling gene expression may lead to alternative drugs for control of lipid metabolism in cases of dyslipidemias.

At the same time, the NIDDK continues to make progress in important clinical nutrition areas. For instance, as part of a study of mortality and morbidity in hemodialysis patients, NIDDK-funded investigators have discovered that many patients on dialysis have significant malnutrition, which worsens as renal failure progresses, and that impaired malnutrition at the initiation of dialysis is related to increased mortality. These findings suggest the importance of aggressive early treatment of impaired nutrition in dialysis patients. Such studies are underway.

Research Highlights: Kidney, Urologic, and Hematologic Diseases

Kidney Diseases

Kidney Disease of Diabetes Mellitus (KDDM): Diabetes is the leading cause of kidney failure in the United States, accounting for nearly one-third of all new end-stage renal disease cases. Researchers have been focusing on the mechanisms involved in the hallmark of KDDM -- the scarring of the kidney's filtering system, the glomeruli. This year, investigators studying the regulation of glucose uptake and metabolism within the kidney found evidence suggesting that a metabolic mechanism involving altered expression of a glucose transporter protein possibly contributes to the increased filtration rate and pressure within the kidney often observed early in the course of diabetes, before scarring becomes severe. If confirmed, this finding offers another possible target for arresting or delaying the development of KDDM. Other studies indicate that insulin may exert a direct effect on the kidney and that insulin-like growth factor may affect the scarring process. Scientists also continue to investigate how an angiotensin-converting enzyme inhibitor affects the kidney at the molecular level, since this inhibitor was found to slow the progression of kidney disease in patients with Type I diabetes and may provide clues for new KDDM therapies.

Kidney Disease and Hypertension: Hypertension is the second leading cause of end-stage renal disease (ESRD) in the United States and is the leading cause of ESRD among African Americans.

The NIDDK-supported African American Study of Kidney Disease and Hypertension (AASK) is collecting data to compare the effects of three classes of antihypertensive medication and two levels of blood pressure in preventing kidney disease. NIDDK also supports epidemiologic research on hypertension-related kidney disease, including studies on the incidence of ESRD associated with high blood pressure. Recent findings suggest there is a graded increased risk of ESRD with increasing systolic and diastolic blood pressure, beginning with blood pressure in the normal range. This information will be useful in estimating the incidence of ESRD among hypertensive individuals, the risk of hypertensive ESRD in the population associated with various levels of blood pressure control, and attributable risk of small elevations of blood pressure, even within the normal range.

Immune Disorders and Kidney Disease: Several kidney diseases are related to underlying disorders of the immune system. These diseases have in common an inflammation of the glomeruli, the filtering units of the kidney, and constitute the third leading cause of end-stage renal disease in Americans. Recent advances in this field include mouse models of Goodpasture syndrome and lupus nephritis; the identification of the putative antigen of Goodpasture syndrome; description of how anti-DNA antibodies enter cells and affect nuclear function in diseases such as systemic lupus erythematosus; cloning of the antigen, and most of its subcomponents, in Hymen's nephritis; and evidence that timely administration of a fusion protein can inhibit antibody-mediated glomerular disease in a mouse model. In addition, the NIDDK supports a multicenter clinical trial to evaluate the efficacy of alternate-day prednisone versus placebo for the treatment of IgA nephropathy in children, adolescents, and young adults.

Pediatric Kidney Disease: Progressive renal disease occurs in all age groups and results from various underlying causes. Congenital structural malformations represent the principle underlying cause of end-stage renal disease in the very young. Older children develop renal failure from glomerular and tubulointerstitial disease, immune complex disease, hemolytic uremic syndrome, IgA nephropathy, focal segmental sclerosis, and hereditary nephropathies. In recent years, research has increasingly focused on molecular biology, revolutionizing research activity in this field. Research progress highlights include the identification of specific mutations in the collagen gene in patients with Alport's syndrome; identification of the Wilm's tumor suppressor gene; mapping of the cystinuria gene to a subregion of chromosome 2; assignment of congenital nephrotic syndrome to chromosome 19; an association between a deletion in the angiotensin converting enzyme gene and incidence of progressive deterioration in renal function; and identification and characterization of specific membrane transport proteins which function as water channels in the kidney.

Hemodialysis: Once an individual has end-stage renal disease (ESRD), life depends on replacement therapy: either dialysis treatments or renal transplantation. Despite sophisticated dialysis equipment, patient mortality and morbidity continue to be unacceptably high. The NIDDK is currently supporting a clinical trial to test whether a higher than conventional hemodialysis dose and/or high-flux membranes will reduce patient mortality and morbidity. Results from the trial are expected in 2001. This trial also permits investigators to examine nutritional status in this patient population. Preliminary data suggests that malnutrition is prevalent in patients with chronic renal failure (CRF), and worsens as CRF progresses towards

ESRD. Another important finding is that germicides currently used in the reprocessing of dialyzers for reuse are not inherently associated with increased risk of mortality.

Urologic Diseases

Prostate Growth: Abnormal prostate growth is a leading cause of morbidity and mortality in adult males. There are two types of abnormal growth in the adult prostate: benign (benign prostatic hyperplasia (BPH)) and malignant (prostate cancer (PCa)). Investigators amplified the role of a particular growth factor in benign and malignant tissue and found that this protein binds to certain receptors on prostate epithelial cells from BPH tissue to a lesser degree than in normal cells, that one of these receptors is lost from epithelial cells in PCa tissue, and that this receptor acts as a negative regulator of prostate growth while another receptor is responsible for stimulating epithelial cell prostate growth. Investigators concluded that alterations in the balance between the growth inhibitory and stimulatory effects of the two receptors play a causal role in benign and malignant neoplastic growth.

Kidney Stones: It is estimated that ten percent of the U.S. population will form a urinary tract stone at some time. Most cases of stone disease are idiopathic, that is, there is no immediately identifiable cause for the occurrence of the stones. Most of these cases are chronic, with several occurrences of stone formation. Recently, NIDDK funded investigators have developed a rat model that exhibits spontaneous stone formation. Studies with renal epithelial cells and their response to calcium oxalate monohydrate suggest there is an increased expression of specific genes which encode transcriptional activators and growth factors. Other studies show that a small number of gene loci are the probably the principal contributors to the observed heritability of calcium oxalate stone disease.

Hematologic Diseases

Hemoglobinopathies: Using maternal blood, NIDDK investigators have now reported the correct determination of fetal genotypes in two pregnancies at risk for sickle cell anemia and Cooley's anemia. As recovery of fetal cells from maternal blood is a noninvasive procedure, it avoids any risk to the fetus. Adaptation of this procedure to the routine diagnostic laboratory should remove the fear of causing a spontaneous abortion, resulting in the loss of a normal pregnancy. In other studies, investigators have cloned two isoforms of the potassium-chloride cotransporter and have found these isoforms in most organs and widely across species. The potassium-chloride cotransporter enhances dehydration of hemoglobin sickle cell red blood cells in patients with sickle cell anemia. Now that the protein has been identified, many aspects of its physiological function can be studied.

Gene Therapy: Hematopoietic stem cells are considered to be ideal targets for gene therapy, since they have the capacity for total hematopoietic reconstitution and the potential for therapy for a large variety of disorders. Unfortunately, attempts at retroviral gene transfer into human long-term repopulating hematopoietic stem cells has been to inefficient to expect clinical benefit. Recently, several recent studies have demonstrated successful engraftment of hematopoietic stem cells into normal mouse hosts that were not subjected to damaging therapies. Other studies have found that cytokine priming may allow collection of increased numbers of primitive cells from

both peripheral blood and bone marrow. This strategy appears to be a useful means to introduce genes into hemotopoietic stem cells.

Intramural Research

Rationale for Budget Request

The FY 1998 budget estimate for the Intramural research program is $93,032,000, an increase of 1.5 percent above the FY 1997 estimate of $91,667,000 and an increase of 1 FTE above the FY 1997 level of 378. The fundamental research and clinical studies supported by the intramural research program help to provide a solid base of knowledge for the development of improved methods to treat and prevent disease. The following are examples of recent research achievements and activities of the NIDDK Division of Intramural Research.

Research Highlights

DNA Replication: NIDDK investigators are using a bacterial virus enzyme, T4 nuclease, as a model system to understand the enzymatic reactions necessary for DNA replication. Investigators have shown that this virus plays an essential role in DNA replication and repair. In collaboration with other NIH researchers, investigators determined the crystal structure of this nuclease. They found a protein that resembled previously characterized DNA enzymes and DNA-binding proteins. Investigators are currently making mutants in this nuclease based on the crystal structure to determine which residues are required for nuclease activity and for interactions with other system replication proteins. Recent progress with this DNA replication system offers significant hope for understanding how the accurate copying of genetic material is achieved, and how defects in copying may lead to cancer-causing mutations.

Genetics of Diabetes: Researchers report evidence for genetic linkage and association of insulin resistance and NIDDM with a cluster of DNA markers found within a particular genomic region. One marker found among this cluster is not only linked with NIDDM in the Pima Indians, but also in Caucasian families living in Utah. Efforts are underway to identify the gene predisposing to NIDDM at this position.

Hearing Loss: NIDDK researchers are studying the role of N-methyl-D-aspartate (NMDA) receptor inhibitors in antibiotic-induced hearing loss (ototoxicity). Using the guinea pig as a model, researchers found that co-administration of NMDA inhibitors with toxic regimens of aminoglycoside antibiotics significantly decreased both the hearing loss and the sensory hair cell destruction that are characteristic of ototoxicity. Researchers also found a high correlation between the relative toxicities of aminoglycosides in humans and the potencies of these same compounds to enhance radiolabelled ligand binding to NMDA receptors *in vitro*. Implications for this data are twofold. First, if the ototoxic effects of these antibiotics are produced through the activation of NMDA receptors, then appropriate regimens of NMDA inhibitors co-administered with the antibiotics should completely block ototoxicity. Second, the positive correlation between relative ototoxicity in humans and ability to enhance radiolabelled ligand binding may serve as a rapid and inexpensive screen for developing aminoglycosides with reduced ototoxic liability.

Hemoglobinopathies: Recent studies have shown that hydroxyurea improves the clinical symptoms in patients with hemoglobinopathies while exerting minimal side effects. Efforts are now underway to find other drugs which, when administered singularly or in combination with hydroxyurea, can achieve levels of fetal hemoglobin higher than with hydroxyurea alone with greater therapeutic benefit. Researchers are collaborating with industry and scientists in the United States and in other countries to screen and assay such agents. From this work has already come the identification of several therapeutic agents. NIDDK scientists, in collaboration with other NIH researchers, are now testing these compounds in primate models. At the same time, NIDDK researchers are studying the mechanism of control of the human globin genes, both in cells in culture and in transgenic mouse models, in order to understand the basic mechanisms by which these compounds work.

Insulin Action: NIDDK researchers are studying transgenic mice that have mutations in two separate genes located in the pathway for insulin action. Mice that possessed only one null allele for each mutation appeared healthy and thrived. Mice that carried null alleles for both mutations were significantly insulin resistant and developed diabetes over time, suggesting that two mutations which by themselves were not active, when combined were capable of causing disease. This data supports a hypothesis that diabetes may arise from a combination of defects and has broad implications for both genetic mapping and treatment.

Kidney Disease: Evidence suggests that production of transforming growth factor-beta (TGF-β) contributes to kidney disease. NIDDK researchers are therefore studying the effects of elevated levels of circulating TGF-β on the kidney through use of a transgenic mouse model. Findings suggest that circulating levels of TGF-β are capable of causing severe kidney disease. NIDDK researchers, in collaboration with other NIH scientists, are currently examining inhibitors of TGF-β in hopes of preventing or slowing the progression of TGF-β induced renal disease. Other studies support a role for osteogenic protein-1 (OP-1), a member of the TGF-β superfamily, in tissue differentiation and kidney development. This research is an important step in defining the molecular signals responsible for kidney development and may lead to new approaches for treating kidney diseases by imitating the events which occur in embryonic development.

Obesity: To help clarify the role of leptin in humans, NIDDK investigators, in collaboration with others, have conducted a study in non-diabetic Pima Indians to determine whether individuals with lower leptin concentrations are more likely to gain weight than individuals with higher leptin concentrations and similar body weight composition. Investigators found evidence that Pima Indians that were prone to weight gain had lower plasma leptin concentrations than weight and body composition matched Pimas who maintained a stable body weight. Investigators postulate that low plasma leptin concentrations may lead to a state of hunger and/or decreased energy expenditure resulting in weight gain or relapse of weight loss. In other studies, NIDDK investigators have assessed the role of physical activity in Caucasian and Pima Indian five year old children. Although researchers were unable to correlate physical activity in Pima Indian children with obesity at a later age, suggesting that excess food intake is the likely candidate in the etiology of obesity in this population, they did find that both Caucasian and Pima Indian children had surprisingly low levels of physical activity at age five, a negative indicator for the prevention of obesity in adulthood.

Prions: NIDDK researchers have proposed that two elements of yeast are infectious proteins (prions) similar to the prion protein implicated in the diseases of mammals. Their research indicates that prions may be a more widespread phenomenon than had been shown previously and that prions can be the basis for infection. NIDDK scientists foresee the utility of yeast as a simple, easy to manipulate, inexpensive, model system in which to study mechanisms of prion formation and reproduction, and in the design of assays to test for prion-inducing substances and conditions, as well as for curative and preventative agents.

Structural Biology: NIDDK scientists, using nuclear magnetic resonance spectroscopy, have recently determined the three-dimensional structure and mapped the binding surface of Nef, a key regulatory protein of HIV-1. Solving the solution structure of Nef permits the pursuit of structure-function studies and allows for the design of anti-HIV drugs. NIDDK scientists have also determined the crystal structure of a single protein kinase C activator- binding domain, both alone and in combination with a tumor promoter, and of the oligomerization domain of the p53 protein, that portion of the protein which is joined with three other p53 molecules to form a complex that binds DNA and exerts a tumor suppressor effect. Knowledge of these structures adds to the base of knowledge that serves as a foundation for the design and development of cancer chemotherapeutics.

Tay-Sachs and Sandhoff Diseases: NIDDK researchers are examining the effect of bone marrow transplantation on a transgenic mouse model which exhibits both the structural and functional abnormalities as well as the profound neurological disturbances typical of Tay-Sachs and Sandhoff diseases. Although bone marrow transplantation does not provide a cure, this is the first time that any therapeutic treatment has been shown to prolong the lifespan of the diseased mice. These results offer the promise of eventual treatment of these otherwise fatal conditions.

Research Management and Support

Rationale for Budget Request

The FY 1998 request for Research Management and Support is $24,032,000 and an employment level of 166 FTEs. This provides for the same level of support as in FY 1997 and is a decrease of 1 in the level of FTEs. A major portion of the resources of this activity is devoted to review and approval of grants functions, including professional and support personnel who are responsible for the administration of the Institute's grants activities. The staff assists in the planning and development of programs in research and training 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 NIDDK Advisory Council and provides required Council staff assistance; and serves as liaison with applicants, grantees, other components of NIH and the Department, and interest organizations.

Priority Setting and Program Planning

The NIDDK promotes its research agenda through balanced program activities and mechanisms. Funding decisions are driven largely by considerations of scientific merit and opportunity. The Institute places highest priority on research project grants, and expends nearly 70 percent of its

appropriated funds in this area, compared with an NIH average of approximately 59 percent in FY 1997. The great majority of grants in this category are awarded for investigator-initiated research, while a small proportion of funds is used to support special Institute initiatives. Historically, investigator-initiated projects have demonstrated sustained high productivity and cost-effectiveness. Special initiatives are undertaken to address areas having particularly compelling scientific opportunities or public health needs that are not receiving adequate attention within the Institute's portfolio of investigator-initiated projects. They also may be responsive to Congressional or Administration directives. These program initiatives/opportunities--which are developed in consultation with outside advisors and the research community--are described in the Institute's annual program planning report. The NIDDK's planning process is designed to facilitate, not direct, research.

The Institute places less emphasis than the NIH generally on research and development contracts (2.9 percent of NIDDK budget versus 6.5 percent of NIH budget), and on research centers (6.6 percent vs. 9.0 percent), while the Institute's Intramural Research Program is supported at approximately the same level as the NIH average, 11.3 percent of budget.

In addition, for many years, to help maximize support for research, the Institute has minimized the allocation of funds directed to research management and support (RM&S). The NIDDK's RM&S budget is the lowest at the NIH of the institutes supporting a full range of programs--2.9 percent of budget versus the NIH average of 4.0 percent.

Funding for the NIDDK's extramural research programs has remained balanced and relatively stable for many years. The Division of Diabetes, Endocrinology, and Metabolism receives approximately 49 percent of the Institute's extramural research appropriation; the Division of Digestive Diseases and Nutrition receives approximately 24 percent; and the Division of Kidney, Urologic, and Hematologic Disease receives approximately 27 percent.

Innovations in Management and Administration

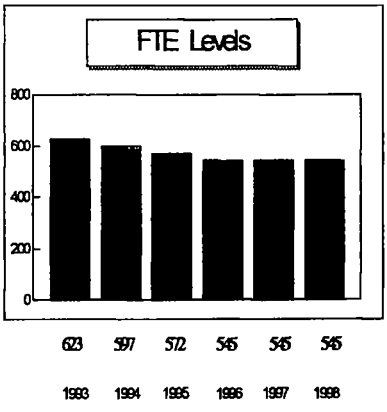
Public and Private Partnerships

Over the past several years, the NIDDK has formed mutually beneficial partnerships with public and private sector organizations. In an era of budgetary constraints, these partnerships are an example of how collaborative arrangements can potentiate the effort of the Nation's research enterprise. Collaborations with the private sector, foundations, and other federal agencies have enabled the NIDDK to pursue and expand research opportunities in both the basic and clinical research arenas.

Streamlining

Streamlining is a long-standing and continuous process through which the NIDDK has achieved historically low administrative costs, reduced FTE usage, and improved efficiency and productivity. NIDDK leadership has held for many years that, in order to maximize resources available for scientific research, administrative costs must be maintained in the most efficient and effective manner possible. This guiding principle is the basis for resource allocation decisions

made across the Institute, particularly with respect to the key administrative component of the budget, Research Management and Support (RM&S); the NIDDK historically has had one of the leanest administrative operations at the NIH. The Institute evaluates process and product on a continuing basis to ensure appropriate use of fiscal and human resources, and employs appropriate span-of-control, economies-of-scale, and other effective management principles. The Institute is committed to meeting FTE ceiling reductions and to using its cadre of FTEs at optimal levels of productivity, and has achieved staff reduction through consolidating or clustering selected functions. Dual and multiple jobs are common at the NIDDK. The NIDDK has accomplished a great deal already to achieve streamlining goals. The focus of future efforts will be to identify additional opportunities for streamlining.



NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects						
Noncompeting	1,640	$394,925,000	1,629	$396,208,000	1,721	$420,110,000
Administrative supplementals	(158)	6,949,000	(160)	8,292,000	(160)	8,458,000
Competing:						
Renewal	250	63,084,000	299	78,255,000	274	72,404,000
New	254	46,372,000	304	57,540,000	273	53,048,000
Supplemental	1	81,000	1	85,000	1	87,000
Subtotal, competing	505	109,537,000	604	135,880,000	548	125,539,000
SBIR/STTR	67	12,606,000	81	15,878,000	85	16,443,000
Subtotal, RPGs	2,212	524,017,000	2,314	556,258,000	2,354	570,550,000
Research Centers						
Specialized/comprehensive	59	52,024,000	59	52,948,000	59	54,007,000
Clinical reseach	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research centers in minority institutions	0	0	0	0	0	0
Subtotal, Centers	59	52,024,000	59	52,948,000	59	54,007,000
Other Research						
Research careers	206	17,542,000	227	19,828,000	232	20,225,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	1,794,000	0	1,848,000	0	1,885,000
Other	25	1,759,000	37	3,574,000	37	3,645,000
Subtotal, Other Research	231	21,095,000	264	25,250,000	269	25,755,000
Total, Research Grants	2,502	597,136,000	2,637	634,456,000	2,682	650,312,000
Training	FTTPs		FTTPs		FTTPs	
Individual	195	5,626,000	200	5,747,000	200	5,930,000
Institutional	725	23,098,000	726	23,839,000	726	24,247,000
Total, Training	920	28,724,000	926	29,586,000	926	30,177,000
Research & development contracts	32	20,725,000	56	23,148,000	56	23,611,000
(SBIR/STTR)	(8)	(693,000)	(15)	(2,000,000)	(15)	(2,000,000)
	FTEs		FTEs		FTEs	
Intramural research	377	86,169,000	378	91,667,000	379	93,032,000
Research management and support	168	24,041,000	167	24,032,000	166	24,032,000
Cancer prevention & control	0	0	0	0	0	0
Construction	0	0	0	0	0	0
Total, NIDDK	545	756,795,000	545	802,889,000	545	821,164,000
(Clinical Trials)		(57,833,000)		(62,350,000)		(63,600,000)

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(dollars in thousands)

	FY 1996 Actual		FY 1997 Estimate		FY 1998 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Diabetes, Endocrinology and Metabolism		315,600		334,364		342,100		7,736
Digestive Diseases and Nutrition		155,571		166,200		170,400		4,200
Kidney Diseases, Urology and Hematology		175,297		186,626		191,600		4,974
Subtotal, Extramural research		646,468		687,190		704,100		16,910
Intramural research	377	86,169	378	91,667	379	93,032	1	1,365
Research management and support	168	23,981	167	24,032	166	24,032	(1)	0
Total obligations	545	756,618	545	802,889	545	821,164	0	18,275
Unobligated balance lapsing		177		0		0		0
Total, Budget Authority	545	756,795	545	802,889	545	821,164	0	18,275

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes

1997 Estimated budget authority				$802,889,000
1998 Estimated budget authority				821,164,000
Net change				18,275,000
	1997 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$38,239,000		460,000
b. Annualization of January 1997 pay increase		$38,239,000		318,000
c. January 1998 pay increase		$38,239,000		819,000
d. Legislative proposal, 1.51% increase in the CSRS rate		$38,239,000		158,000
e. Service and supply fund		20,213,000		527,000
f. Increased cost of laboratory supplies, materials, and other expenses		9,956,000		260,000
Subtotal				2,542,000
2. Research Management and Support:				
a. Within grade increase		11,587,000		201,000
b. Annualization of January 1997 pay increase		11,587,000		96,000
c. January 1998 pay increase		11,587,000		250,000
d. Legislative proposal, 1.51% increase in the CSRS rate		11,587,000		40,000
e. Service and supply fund		4,563,000		119,000
f. Increased cost of laboratory supplies, materials, and other expenses		2,247,000		58,000
Subtotal				764,000
Subtotal, Built-in				3,306,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases
Summary of Changes—continued

	1997 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	1,629	404,500,000	92	24,068,000
b. Competing	604	135,880,000	(56)	(10,341,000)
c. SBIR/STTR	81	15,878,000	4	565,000
Total	2,314	556,258,000	40	14,292,000
2. Centers		52,948,000		1,059,000
3. Other research	264	25,250,000	5	505,000
4. Research training		29,586,000		591,000
5. Research and development contracts		23,148,000		463,000
	FTEs		FTEs	
6. Intramural research:				
a. Programmatic changes		91,667,000		(1,179,000)
b. Special emphasis areas				0
Subtotal, intramural		91,667,000		(1,179,000)
7. Research management and support		24,032,000		(762,000)
Subtotal, program				14,969,000
Total changes				18,275,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Object

		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
Total compensable workyears:				
Full-time employment		545	545	---
Full-time equivalent of overtime and holiday hours		1	1	---
Average ES salary		$110,433	$113,658	$3,225
Average GM/GS grade		11	11	---
Average GM/GS salary		$52,801	$54,343	$1,542
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)		$87,378	$89,933	$2,555
Average salary of ungraded positions		$50,571	$52,049	$1,478
		FY 1997 Estimate	FY 1998 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	23,579,000	24,522,000	$943,000
11.3	Other than Full-Time Permanent	7,003,000	7,283,000	280,000
11.5	Other Personnel Compensation	1,314,000	1,374,000	60,000
11.8	Special Personnel Services Payments	9,856,000	10,408,000	552,000
11.9	**Total Personnel Compensation**	**41,752,000**	**43,587,000**	**1,835,000**
12.0	Personnel Benefits	8,048,000	8,372,000	324,000
13.0	Benefits for Former Personnel	26,000	27,000	1,000
	Subtotal, Pay Costs	**49,826,000**	**51,986,000**	**2,160,000**
21.0	Travel & Transportation of Persons	900,000	900,000	0
22.0	Transportation of Things	275,000	275,000	0
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	3,000	3,000	0
23.3	Communications, Utilities & Miscellaneous Charges	1,600,000	1,675,000	75,000
24.0	Printing & Reproduction	630,000	645,000	15,000
25.1	Consulting Services	450,000	450,000	0
25.2	Other Services	2,455,000	2,455,000	0
25.3	Purchase of Goods & Services from Government Accounts	47,206,000	46,047,000	(1,159,000)
25.4	Operation & Maintenance of Facilities	2,700,000	2,700,000	0
25.5	Research & Development Contracts	14,367,000	14,830,000	463,000
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	1,530,000	1,550,000	20,000
25.8	Subsistance & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**68,708,000**	**68,032,000**	**(676,000)**
26.0	Supplies & Materials	10,440,000	10,500,000	60,000
31.0	Equipment	8,480,000	8,500,000	20,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	661,866,000	678,488,000	16,622,000
42.0	Insurance Claims & Indemnities	151,000	150,000	(1,000)
43.0	Interest & Dividends	10,000	10,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**753,063,000**	**769,178,000**	**16,115,000**
				0
	Total, Budget Authority by Object	**802,889,000**	**821,164,000**	**18,275,000**

Note: Includes FTEs associated with HIV/AIDS research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Administrative Costs

	FY 1997 Estimate	FY 1998 Estimate	Change
Personnel Compensation:			
Full-Time Permanent (11.1)	$23,579,000	$24,522,000	$943,000
Other Than Full-Time Permanent (11.3)	7,003,000	7,283,000	280,000
Other Personnel Compensation (11.5)	1,314,000	1,374,000	60,000
Special Personnel Services Payments (11.8)	9,856,000	10,408,000	552,000
Total Personnel Compensation (11.9)	**41,752,000**	**43,587,000**	**1,835,000**
Civilian Personnel Benefits (12.0)	8,048,000	8,372,000	324,000
Benefits to Former Personnel (13.0)	26,000	27,000	1,000
Subtotal, Pay Costs	**49,826,000**	**51,986,000**	**2,160,000**
Travel (21.0)	900,000	900,000	0
Transportation of Things (22.0)	275,000	275,000	0
Rental Payments to Others (23.2)	3,000	3,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	1,600,000	1,675,000	75,000
Printing and Reproduction (24.0)	630,000	645,000	15,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	450,000	450,000	0
Other Services (25.2)	2,455,000	2,455,000	0
Purchases from Govt. Accounts (25.3)	36,108,000	35,125,000	(983,000)
Operation & Maintenance of Facilities (25.4)	2,700,000	2,700,000	0
Operation & Maintenance of Equipment (25.7)	1,530,000	1,550,000	20,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**43,243,000**	**42,280,000**	**(963,000)**
Supplies and Materials (26.0)	10,440,000	10,500,000	60,000
Subtotal, Non-Pay Costs	57,091,000	56,278,000	(813,000)
Total, Administrative Costs	**106,917,000**	**108,264,000**	**1,347,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 1997 House Appropriations Committee Report Language

Item

Diabetes - The Committee states that diabetes is a leading cause of death by disease in America, contributing to the deaths of more than 160,000 annually....Given the enormous economic and personal costs of diabetes, the Committee considers diabetes research a top priority and urges the Directors of NIH and NIDDK to review the growth rate in diabetes research funding over the past few years to assess whether this field has received appropriate support relative to other areas in the NIH portfolio. The Directors should be prepared to discuss their finding in the fiscal year 1998 appropriations hearings.

Action Taken or to be Taken

Led by the NIDDK, NIH funding for diabetes research is estimated at $309.6 million for FY 1996, representing the research effort of 16 NIH Institutes and Centers. In the last 10 years, diabetes research funding at the NIH has increased 64 percent. Within the NIH total, the NIDDK contribution is estimated at $202.7 million. This figure represents a 95 percent increase during the last decade, exceeding the 60 percent increase in the total NIDDK budget over the same period. The NIDDK Director will be prepared to discuss the Institute's funding for diabetes research at the FY 1998 budget hearings.

Item

Prevention through education - The Committee states that since certain preventable risk factors, such as diet and obesity, have already been identified for diabetes, the Committee encourages NIDDK to focus on prevention through education programs, including collaborative efforts with the affected Institutes.

Action Taken or To Be Taken

The NIDDK's National Diabetes Outreach Program is the first Government-sponsored effort to increase public awareness of the benefits of improving blood sugar control in people with diabetes. Launched through a mass media campaign in late 1994, the program promotes the message that improved blood sugar control in people with insulin-dependent diabetes reduces eye, kidney, and nerve damage associated with the disease. Patients calling a toll-free recording can obtain a free information kit with a variety of material about diabetes, including information about diabetes-related publications of the National Eye Institute and the National

Institute of Dental Research, and fact sheets about voluntary associations. To date, over 30 million people have received mass media information in this campaign, and over 200,000 booklets have been distributed.

Because of poor circulation and nerve damage, people with diabetes are more likely to develop infections from even a minor injury, too often leading to severe damage and amputation. A new foot awareness campaign, "Feet Can Last a Lifetime," is the result of collaborative effort by the NIDDK, the American Diabetes Association, the Juvenile Diabetes Foundation International, the Centers for Disease Control and Prevention and Health Promotion, and other government and private organizations to educate diabetic patients about the importance of proper foot care. More than 15 million people have received mass media information about foot care.

Controlling obesity also is likely to play an important role in preventing or ameliorating diabetes. To this end, the Weight-Control Information Network, or WIN, is being developed to provide up-to-date science-based information on obesity, nutrition, and related nutritional disorders to health professionals and the public. This clearinghouse features a toll-free number for information, a range of fact sheets based on the current scientific knowledge in obesity, and a central database of obesity literature. Over the past year, WIN has initiated an important pilot communication program to raise awareness about the benefits of eating healthier foods and exercising regularly among African-American women aged 18-35 in three Boston neighborhoods. A newsletter and exhibits at professional meetings are used to directly inform health professionals of recent nutrition and obesity research advances. The NIDDK also is cosponsoring the National Heart, Lung, and Blood Institute's Obesity Education Initiative and is represented on the expert panel that advises this effort.

Item

[Diabetes genetic research] - The Committee states that the Committee is....pleased to learn of the progress being made in the area of genetic research. The NIDDK is encouraged to pursue this area since it holds great promise for gaining a better understanding of this disease and its complications.

Action Taken or to be Taken

Efforts to understand the genetic factors involved in Type 1 and Type 2 diabetes are progressing rapidly, with many findings of genetic associations with diabetes reported in the past year. The NIDDK continues to identify scientific and research funding opportunities, including collaborative arrangements, in this important and exciting area.

Item

Prostate cancer - The Committee is encouraged by the (NIDDK) prostate cancer activities and encourages the Institute to continue and to strengthen its basic and clinical research, and outreach and public education in prostate cancer.

Action Taken or to be Taken

The NCI and the NIDDK have a formalized working agreement under which the NCI assumes primary research responsibility for all aspects of carcinoma of the prostate, and the NIDDK assumes primary research responsibility for non-cancerous conditions. Under this agreement, many areas of mutual interest important to prostate cancer research require collaboration. They include the cofunding of three NIDDK George M. O'Brien Urologic Research Centers; the co-funding of grants that examine factors associated with benign prostatic hyperplasia and prostate cancer risk; the planning of a co-sponsored workshop on prostate disease, mainly prostate cancer, in minority populations; and the possible co-funding of grant applications related to the molecular biology of normal and abnormal prostate growth that are currently under review.

Also relevant is the NIDDK-supported clinical trial on BPH comparing the effects of different medications on the prevention of progression of symptoms of benign prostate disease. The clinical trial is expected to provide insights about the natural history, effective treatment, and interrelationships of the various prostate diseases. The National Kidney and Urologic Diseases Information Clearinghouse-- an information and referral service of the NIDDK and a recognized resource for health care professionals, patients, and patient and professional organizations-- distributes information on BPH and other urologic diseases and disorders.

Item

End stage renal disease - The Committee states that...the Committee encourages the NIDDK to continue its research programs in clinical and basic sciences to further elucidate the mechanisms which cause progressive kidney disease and to define new ways to treat or prevent these diseases, including the major kidney diseases which begin in, or cause kidney failure in, children.

Action Taken or to be Taken

Individuals diagnosed with end-stage renal disease have irreversible kidney failure and require regular and frequent dialysis or a kidney transplant to survive. There is significant morbidity associated with hemodialysis, and the exact protocol for dialysis has not been universally standardized. The NIDDK-funded Hemodialysis study is a multicenter clinical trial designed to determine whether a higher than usual dose of dialysis and high-flux dialyzers can significantly improve morbidity and mortality in hemodialysis patients. Specific parameters for approaches to many procedures were defined for the trial and, if successful, will become standards for dialytic therapy in the U.S. This trial also permits investigators to assess important parameters of nutrition in this population.

African American Study of Kidney Disease and Hypertension is a clinical trial designed to evaluate whether lower than usual blood pressure control alone, or in combination with certain classes of antihypertensive drugs, can slow the progression of hypertension-related

kidney disease in African Americans. Studies are also underway that will help in estimating the incidence of ESRD among hypertensive individuals, the risk of hypertensive ESRD associated with various levels of blood pressure control, and attributable risk of small elevations of blood pressure, even within the normal range.

Item

Polycystic kidney disease - The Committee states that the Committee encourages the Institute to redouble its efforts to support PKD research in order to capitalize on these recent scientific advances.

Action Taken or to be Taken

PKD research is a very active and promising area of investigation and the NIDDK is committed to intensifying PKD research. Funding for PKD research has grown from $1.4 million in FY 1986 to an estimated $7.9 million in FY 1997. In FY 1997, the NIDDK will support both a scientific workshop and a Program Announcement on PKD. The workshop will provide a useful forum for the exchange of scientific information among investigators working in the field, with particular emphasis on the possible functional role of the PKD protein, polycystin. The Program Announcement will solicit high-quality research grant applications from both established PKD researchers and investigators new to the study of PKD. The Program Announcement will encourage research to capitalize on the discovery and sequencing of the genes for PKD1 and PKD2 and the identification of the protein which these genes may regulate.

Item

Urological diseases - The Committee states that the Committee has heard testimony on prostatitis and its resulting disabilities and encourages NIDDK to enhance its research in this area.

Action Taken or to be Taken

A recent NIDDK-sponsored workshop convened to develop a research plan for chronic prostatitis determined that there are three priority issues which must first be addressed before any basic and/or clinical research can be initiated to study this disease; diagnostic criteria designated by the workshop must be validated in a representative cohort of men; a symptom score must be developed and validated; and treatment outcome measures must be developed and validated. The workshop also developed a classification system for the various forms of this disease and this system must also be tested and validated on a representative cohort of patients. The NIDDK is planning to release a Request for Applications in the near future that will address these issues.

Item

Interstitial cystitis - The Committee states that the Committee also requests that the NIH continue to address and resolve the problem of the lack of urological expertise on some of the NIH study sections which review urology grants.

Action Taken or to be Taken

The NIH has received numerous requests to establish a new urology study section or to increase the number of urologists in existing study sections. In the fall of 1995, NIH's Division of Research Grants, with the endorsement of the American Urological Association, began a pilot project to address the concerns regarding lack of urological expertise on some of the NIH study sections. Three important steps have been taken.

First, most urology applications, including those on interstitial cystitis (IC), will be reviewed by a Special Emphasis Panel (SEP) consisting of urology experts, with significant overlapping membership from round to round. (An SEP is generally the first step in the establishment of a permanent study section, provided that significant numbers of such applications continue to be received from round to round). Second, remaining applications that do not fit thematically into the SEP will be clustered into fewer existing study sections than has previously been the case, providing a better "critical mass" of urology applications per study section. Finally, in order to accommodate the increased number of applications, additional urologists will be recruited for those study sections. The NIDDK remains committed to combating IC, and we will continue to convey to researchers our interest in funding innovative, high-quality projects in this area.

Item

[Digestive disorders] - The Committee states that the Committee encourages the NIDDK to continue its efforts to develop the appropriate balance between conducting basic studies on digestive diseases and bringing this critical knowledge gained to the bedside to improve patient care.

Action Taken or to be Taken

The NIDDK has been mindful of the need to increase clinical research in digestive diseases and has taken deliberate steps to encourage this research with the goal of promoting an effective transfer of advances in basic science to improved clinical care. Acting on a recommendation of the National Digestive Diseases Advisory Board in 1990, the NIDDK created a Clinical Trials Program and then developed guidelines to assist investigators in their preparation of grant applications for clinical studies. Using such award mechanisms as the traditional research project grant, the exploratory grant, and the small research grant, the NIDDK has built-up its portfolio of clinical trials considerably. Approximately nine clinical trials are currently supported in digestive diseases, with plans to fund three more in FY 1997.

Item

Cooley's anemia - The House in its report 104-659, page 66 states that the Committee has long supported research in the area of Cooley's anemia. Due to the red blood cell transfusions that patients must undergo, iron builds up in the major organs. The effective removal of this iron by chelating drugs requires an assessment of iron levels in the patient, but therapy is impeded by the lack of accurate non-invasive tests for iron overload. Therefore the Committee encourages NIDDK to move forward in an effort to develop an accurate non-invasive test for iron overload that can be utilized for Cooley's anemia patients, as well as for patients with conditions such as hemochromatosis and iron deficiency anemia. The Committee also supports research aimed at developing an oral iron chelator.

Action Taken or to be Taken

The NIDDK has completed preclinical studies on the oral chelating drug DmHBED, and a NIH-supported investigator is preparing a request to the FDA for approval of human clinical studies of this drug. In addition, human and nonhuman primate studies of the parent drug, HBED, have shown that this drug has exceptionally low toxicity and is highly effective in the removal of iron. Consequently, preclinical studies are being planned for HBED, which, while not envisioned as an oral agent, could be administered by injection a few times a week. This is a major improvement over Desferal, currently the only FDA-approved drug, which must be administered over a 12-hour period daily. For this reason alone, HBED would receive better acceptance by patients. Finally, it is clear that the basic understanding of the biology of chelation needs to be improved in such aspects as the kinetics of iron chelation, the identity of the iron pools addressed, and ways to enhance chelating activity while reducing the toxicity of known iron chelators. A Program Announcement is planned by the NIDDK to address these issues.

Item

[Nutrition research] - The Committee states that the Committee was encouraged by the NIDDK cosponsorship of a research conference on nutrition support and encourages NIDDK to take steps to implement the research agenda developed by the conference, including the use of nutrient pharmacology and the role of anabolic treatments for wasting diseases such as AIDS and cancer.

Action Taken or to be Taken

The NIDDK Division of Nutrition Research Coordination both cosponsored and participated in the conference "The Current Role of Nutrition Support," reflecting the Institute's interest in this research topic. When the report of the conference becomes available, the Institute will work with the nutrition research community to develop a program initiative reflecting its recommendations. In addition, the NIDDK is jointly organizing a scientific workshop on "AIDS Wasting Syndrome" with the Office of AIDS Research and the National Institute of Allergy and Infectious Diseases. The workshop, to be held at the NIH on May 20-21, 1997,

will bring together leading researchers investigating the pathogenesis and therapy of AIDS Wasting Syndrome and investigators in other related areas. The purpose of the workshop is to promote the exchange of new developments and to anticipate future directions of investigation.

Item

Liver disease - The Committee states that the Committee urges NIDDK to focus on research to prevent, treat and cure liver diseases and suggests that the Institute consider convening a meeting to develop a well focused and comprehensive research program. The Committee urges NIDDK to include in this effort all Institutes now conducting liver disease research.

Action Taken or to be Taken

The NIDDK continues to build a comprehensive research program to study hepatitis and other liver and biliary tract diseases. The NIDDK chairs the National Digestive Diseases Interagency Coordinating Committee (NDDICC) -- the institutional mechanism for coordinating efforts of the NIH and other Federal agencies with respect to research in liver diseases. Last year, the American Liver Foundation (ALF) presented to the NDDICC its *Research Agenda for 25 Million Americans – Research Goals and Strategies To Treat, Prevent, and Conquer Liver Diseases.* The broad scope of the ALF's Research Agenda has relevance for many NIH institutes such as the NIDDK, NIAID, NCI, NICHD, NIGMS, NIEHS, NIDR, as well as the FDA and VA. In March 1997, NIDDK will co-sponsor with NIAID a Consensus Development Conference on "Management of Hepatitis C." With the goal of developing a scientifically appropriate plan for addressing areas outlined in the ALF Research Agenda, the NDDICC will conduct an overview of the Agenda at a mini-symposium in June 1997. Later in the year, the NDDICC plans to discuss research directions in gallstone and biliary tract diseases.

The NIDDK has undertaken several new initiatives in the past year, including publication of program announcements on cellular ontogeny and differentiation of the liver and biliary tree, and etiology of biliary atresia. In addition, the Institute has funded two large multi-center trials in liver disease on the use of transjugular intrahepatic porto-systemic shunts (TIPS) in the management of variceal hemorrhage and ascites related to chronic liver disease. Meetings on "Liver Transplantation for Alcoholic Liver Disease," co-sponsored by NIDDK and NIAAA, and an international meeting on "Targeting of Novel Therapeutics to the Liver and GI Tract," sponsored by the NDDICC, also were held over the past year.

FY 1997 Senate Appropriations Committee Report Language

Item

Diabetes - The Committee states that given the enormous economic and personal costs of diabetes, the Committee urges the NIH to review the growth rate in diabetes research funding over the past few years to assess whether this field is receiving appropriate support. The

Committee expects the NIH and the NIDDK to be prepared to discuss this issue during the fiscal year 1998 hearings.

Action Taken or to be Taken

NIH funding for diabetes research is estimated at $309.6 million for FY 1996. Of this amount, the NIDDK contribution is estimated at $202.7 million. Since FY 1987, diabetes research funding at the NIH has increased 64 percent. This figure represents a 95 percent increase during the last decade, exceeding the 60 percent increase in the total NIDDK budget over the same period. The NIDDK Director will be prepared to discuss the Institute's funding for diabetes research at the FY 1998 budget hearings.

Item

[Diabetes research] - The Committee states that the Committee is aware that an array of research possibilities were outlined by the National Diabetes Research Coalition (NDRC) in its document entitled "Diabetes Research: A National Opportunity-The Blueprint for the Cure." The Committee believes that a significant investment in this research now could materially alleviate, delay, and prevent diabetes and its complications and urges the NIDDK to redouble its efforts on all facets of diabetes research. The Committee urges the Institute to support an aggressive research program directed at the development of engineered biomaterials for diabetes management.

Action Taken or to be Taken

The NIDDK promotes its research agenda through balanced program activities and mechanisms. Funding decisions are driven largely by considerations of scientific merit and opportunity. Through an ongoing planning process, the NIDDK -- with the assistance of outside advisors and the research community-- identifies areas of particularly compelling scientific opportunity that are not receiving adequate attention within the Institute's portfolio of investigator-initiated projects. Many opportunities the Institute has identified presently coincide with those described in the National Diabetes Research Coalition's report. The Institute generally implements several diabetes special initiatives based on such opportunities each year.

Item

[Diabetes among Native Americans, Native Hawaiians, and Pacific Islanders] - The Committee states that the Committee continues to be concerned about the high incidence of diabetes among native Americans, native Hawaiians, and Pacific islanders, particularly residents of the Commonwealth of the Northern Marianas Islands where about 50 percent of the population has diabetes. The Committee urges the Director to develop specific interventions, using a multidisciplinary approach, to target these high-risk populations.

Action Taken or to be Taken

The minority populations of Native Americans, Native Hawaiians, and Pacific Islanders suffer disproportionately from non-insulin-dependent, or Type 2, diabetes mellitus. The NIDDK recently initiated a major multi-center clinical trial, called the Diabetes Prevention Program, to investigate whether Type 2 diabetes might be prevented or delayed. Four types of interventions will be studied. Minority volunteers will represent approximately 50 percent of the DPP's participants. The Institute also supports many individual research projects that are testing intervention strategies for the treatment of Type 2 diabetes in minorities.

Item

[Diabetes among Hispanic and Native Americans] - The Committee states that the Committee believes that the NIDDK should pay particular attention to the inordinately high prevalence of diabetes in the Hispanic population and the Native American population. The Committee understands Hispanics develop diabetes 3 to 5 times more often than the general population, and native Americans develop diabetes 10 times more often. The Committee believes that the Hispanic and Native American populations constitute one of the highest priorities in diabetes research, and stresses the need for expanded NIDDK research activities in these areas.

Action Taken or to be Taken

As stated previously, NIDDK initiatives are addressing the problem of diabetes in minorities, including Hispanics and Native Americans. Moreover, scientists at the Institute's Phoenix Epidemiology and Clinical Research Branch have studied Type 2 diabetes in the Pima Indians for over 30 years, research that has uncovered many clues to the causes of diabetes, and that has permitted the development of treatment strategies. In addition, this past year, NIDDK grantees identified two gene regions that are associated with Type 2 diabetes in Mexican Americans, knowledge that ultimately may lead to a treatment for or prevention of this disease.

Item

Liver disease - The Committee states that the Committee is aware that liver diseases affects 25 million people. Therefore, the Committee is pleased that NIDDK and NIAID will sponsor a consensus conference on chronic hepatitis C in 1997. The Committee encourages, other efforts by NIDDK to prevent, treat, and cure liver diseases, including convening a national scientific meeting to review the research agenda developed by the American Liver Foundation and produce an action plan for a well-focused liver research program for 1997 and beyond. The action plan should include to the extent possible all Institutes now conducting liver disease research.

Action Taken or to be Taken

The NIDDK is making steady progress on a number of fronts in priority areas of research in liver and biliary tract diseases with the issuance of program announcements, funding of clinical trials, and sponsorship of national and international meetings. The American Liver Foundation (ALF) -- a private partner in federal efforts to enhance liver disease research -- developed a research agenda for liver diseases which was presented to the National Digestive Diseases Interagency Coordinating Committee (NDDICC). This committee acts as the institutional coordinating mechanism for all federal research efforts in this area. Represented on the Committee are such NIH components as the NIDDK, which acts as chair, the NIAID, NCI, NICHD, NIAAA, NIGMS, NIEHS, and NIDR, as well as the FDA, HRSA, and the AHCPR. The NDDICC is planning to implement the research agenda developed by the ALF through a series of meetings, the first of which will be held in June to conduct an overview of the priority areas outlined in the document. Later in the year, the NDDICC will dedicate a meeting to research in gallstone and biliary tract diseases. Other recent meetings include one sponsored by the NIDDK and NIAAA on "Liver Transplantation for Alcoholic Liver Disease," and an international meeting sponsored by the NDDICC dedicated to "Targeting of Novel Therapeutics to the Liver and GI Tract."

Item

Bionutrition - The Committee states that the Committee is encouraged by the leadership of NIDDK in the nutrition and obesity research areas. The cloning of genes involved in animal obesity opens the way for the study of molecular genetics in human obesity, which the Committee hopes will remain a high priority of the NIDDK. The Committee encourages the Institute to expand its work on pharmacology and obesity management. Furthermore, the Committee was encouraged by the cosponsorship of a research conference on the current role of nutrition support and encourages NIDDK to take steps implementing the research agenda developed by the conference including the use of nutrient pharmacology and the role of anabolic treatments, such as human growth hormones, in the treatment of wasting diseases such as critical illness, AIDS, and cancer.

Action Taken or to be Taken

The NIDDK is continuing its focus on the highly fruitful area of obesity molecular genetics. The Institute also will be cosponsoring a scientific workshop with the North American Association for the Study of Obesity to identify research needs, strategies and methods for advancing the study of the genetic influences on obesity. At the same time, the Institute recognizes the need to address the current clinical issues in obesity research. A recent position paper on the topic of pharmacologic interventions for obesity was developed by the National Task Force on Prevention and Treatment of Obesity, a group of outside experts that provides NIDDK with scientific assessments of research opportunities and appropriate scientific messages to be communicated to the public. This paper has been translated into a

fact sheet for the general public, "Prescription Medications for the Treatment of Obesity," stressing that few studies have examined the safety or effectiveness of pharmacologic interventions over a period of longer than one year, and concluding that appetite suppressant medications should be used only by patients who are at increased medical risk because of their obesity. Recognizing the lack of sufficient information about the benefits and risks associated with long-term weight loss, the Task Force will be meeting this spring to discuss the design and feasibility of a randomized clinical trial of long-term intentional weight loss and health outcomes.

The NIH Division of Nutrition Research Coordination, located within the NIDDK, will work with the research community to develop appropriate means for implementing the recommendations of the conference on "The Current Role of Nutrition Support." The Institute also is jointly organizing a 1997 workshop on "AIDS Wasting Syndrome" with the Office of AIDS Research and the National Institute of Allergy and Infectious Diseases to focus on exchanges of new developments and identification of future research directions in the pathogenesis and therapy of this syndrome. In addition, the NIDDK led the NIH last year in developing a trans-NIH Program Announcement to encourage research on the pathophysiology of anorexia in disease and aging, with the expectation that this research will lead to an increased understanding of and the design of new interventions for the wasting associated with many chronic diseases and AIDS.

Item

Urological diseases - The Committee states that the Committee continues to be pleased with the growth of research on urological diseases which are a significant health burden. The Committee encourages the NIDDK to increase support for new research grants in the basic science of the prostate, including growth factors and their influence on prostate cancer and benign prostatic hypertrophy, and prostatitis. The Committee is concerned that no progress has been reported on the development of a urological disease data base. Such a data base could be a valuable tool for establishing research priorities. The Committee also urges the Institute to expand its activities in the area of women's urological health by working collaboratively with the Office of Research on Women's Health, in particular by placing special emphasis on grants related to interstitial cystitis, urinary in continence, and urinary tract infections. Finally, the Committee is concerned about the heavy impact of prostate disease on minority populations and urges the NIDDK to expand support for research in this area.

Action Taken or to be Taken

The NIDDK continues its research efforts in the basic and clinical science of prostate growth. To further encourage research in this area, the NIDDK released an RFA on the "Regulation of Prostate Growth." The intent of this solicitation is to increase the diversity of approaches to the study of prostate growth regulation and related abnormalities by encouraging investigators from diverse research areas to apply their expertise in this area. It is anticipated that 12 to 14 awards will be made in FY 1997.

The NIDDK is exploring with the American Urological Association the possibility of compiling a compendium of data for urological diseases generally. This compendium will be modeled after the NIDDK publications Diabetes in America and Digestive Diseases in the United States: Epidemiology and Impact.

The NIDDK and the Office of Research on Women's Health have developed an active collaboration to vigorously pursue research that addresses women's urological health. This collaboration began in FY 1994, with the ORWH cosponsorship of an NIDDK RFA, "Interstitial Cystitis and Other Bladder Disorders of Women." ORWH has been providing ongoing funding for three research grants arising from this RFA. This initiative was expanded in FY 1996, when ORWH agreed to co-fund 10 grants that were received in response to an RFA on "Basic and Epidemiologic Research Related to Disorders of the Urinary Bladder." In addition, ORWH is working with the NIDDK to develop a 1997 workshop on research opportunities in urinary incontinence. This workshop will include a special focus on urinary disease of diabetes. A Program Announcement will likely arise from the deliberations of the participants. Finally, the NIDDK is launching a national awareness campaign on urinary continence in women and the ORWH will be participating in this campaign.

The NIDDK has convened a subgroup of the Urology Interagency Coordinating Subcommittee, a subcommittee of the Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee, to plan an initiative that addresses prostate disease in minorities. The first phase of this initiative will be a scientific workshop to be held in the Spring of 1997. The NIDDK-funded Medical Therapy of Prostatic Symptoms clinical trial has undertaken special recruitment efforts to encourage enrollment of minority populations.

Item

Polycystic kidney disease - The Committee states that polycystic kidney disease (PKD) affects some 600,000 Americans and is the third leading cause of kidney failure, annually generating more than 2,000 additional cases of end stage renal disease. Rapid research progress in recent years has resulted in identification and complete sequencing of the gene that causes 90 percent of PKD and its protein product has also been discovered. The Committee understands that scientists worldwide agree that PKD science is mature and that discoveries leading to a treatment and ultimately a cure are now foreseeable. The Committee, therefore, urges the NIDDK to increase support for PKD research, including giving consideration to the establishment of up to four interdisciplinary basic research centers on progressive renal failure with emphasis on polycystic kidney disease.

Action Taken or to be Taken

In the last two years, dramatic progress has been witnessed in the etiology, pathogenesis, and clinical course of PKD. The genes that are mutated in PKD1 and PKD2 have been cloned, sequenced and the protein structures deduced. To further encourage meritorious research in FY 1997, the NIDDK will support both a scientific workshop and a Program Announcement on PKD. The workshop will provide a useful forum for the exchange of scientific information

among investigators working in the field, with particular emphasis on the possible functional role of polycystin, the PKD1 protein. The Program Announcement will solicit high-quality research grant applications from both established PKD researchers and investigators new to the study of PKD. The Program Announcement will encourage research to capitalize on the discovery and sequencing of the genes for PKD1 and PKD2 and the identification of the protein which these genes may regulate.

The current Kidney, Urology, and Hematology Centers program is anchored in very broad areas: the George M. O'Brien Kidney and Urological Research Centers, Research Centers of Excellence in Pediatric Nephrology, and Centers of Excellence in Molecular Hematology. This allows the wide competition necessary to ensure that the Centers established focus on those topics most likely to benefit from the Centers mechanism. PKD researchers are encouraged to apply and compete for the George M. O'Brien and Pediatric Nephrology Center awards.

Item

Digestive diseases - The Committee states that the Committee encourages the NIDDK to continue its efforts to develop the appropriate balance between conducting basic studies on digestive diseases and bringing this critical knowledge gained, to the bedside to improve patient care. Clinical research opportunities that exist include transjugular intrahepatic portal-systemic shunts (TIPS) for variceal bleeding, treatment, and prevention of recurrence of *H .pylori*, bleeding ulcers; and hepatic assist devices for fulminant hepatic failure.

Action Taken or to be Taken

The NIDDK has made a concerted effort to enhance the translation of basic research outcomes to improved patient care. In response to a recommendation of the National Digestive Diseases Advisory Board in 1990, the NIDDK created a Clinical Trials Program and developed guidelines to assist investigators in the preparation of their applications. Various funding mechanisms have been used to encourage researchers to undertake prospective, randomized, controlled, single or multi center clinical trials in digestive diseases. These mechanisms include traditional research project grants (RO1), exploratory grants (R21), and small research grants (RO3). The clinical trials portfolio in digestive diseases has grown impressively and includes studies in such areas as bleeding esophageal varices, cirrhosis and portal hypertension, gastrointestinal bleeding from ulcers, functional bowel disorders, primary biliary cirrhosis, transjugular intrahepatic portal-systemic shunt (TIPS) for variceal bleeding and refractory ascites, prevention of ulcer hemorrhage by *H. pylori* eradication, hereditary pancreatitis, and human enterohemorrhagic *E. coli* infection. It is anticipated that several new clinical trials will be funded in FY 1997.

Item

[Inflammatory bowel diseases] - The Committee states that the Committee continues to be concerned about the prevalence of inflammatory bowel diseases, including Crohn's disease and

ulcerative colitis, as well as with irritable bowel syndrome. These extremely complex disorders represent the major cause of morbidity from intestinal illness. The Committee recommends that the Institute continue its investigations into the genetic structure of IBD as well as the roles played by environmental factors and the immune system in the development of the disease. Additionally, the Committee recommends that the NIDDK maintain adequate support for irritable bowel syndrome/functional bowel disorders research and give priority consideration to funding IBS education/scientific symposiums.

Action Taken or to be Taken

The NIDDK continues to encourage investigations into the environmental, genetic and immune factors involved in the development of inflammatory bowel disease (IBD). A Program Announcement co-sponsored by the NIDDK and NIAID should be published shortly which will seek applications on the immune aspects of this complex disease. In the area of irritable bowel syndrome/functional bowel disorders, the NIDDK is currently funding a large-scale clinical study to compare treatments for chronic, painful functional bowel disorders that most often affect women. It is anticipated that the study will provide clinicians with predictors of success among types of IBS patients and types of therapy that offer the most promise of improving the symptoms of this disorder and quality of life. The Institute also plans to lend support to the education and biofeedback components of a proposed conference grant on IBS.

Item

Human tissues - The Committee states that last year the conferees stated their support for the creation of a multi-Institute initiative to expand access to alternative resources to the use of animals in research, particularly through ensuring access to human tissues and organs. The Committee understands that human tissues are particularly important to researchers studying diabetes, and other diseases under the purview of the Institute. Accordingly, the Committee urges the NIDDK to give consideration to supporting programs that provide human tissues and organs to researchers.

Action Taken or to be Taken

At the NIH, the support of research resources is the primary mission of National Center for Research Resources; the NIDDK supports a very limited number of programs for human tissue and organ resources. The Institute is aware that NIDDK grantees, through their institutions, provide these types of resources to interested colleagues and other researchers.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1997 Amount Authorized	1997 Estimate	1998 Amount Authorized	1998 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
				$773,303,000		$790,987,000
National Institute of Diabetes and Digestive and Kidney Diseases	Title IV, Part C Subpart C	42§285 c et seq	Indefinite		Indefinite	
Research on Osteoporosis, Paget's Disease, and Related Bone Disorders	Section 409A	42§284 e	Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208)		Reauthorizing legislation will be submitted	
National Research Service Awards	Section 487(d)	42§288 d	Funding provided under Omnibus Consolidated Appropriations Act, 1997 (P.L. 104-208)	$29,586,000	Reauthorizing legislation will be submitted	$30,177,000
Total, Budget Authority				$802,889,000		$821,164,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1989	562,258,000 2/	546,902,000 3/	565,908,000	559,538,000
1990	577,235,000 4/	590,276,000	593,497,000	589,594,000 5/
1990 Sequester				(8,117,000)
1991	605,349,000	613,686,000 6/	626,986,000	615,272,000 7/
1991 Sequester				(8,000)
1992	658,557,000	667,820,000	652,861,000	659,538,000 8/
1993	699,809,000	688,633,000	688,633,000	681,342,000 9/
1994	677,135,000	716,054,000	716,054,000	716,054,000
1995 10/	731,500,000	726,784,000	728,784,000	727,628,000 11/
1995 Rescission				(679,000)
1996	748,798,000 10/	771,252,000	738,456,000 10/	771,252,000
1996 Rescission				(670,000)
1997	758,847,000 10/	806,542,000	787,473,000 10/	815,607,000 13/
1998 10/	821,164,000 10/			

1/ Reflects enacted supplementals, rescissions, reappropriations and reductions.
2/ The 1989 request excludes funds for AIDS research and education ($3,650,000) that has been proposed for consolidation in the Office of the Assistant Secretary for Health.
3/ Excludes $25,509,000 in NRSA training programs not considered.
4/ The 1990 request excludes funds for National HIV program ($5,394,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
5/ Excludes enacted administration reduction of $2,293,000.
6/ Excludes $23,872,000 in NRSA training programs not considered.
7/ Excludes enacted administration reductions of $15,238,000 and $1,762,000.
8/ Excludes enacted administration reductions of $435,000 and $4,107,000.
9/ Excludes enacted administration reduction of $7,291,000.
10/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
11/ Excludes enacted administrative reduction of $679,000.
12/ Excludes enacted administrative reduction of $670,000.
13/ Excludes enacted administrative reduction of $375,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Full-Time Equivalent Employment (FTE)

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
Office of the Director	62	62	61
Division of Diabetes, Endocrinology and Metabolic Diseases	17	17	17
Division of Digestive Diseases and Nutrition	15	15	15
Division of Kidney, Urologic and Hematologic Diseases	16	16	16
Division of Nutrition Research Coordination	6	6	6
Division of Extramural Activities	52	51	51
Division of Intramural Research	377	378	379
Total, NIDDK	545	545	545
	Average GS/GM Grade		
1993	10.5		
1994	11.0		
1995	10.4		
1996	11.0		
1997	11.0		
1998	11.0		

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Positions

	FY 1996 Actual	FY 1997 Estimate	FY 1998 Estimate
ES-6	0	0	0
ES-5	1	3	3
ES-4	12	10	10
ES-3	3	3	3
ES-2	0	0	0
ES-1	1	1	1
ES-0	0	0	0
Subtotal	17	17	17
Total - ES Salary	$2,032,099	$2,244,185	$2,325,524
GS/GM-15	55	55	55
GS/GM-14	43	44	44
GS/GM-13	33	33	33
GS-12	44	46	47
GS-11	48	47	47
GS-10	1	3	2
GS-9	27	25	26
GS-8	32	35	34
GS-7	44	42	43
GS-6	23	22	21
GS-5	6	7	7
GS-4	10	9	9
GS-3	5	4	4
GS-2	1	1	1
GS-1	1	0	0
Subtotal	373	373	373
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	24	24	24
Senior Grade	5	5	5
Full Grade	12	12	12
Senior Assistant Grade	1	1	1
Subtotal	43	43	43
Ungraded	122	122	122
Total permanent positions	410	399	405
Total positions, end of year	555	555	555
Total full-time equivalent (FTE) employment,end of year	545	545	545
Average ES level	4	4	4
Average ES salary	$107,102	$110,433	$113,658
Average GS/GM grade	11.0	11.0	11.0
Average GS/GM salary	$51,208	$52,801	$54,343

NIDDK-50

WITNESSES

	Page
Adderly, Donna	2155
Alexander, Duane	1635
Baldus, A.C	2001
Baldwin, Wendy	1
Barros, C.F	1915
Beldon, Bill	711, 805
Benowitz, S.C	2249
Berkowitz, S.J	583
Burgess, E.S	495
Bursenos, S.J	1443
Casady, D.S	1635
Cassman, Dr. Marvin	2095
Collins, F.S	495
Counts, G.W	583
Cushing, Mary	1377
Du Buy, Y.H	1737
Dufour, Dr. Mary	1091
Fauci, A.S	583
Ficca, S.A	2249
Fitzsimmons, W.T	1809
Fivozinsky, C.L	419
Fulton, B.E	1635
Gekas, Hon. George	2431
Gorden, Phillip	1177, 2431
Gordis, Dr. Enoch	1091
Gottesman, Michael	1
Grady, Dr. P.A	1377
Hall, Dr. Z.W	2001
Haseltine, Dr. F.P	1635
Hausman, Dr. S.J	1491
Hodes, R.J	1915
Hodgkins, G.E	2095
Hudson, Kathy	495
Hyman, S.E	1809
Itteilag, Anthony	1, 2249
Jaron, Dr. Dov	1573
Johnson, Laurie	711
Jones, D.M	983
Jordan, Elke	495
Katz, Dr. S.I	1491
Kerr, W.D	805
Kerza-Kwiatecki, M.S	1491
Kirschstein, Dr. R.L	1, 1377, 1443, 1915, 2249

Page

Klausner, R.D 199, 2431
Kleinman, D.V 1737
Kupfer, Carl 419
Laurence, L.E 1177
Leasure, C.E., Jr 711
Lenfant, Dr. Claude 865, 2431
Leshner, A.I 983
Levine, S.U 1309
Lindberg, D.A.B 1309
Lipman, D.J 1309
Little, Francine 1
Long, Stephen 1091
Luecke, D.H 805
Maddox, Dr. Y.T 1635
McGowan, J.J 583
McLaughlin, Jack 419
McManus, Edward 419
Merritt, Sheila 865
Miller, Richard 1443
Millstein, R.A 983
Mink, Hon. P.T 2431
Moore, Marshall 805
Morella, Hon. C.A 2431
Moul, Ellen 1377
Nakamura, R.K 1809
Nethercutt, Hon. G.R., Jr 2431
Olden, Kenneth 711
Paul, W.E 2155, 2431
Penn, Dr. A.S 2001
Pine, J.R 1809
Pine, Martha 2095
Poppke, D.C 1309
Rabson, Alan 199
Ramm, Dr. L.E 1573
Richardson, C.M 1091
Rosenthal, Laura 983
Ross, K.S 1915
Roth, Dr. Carl 865
Schambra, P.E 1443
Shafer, Dr. W.S 2095
Sherbert, R.L., Jr 2001
Slavkin, H.C 1737
Smith, K.A 1309
Snow, J.B., Jr 805
Sparks, P.T 805
Strachan, R.J 1491
Summers, A.E 1573
Taylor, E.S 1737
Trusty, M.K 1091
Vaitukaitis, Dr. J.L 1573
Varmus, Dr. Harold 1, 199, 419, 495, 583, 711, 805, 865, 983, 1091, 1177, 1309, 1491, 1573, 1635, 1737, 1809, 1915, 2001, 2095, 2155, 2249, 2431
Vennetti, J.C 495
Wehling, James 865

Page

Weiblinger, G.M 1809
Wertheimer, Wendy 2155
Wetle, Terrie 1915
Williams, D.P..... 1, 199, 419, 495, 583, 865, 983, 1091, 1177, 1309, 1377, 1443, 1491, 1573, 1635, 1737, 1809, 1915, 2001, 2095, 2155, 2249, 2431
Williams, T.D 583
Wilson, S.H 711
Zellers, C.R 1177

INDEX

National Institutes of Health Overview

	Page
Administrative Costs	53
AIDS/HIV:	
AIDS and Minorities	111
AIDS Research	83
Culminations in HIV Research	3
HIV Vaccine	29
Inspiration in HIV Research	4
Areas of Research Emphasis	79
Awareness Relating to Biomedical Research	67
Biomedical Engineering Research	116
Budget Estimates:	
Budget Estimates	11
Budget Estimates, Justification of	148
Five Year Budget	91
FY 1998 Budget Request	43
Funding for NIH	96
Impact of 7.5 Percent Increase	22
1st President's Budget Proposal	5
Professional Judgment Budget	11
Cancer:	
Ovarian Cancer	33
Advances in Ovarian Cancer Research	34
Child Abuse and Neglect	134
Child Development and the Brain	34
Clinical Research:	
Clinical Research at Academic Medical Centers	143
Clinical Research Panel	129, 144
Clinical Research Program	80
Funding for Clinical Research	80
Initiatives for Clinical Research	145
IOM Recommendations	19, 81, 142, 145
Peer Review of Clinical Research	145
Progress in Support for Clinical Research	22
Subscribers Participation in NIH Protocols	21
Third Party Payments, Impact of	35
Cloning:	
Cloning	13
Cloning of Humans	26
Earlier Cloning Experiment	14
Ethical Implications	17
How Genes Turn On and Off	16

Page

Cloning—Continued
Legislating Cloning 18
Medical Uses of Cloning 15
Scientific Significance of Cloning 15
Use in Bone Marrow Transplants 16
Comparison of Medicare Costs and Disease Research Costs 36
Congressional Earmarks 85
Consensus Development Panels 23
Contraceptive and Reproductive Health Training Programs 136
Contraceptive Research 70
Coordination with Other Agencies 82
Culminations of Research 2
Department of Defense, Collaboration with 89
Department of Education, Cooperation with 130
Diabetes:
Commitment to Diabetes Research 30
Diagnosis and Detection of Diabetes 31
Increase in Diabetes Research 131
Initiatives for Diabetes Research 131
New Approaches to Pathogenesis 65
NIH-Wide Diabetes Research Efforts 64
Direct and Indirect Costs 72
Director's Discretionary Fund, FY 96 and 97 45
Employment Rates for African-American Males 120
Ethical, Legal and Social Implications Working Group 94
Ethics Training 29
Extramural Construction 107
Extramural Programs 86
Full Time Equivalents (FTES):
FTE Detail by Grade Level 59
FTE Ceiling 61
FTE Total by Institute 48
FTE Total by Mechanism 49
Human Embryo Research 92
Grants:
Administrative Burdens on Grantees 88
New and Competing Research Project Grants 142
Number of Applications 51
Research Project Grants 104
RPGs as Priority 113
Success Rates 12, 110
Imaging Research 32
Indirect Cost Cap 66
Inspirations of Research 3
Instrumentation 61
Intramural Programs 87
Mammography:
Mammography 108
Mammography Policy 25
Medicare Spending by Disease, 1995 37
Minorities:
Inclusion of Minorities in Clinical Research 122
Investment in Minority Research Programs 116
IOM Study 103
Minority Health Standing Advisory Committee 102

Page

Minorities—Continued
Minority International Research Training Program 100
Minority Investigators 113
Number of Minority and Women Investigators 105
Pipeline 127
Reseach Centers in Minority Institutions 128
Research Related to Minorities 95
National Bioethics Advisory Commission 28
National Center on Sleep Disorders Research 52
Needle Exchange 24
Neuroscience 126
Obstetrics and Gynecology, Research in 135, 138
Office of Research in Minority Health (ORMH):
Funding for Office 96, 97
ORMH Co-funding 99
Role of the ORMH 103
Opening Statement 6
Oversight and Administrative Activities 4
Panel on Potential Research on Marijuana 24
Pediatric Research:
Number of Intramural Pediatricians 138
Pediatric Research 137
Permanent Separations Profile 121
Pipeline for Young Investigators 93
Population Research 70
Prenatal Research 71
Public Education 50
Pulmonary Hemorrhage Among Cleveland Infants 104
Priority Setting:
Allocation of Research Dollars 40
Criteria for Funding Allocations 40
Establishing Priorities 12
NIH Priority Setting Process 42, 73
Priority Setting at NCI 76
Reducing Health Care Costs 41
Research Infrastructure 114
Research on Learning 130
Research Management and Support (RMS):
Cap on Management and Support Costs 94
One-Percent Evaluation Funding In 49
RMS Funding 1990–1998 50
Research Spending Per Death for Selected Disease 67
Research Training 86
Shannon Awards 61
Small Business Innovation Research Grants 115
Spending by Disease 56
Taps and Assessments:
One-Percent Evaluation Set-Aside 61
Taps and Assessments 63
Toll-Free Numbers 54
Women in Clinical Trials 141

National Cancer Institute

Abortion and Breast Cancer 255
Access to Care 236

Page

Advances Against Cancer 273
Angiogenesis 231
Areas Impacting on Cancer 232
ASSIST 252
Behavioral Research 321
Breast Cancer-ABMT 236
Cancer Genetics 259
  Cancer Genetics Network 260
  Cancer Genetics and Molecular Biology 305
  Genetics Testing 261
Cancer Survivors 230, 272
  Breast Cancer Survival 235
  Five-Year Survival Rates 230
  Office of Cancer Survivorship 242
Cancer Vaccines 263
Cancer Centers Program Review Group 269
Cancer Genome Anatomy Project 269
Cancer Mortality by Race 317
  Decline in Cancer Mortality 271
Cancer Prevention 203
Clinical Trials 204, 278
  African American Women and Clinical Trials 299
  Breast Cancer-Molecular Markers 207
  Clinical Trials in FY 1998 286
  Clinical Trial Educational Efforts 267
  Clinical Trial Agreement with The Department of Defense 265
  Clinical Trial Agreement with The Veteran's Administration 266
  Dissemination of Clinical Trial Results 284
  Women in Clinical Trials 328
Clinical Treatment 236
Cloning 318
Collaborative Efforts 307
Combination Therapies 308
Comprehensive Cancer Centers 251
Construction 246
Coordination Efforts with DOD 237, 238
Coordination of the National Cancer Program 251
Detection Technologies For Breast Cancer 225
  Other Detection Technologies For Breast Cancer 224
Diet and Cancer 258, 311
Dissemination of Cancer Information 319
Environmental Links to Breast Cancer 233
  San Francisco Bay Area 234
Environmental Justice Research Activities 313
  Environmental Justice Collaborative Activities 315
Estrogen and Breast Cancer 325
"Five A Day" Program 249
FTE Decrease 245
Funding Allocation Decisions 226
Funding for NIH 228
Gynecologic Cancer Research 328
Human Papillamovirus 241
Imaging 263
  Imaging Technologies 297
Infectious Causes of Cancer 294

Page
Institute of Medicine Cancer Study 317
Intramural Program at Frederick 244
Justification of The Budget Estimates 331
Mammography 221, 295
Mammography Imaging 265
Screening 223
Measure of Successes 268
Minorities and Cancer 229
Advances in Minority Health 227
Cancer in Minority Population 312
Excess Cancer Death Rate 271
Office of Special Populations 229
Molecular Characteristics of Cancer 310
NCAB Subcommittee 224
NCI Panels and Advisory Boards 329
New Cancer Drugs 268
NIH Reauthorization 231
Opening Statement 199
Ovarian Cancer 240, 327
Professional Judgment Budget 238
Opportunities 239
Prostate Cancer 236, 278
Prostate Cancer Initiatives 300
Prostate Cancer Treatment and Early Detection 302
African Americans and Prostate Cancer 304
Radiation Therapy 246
Role of Stress in Cancer 277
San Antonio Cancer Institute 251
Science Information System 323
Implementation of The Science Information System 324
Statement of The Director 212
Tobacco Use and Children 247
Biology of the Brain 431
Cataract Surgery 437
Contact Lenses 437
FDA Approval 429
Fetal Tissue 434
Glaucoma Gene 427, 429
Introduction of Witnesses 419
Long-Range Research Plan 436
Macular Degeneration 429, 434
Marijuana use for Glaucoma 434
Neuron Survival 428
Nutritional Supplements for Retinitis Pigmentosa 436
Opening Statement 419
Private Foundations 435
Professional Judgement Budget 426
Radial Keratotomy Versus Laser Technique 428
Retinopathy of Prematurity 430
Statement of Director 422
Transplanted Retinal Cells 433
Vision Conditions Needing More Research 437
Budget Increase 506
Bureaucratic 531
Center for Inherited Disease Research 497, 529, 543

Page

Cloning:
- Cloning and Ethics ... 547
- Cloning Humans ... 515
- International Cooperation ... 511
- Potential for Hoax ... 514
- Scientific Opportunities ... 507, 536
- Why a Sheep ... 515

Designer Drug Strategies ... 513
Diversity ... 544
Ethical, Legal, and Social Implications ... 499, 535
Finding the Gene ... 497, 505
Finishing Faster:
- Additional Funds Needed ... 525
- Finding A Cure ... 507

Future Health Care Delivery ... 512
Genetic Discrimination and Privacy ... 519, 529
Genetic Testing:
- Breast Cancer ... 508
- Counseling and Control ... 510
- Guidance ... 526

Health Insurance Portability and Accountability Act of 1996 ... 537
Howard University Center ... 543
Human Embryo Research ... 516
Human Genome Project:
- Creation of ... 541
- Mapping Progress ... 534

Intramural Program ... 540
Minorities and Women ... 533
Newest Research Institute ... 495, 523, 532
Opening Statement ... 501
Oral Remarks ... 495
Ovarian, Breast, and Cervical Cancer ... 546
Prostate Cancer ... 496
Protection of Patient Medical Information ... 538
Sequencing:
- Complete DNA Sequence ... 498
- Beyond the First Sequence ... 498
- Large Scale Sequencing ... 528

National Institute of Allergy and Infectious Diseases

Introduction of Witnesses ... 583
Opening Statement ... 583
AIDS:
- AZT ... 586, 588, 618
- Behavioral Research ... 614
- Clinical Trials ... 602, 606
- Global Threat ... 612
- Minorities ... 632
- Office of AIDS Research ... 611
- Pediatric ... 657
- Protease Inhibitors ... 601, 605, 614, 623
- Therapy ... 605, 608
- Treatment Strategies ... 586, 605, 612
- Vaccines ... 593, 601, 609, 633

Page

AIDS—Continued
Women 654
Asthma 636
Basic Research 594, 599, 601
Benefits of AIDS Research 654
Budget Estimates, Justification of 661
Cholera 619
Chronic Fatigue Syndrome 603, 623, 631, 641
Clinical Trials 649
Cloning 640
Diarrheal Diseases 602, 630
Drug Issues 617
Emerging Infectious Diseases 647
Grant Success Rate 648
Hansen's Disease 620
Hemophilia 617
Hepatitis A 626
Lyme Disease 603
Malaria 618, 633
Media Involvement 616
Multiple Sclerosis 603
Patient Registries 639
Primary Immune Deficiency 622
Priority Setting 628
Research Accomplishments 643
Rotavirus 602
Sexually Transmitted Diseases 602, 628, 652, 658
Topical Microbicides 655
Tuberculosis 619, 626, 630, 640
Vaccines 596, 597, 603, 642

National Institute of Environmental Health Sciences

Air Quality 763
Air Quality Standards 730, 736, 745
Artificial Sweeteners 725
Asthma 728, 763
Autism 731
Beryllium 770
Breast Cancer 766
Budget 747
Budget Formulation 762
Cancer 764
Clinical Program 748, 750
Clinical Research 754
Clinical Trials 762
Cloning 756
Collaboration with Industry 723
Collaborations 757
Congressional Visit 719
Contract Mechanism 727
Endocrine Disruptors 719, 723
Environmental Genome Project 720
Environmental Health Hazards 756
Environmental Justice 752, 767
EPA 749

Page
Funding Increase 717
Grant Funding Mechanisms, Major 758
Gulf War Syndrome 724
Justification of the Budget Estimates 772
Knowledge "Bottleneck" 754
Link Between Science and Public Health 721
Minorities, Improving Health of 752
Mixtures 718
Nanofabrication 726
National Toxicology Program 734, 768
New Testing Methodologies 720, 734
Opening Statement 711
Particulate Matter 736
Pulmonary Hemorrhage Among Cleveland Infants, Epidemic of 764
Retesting of Chemicals 728
Secondhand Smoke 746
Smoking 730
Statement of the Director 713
Success Rate 759
Superfund 734, 750
Toxicity Test Systems 747
Vitamin D and Prostate Cancer 718

National Institute on Deafness and Other Communication Disorders

Autism Research 811
Balance Disorders in Elderly 816
Clinical Trials 818, 831
Cloning Technology 828
Collaborative Effort in Hearing Aid Technology 822
Eating Behavior and Nutrition 815
Government Performance and Results Act 818
Hair Cell Regeneration 811
Hearing Aid Research 827
Hearing Impairment:
Consensus Conference Findings 813
Incidence 824
Introduction of Witnesses 805
Investigator-Initiated Research Applications 832
Justification of the Budget Estimates 834
Loss of Voice 816
Multi Cultural Language Assessment 830
Opening Statement 805
Otitis Media 823
Partnership Program 832
Public Information Activities 821
Presbycusis 826
Research Funding 821
Sense of Smell 816
Sensory Regeneration 815
Specific Language Impairment 820
Statement of Director 807
Stochastic Resonance 812
Vaccine for Otitis Media 819, 826

Page

National Heart, Lung, and Blood Institute

Allocating Funds 888
Asthma 876, 928
Benefits from Research 890
Cardiovascular Disease in Mississippi 887, 926
Cell Death 875
Child and Adolescent Trial for Cardiovascular Health (CATCH) 916
Chronic Obstructive Pulmonary Disease 921, 922
Clinical Trials and Research 925, 939, 942
Comprehensive Heart, Lung, and Blood Center 911
Cooley's Anemia 882
Cost Recovery 902
Diet and Blood Pressure 936
Education Programs 893, 900, 932
Folic Acid 918
Gender Differences 930
Gene Therapy 875, 878, 914
Government Performance and Results Act 895
Heart Disease Death Rate 915
Heart Diseases 884, 892, 902, 912, 926, 927, 932, 938
Human Cloning Research 892, 941
Hypertension and Children 935
Hypertrophic Cardiomyopathy 905
Imaging Technology 866, 873
Infants and Congenital Heart Disease 934
In Utero Bone Marrow Transplantation 874
Knowledge "Bottleneck" 940
Lung and Blood Diseases 868, 880, 887, 896
Lung Volume Reduction Surgery 895, 924
Major Opportunities 927
Minority Health 879, 881, 925, 931, 933, 938
Organ Damage 935
Primary Pulmonary Hypertension 906, 909
Salt Intake 901
Selected Areas of Research 898
Select Pay 903
Service Centers 894
Sleep Disorders Research 876, 893, 901, 907, 908, 922, 923, 936
Smoking 884, 927
Specialized Centers of Research 899
Statement of the Director 870
Stroke Research 877, 919
Women's Health 913, 920, 944

National Institute on Drug Abuse

AIDS and Drug Abuse 1002
AIDS/HIV and Drug Abuse 1017
Alaska Needle Exchange 995
Alcohol and Substance Abuse 993
Biology of the Brain 1028
Brain Development in Adolescent Drug Users 1050
Brain Imaging 1032
Bupropion 1006
Clinical Research 1038

Page

Clinical Trials 1041
Cloning 1040
Cocaine Craving 1009
Cocaine Medication 999
Cocaine Medication Development 1005, 1006
Collaborative Effort 1027
Comparing United States Drug Abuse 1003
Cost to the Nation 1029
Craving 1012
Demographics of Addicts 1003
Disease Specific Budgets 996
Drug Abuse Budget Increase 994
Drug Abuse Costs 1009
Drug Intoxication 1030
Effect of Welfare Reform on Addicts 1052
Effective Drug Treatments 1009
Effectiveness of Prevention Programs 1007
Essense of Addiction 1001
Extent of the Problem 1020
Genetic and Environmental Influences 1034
Impact of Drug Abuse 1030
Improving the Health of Minorities 1037
Information Dissemination 1007, 1048
Introduction of Witnesses 983
Justification of the Budget Estimates 1054
Knowledge "Bottleneck" 1039
Marijuana for Medical Purposes 1026
Medical Marijuana Concerns 1008
Medical Use of Marijuana 997
Methadone Treatment 998
Minority and Women's Health 1044
Minority Related Research 1004
National Institutes of Health Disease-Specific Budgets 996
Needle Exchange 997, 1023
Needle Exchange and AIDS 1008
Needle Exchange Programs 1004
Nicotine Addiction 994, 1000
NIDA–SAMHSA Coordination 1053
Opening Statement 983
Our Nation's Youth 1047
Outreach 1037
Prenatal Drug Use Study 1007
Prevention Increase 1008
Prevention Principles Book 1006
Prevention Program 1005
Prevention Programs for Elementary and Secondary School Students 1016
Prevention Research 1012
Progress 1031
Relationship Between Marijuana and Abrupt Termination of Pregnancy 1011
Relationship with ONDCP 992
Research 1012
School Based Drug Prevention 1014
Search for a Cure 1046
Statement of the Director 988
Successor Drugs of Abuse 999

Page
Tobacco 1014
Vaccine Development 992

National Institute on Alcohol Abuse and Alcoholism

Adolescent Consumption, Trends of 1101
Alcoholics Anonymous, Evaluations of 1103
Animal Models 1092
Brain Function in Adolescents 1140
Chromosomes Associated with Alcoholism 1123
Clinical Research 1136
Clinical Trials 1139
Cloning 1138
Comparing Drug and Alcohol Use and Abuse 1108
Consumption 1109
Coordination 1122
Coordination of Research Findings 1142
Cure for Alcoholism 1105
Dissemination of Research Findings 1131
Effects of Alcohol on Development 1110
Estrogen, Effect of Alcohol on 1112
Extent of the Problem 1124
Fetal Alcohol Syndrome, Correlation of Heavy Drinking to 1111
Fetal Alcohol Syndrome 1125
Fetal Alcohol Syndrome and Early Childhood Development 1143
Genetic Testing 1107
Genetics Research, Practical Applications of 1107
Incidence by Gender 1121
Institute of Medicine Assessment 1132
Justification 1145, 1176
Knowledge of "Bottlenecks" 1137
Liver Transplantation for Alcoholic Liver Disease 1113
Major Research Opportunities 1125
Medications for Alcohol Treatment 1104
Medications, Promising 1118
Minorities, Improving the Health of 1135
Moderate Drinking 1117
Naltrexone Research 1133
New Opportunities for Developing New Drugs 1119
Opening Statement 1091
Pregnancy 1128
Prevention 1094
Prevention Research versus Behavioral Research 1121
Project Match, Rigorous Design and Findings of 1101
Project Northland: Positive Outcome and Lower Drug Use 1121
Research Advances, Application of 1093
Research Dissemination 1095
Safe and Drug Free Schools 1115
Serotonin 1112
Significant Research Opportunities 1125
Statement of the Director 1096
Tobacco and Alcohol Use 1134
Treatment Research 1094
Vulnerability to Alcoholism 1091
Welfare Reform 1141

Page
Witnesses, Introduction of 1091

National Institute of Diabetes and Digestive and Kidney Diseases

Administrative Issues 1218
Artificial Pancreas 1194
Budget Estimates, Justification of 1184
Chromium Diabetes Study 1236
Clinical Research 1251
Clinical Trials 1254
Clinical Trials—Participation 1249
Cloning 1253
Collaborative Efforts 1225, 1246
Cooley's Anemia 1209
Costs of Treating Diabetes 1194
Crohn's Disease 1257
Diabetes Education Program 1191
Diabetes Education and Research 1224
Diabetes Emphasis 1184
Diabetes Gene 1243
Diabetes in African Americans 1256
Diabetes in Minorities 1244
Diabetes Initiative 1240
Diabetes Prevention 1237
Diabetes Prevention Trials 1225
Diabetes Regimen 1209, 1219
Diabetes Research 1228, 1231
Digestive Diseases 1205
Disease Funding 1214
Drugs That Work Selectively 1204
Effects of Alcohol 1201
End-Stage Renal Disease 1241
Funding for Diabetes Research 1189, 1217, 1223
Genetics of Diabetes 1191
Helicobacter Pylori 1249
H. Pylori Applications 1202
Health Status of Women and Minorities 1245
Hepatitis 1207
Hepatitis C 1214
Identifying Areas of Research Emphasis 1184
Immune Modulation in Diabetes 1185
Impact of Diabetes Trial 1210
Improving the Health of Minorities 1251
Intramural Decision-Making 1196
Intramural Research 1195
Introduction of Witnesses 1177
Justification of the Budget Estimates 1258
Knowledge "Bottleneck" 1252
Liver Disease in Children 1221
Liver Disease Information 1219
Locating Diabetes Information 1193
New Methods for Treating Diabetes 1237
Newly Diagnosed Diabetics/Early Intervention 1227
Nutrition 1200
Nutrition and Diabetes 1255

Page
Obesity 1211, 1222, 1241, 1244
Opening Statement 1177
Organ Donations 1250
Outside Input for Diabetes Research 1226
Peer Review 1230
Polycystic Kidney Disease 1208, 1217, 1255
Prevalence of Diabetes 1188
Professional Judgment Budget 1189
Prostate Cancer 1247
Prostatitis 1206
Public Education Activities 1216
Public/Private Research Partnerships 1255
Research Centers 1215
Restoring Insulin Production 1187
Review Process for Clinical Studies 1226
Risk for Diabetes 1239
Small Business Research 1197
Special Research Areas in Diabetes 1192
Statement of the Director 1180
Stress in Diabetes 1185
Treating and Preventing Diabetes 1223
Ulcer Diagnosis and Treatment 1203
Ulcers 1199, 1228
Upcoming Diabetes Conference 1192
Urology 1206, 1218
Women's Health 1193

National Library of Medicine

Bioinformatics 1325
Electronic Patient Records 1338
Genetic Databases 1336, 1346
Gpra Standards 1341
High Performance Computing 1337, 1347
Human Genome Map 1316, 1324
Iaims Program 1337
Internet 1312, 1326, 1331, 1339
Justification of The Budget Estimates 1355
National Information Infrastructure 1309
Next Generation Internet Initiative 1326, 1352
Opening Statement 1309
Outreach 1324, 1330
Personal Services Contracts 1337
Project Phoenix 1342
Pubmed 1339, 1348
Statement of the Director 1319
Telemedicine 1314, 1327, 1328, 1334, 1343, 1351
Toxicology Center 1337
Underserved Populations 1345
User Fees 1349
Video Tapes 1349
Visible Humans 1310
World Wide Web 1333, 1343

National Institute of Nursing Research

Aging 1402

Page
Alzheimer's Disease 1400
Breast Cancer 1399
Breast Self-Exams 1389
Cardiovascular Disease 1378
Cardiovascular Disease in Children 1396
Chronic Illness 1395
Clinical Research Conference 1385
Collaborative Efforts 1401
Communication with Health Care Providers 1384
Counseling for Genetic Screening 1389
Cultural Diversity 1378
Currency with Research 1386
End of Life 1379
End of Life Care 1397
Future Research Emphases 1379
FY98 Budget Request 1379, 1413
Infant Colic 1396
Irritable Bowel Syndrome 1378
Justification of the Budget Estimates 1384
Minority and Women's Health 1406
Minority Researchers 1403
Nurse Education Act—FY 1988 Budget 1393
Nursing and Oncology 1410
Nursing Publications 1385
Opening Statement 1377
Opportunities for Ethnic Nurses 1392
Outreach and Information Dissemination 1405
Pain Research 1377, 1399
Professional Judgment Budget 1384
Provider Care 1398
Quality of Care 1393
Quality of Life 1394
Research Training Issues 1387
Rural and Ethnic Populations 1391
Sister to Sister Study 1405
Stroke 1406
Targeted Research 1404
Transplantation 1379
Traumatic Brain Injury 1386, 397
Women's Health 1411
Women's Health Issues 1388

Fogarty International Center

Biodiversity Program 1455
Budget Increase 1460, 1461
Emerging Infectious Diseases 1463, 1464
External Panel Review 1452
Fellowship Programs 1450, 1451
Former Soviet Union—State of Science 1454
Human Frontier Science Program 1453
International Agreements 1460
International Activities Expenditures 1458, 1459
Justification of Budget Estimates 1466–1489
Minority International Research Training Program 1462, 1463

Page
Opening Statement 1443
Other Countries Leading in Biomedical Research 1450
Vitamin A Supplementation 1464, 1465

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Antibiotic Treatment 1507
AIDS Research 1529
Arthritis Treatment 1522
Breast Cancer and Osteoporosis 1535
Breast Implants and Autoimmune Diseases 1512
Budget Estimates, Justification of 1537
Budget Request, FY 1998 1494
Cartilage Repair 1512
Central Nervous System Lupus 1514
Clinical Research 1530
Clinical Trials 1533
Collaborative Research 1515
Depression and Osteoporosis 1513
Epidemiological Data Concerning Repetitive Motions Injuries 1520
Ergonomics 1500, 1502
Fibrodysplasia Ossificians Progressiva 1514
Funding for Disease Areas 1517
Gender and Autommunity 1511
Gulf War Syndrome 1513
Human Cloning 1502, 1503, 1505, 1532
Health Status 1528
Low Back Pain 1518
Minority Health Research 1530
Musculoskeletal Disorder 1500, 1518
Osteoarthritis 1526
Osteoporosis 1493, 1509, 1510
Psoriasis 1535
Professional Judgment Budget 1507
Repetitive Motion Injury 1499, 1525
Research Centers 1517
Research Opportunities 1522
Research Challenges 1532
Rheumatoid Arthritis 1493
Sexualy Transmitted Diseases 1536
Skin Cancer 1493, 1524
Statement of the Director 1491, 1495
Stress and Arthritis 1511
Success Rate 1536
Systemic Lupus Erythematosus 1493, 1528
Total Joint Replacement 1492
Trauma Injuries 1521

National Center for Research Resources

National Center for Research Resources 1573, 1604
Broader Participation 1602
Clinical Research 1591
Chimpanzees in Research 1579
Chimpanzee Retirement 1580, 1581
Coordination of Imaging Activities 1586

Page
Education 1597
Euthanasia of Research Animals 1583
Extramural Construction 1600
Extramural Facilities Construction 1585, 1587, 1588, 1592
Extramural Programs 1596
Faculty Investigators 1598
Funding for Selected Programs 1588
General Clinical Research Centers 1583
Interest in Biomedical Research 1590
Introduction of Witnesses 1573
Minority and Women's Health 1600
Minority Research Investigators 1597
NCRR Appropriations 1595
NCRR Strategic Plan 1582
Near Infrared (University of Kentucky) 1590
Office of Research on Minority Health 1597
Opening Statement 1573, 1575
Pipeline 1596
RCMI Clinical Initiative 1601
RCMI Cofunding 1600
Regional Primate Research Centers 1586, 1587
Research Centers in Minority Institutions 1592
Research Infrastructure in Minority Institutions 1595
Review Committees 1598
Shared Instrumentation Grants 1588
Use of Animals in Research 1579
Virtual Laboratories 1585

National Institute of Child Health and Human Development

AIDS 1681
Alcohol and Drug Addiction 1673
Asthma 1649
Autism 1643
Autism Centers 1644
Autism Research Investigators 1644
Child Day Care 1674
Childhood Nutrition 1667
Children with Learning Disabilities 1660
Children with Reading Disabilities 1655
Clinical and Basic Research 1689
Clinical Research 1665
Clinical trials 1691
Cloning 1691
Diabetes Research 1679
Drug Dosages for Children & Pediatric Pharmacology Res. Units 1653
Drug Use before Pregnancy 1657
Early Child Care 1646
Funding—Disease Areas 1671
Grant Funding 1666
Health Status of Minority Children 1684
Infant Mortality 1676
Infertility Research 1656
Infertility 1673
Intervention Programs 1660

Page
Intramural Clinical Research 1669
Justification 1693
Learning Disabilities 1688
Learning Disabled Children 1644
Learning to Read 1648, 1654
Maternal Mortality 1656
Middle School Children 1652
Minority Representation in Basic Research and Training 1689
National Center for Medical Rehabilitation Research 1672
Obesity Research 1680
Opening Statement 1635
Perinatology Research—District of Columbia 1665
Phonics Based Reading System 1659
Phonics Based System 1661
Phonics 1663
Premature Labor and Delivery 1646
Prevention Problem Behavior 1651
Protection from Asthma 1650
Pulmonary Hemorrhage in Infants 1687
Research Bottlenecks 1690
Research Centers 1670
Research on Fatherhood 1663
Research Opportunities 1685
SIDS Back to Sleep Campaign 1645
SIDS 1670, 1688
Spinal Cord Injury 1668
Strengthening Families 1670
Teenage Drug Use and Pregnancy 1658
Vaccine Development 1666
Web Page 1649

National Institute of Dental Research

50th Anniversary 1772
AIDS/HIV 1775
Biomimetics 1749
Bone Research 1762, 1780
Cleft Palate 1755
Clinical Trials 1768
Clinical Research 1777
Cloning 1778
Congressional Justification 1782
Dental Amalgams 1748
Dentist Scientist Program 1756
Diabetes, Oral Complications of 1750
Flouridation 1749, 1754
Future Expectations 1750
Health Status 1767
Immune Systems 1770
Introduction of Witneses 1737
Knowledge "Bottleneck" 1771
Medicare Coverage for Dental Care 1755
Minorities, Improving the Health of 1776
Minority Groups, Reaching Ethnic and 1762
NIDR Strategic Plan 1759

Page
Opening Statement 1737
Oral Cancer 1757, 1764, 1769
Osteoporosis and Oral Bone Loss 1751
Pain Research 1752, 1780
Priority Setting 1760
Public Education 1774, 1780
Research Centers 1759, 1765
TMD 1750, 1753

National Institute of Mental Health

Basic Neuroscience 1852
Brain as the Touchstone of NIMH Research 1828–1829
Brain Development and Mental Illness 1840–1842
Children 1854–1856, 1866–1867
Prevention of Childhood Mental Illness 1823–1824
Proceedings of Workshop (Inclusion of Children in Clinical Research) 1837–1839
Research Needed on Childhood Disorders 1829–1830
Treatment of Mental Illness in Children 1834–1840
Circadian Rhythms and Mental Illness 1843–1844
Clinical and Services Research 1852
Eating Disorders 1844–1845, 1849–1850, 1856
Funding Amounts FY 1996–FY 1998 1846
Gene Therapy 1868–1869
Global Burden of Disease 1818–1819
Table 1 1811
Inclusion of Women and Minorities 1865–1866
Initiative to Track Enrollment of Women and Minorities 1827
Justification of Budget Estimation 1870–1913
Managed Care 1857–1858
Mental Illness in the U.S 1859–1862
Mental-Physical Relationship 1867–1868
Minority Employment 1826
Minority Investigators and Research Subjects 1825–1827
Needle Exchange Programs 1821–1822
New Drugs for Schizophrenia 1831–1832
Nutritional Factors 1850–1851
Opening Statement of Director 1809–1817
Prevention of Childhood Mental Illness 1823–1824
Proceedings of Workshop (Inclusion of Children in Clinical Research) 1837–1839
Regulation of Emotion 1853
Relationship of Mental Illness to Other Physical Illnesses 1842–1843
Research Needed on Childhood Disorders 1829–1830
Schizophrenia 1859
Setaside for Mental Health Services Research 1821
Sexual Abstinence in AIDS Prevention 1823
Social Work Research 1830
Suicide and Suicide Prevention 1862–1865
Training 1858
Training of Minority Researchers 1831
Translation of Research into Treatment 1832–1834
Treatment of Mental Illness in Children 1834–1840
UNOCCAP (Use, Needs, Outcomes,and Costs for Child and Adolescent Populations) 1819–1820

Page
Victims of Torture 1846–1849
Vulnerability 1854
World-wide Burden of Disease (Table 1) 1811
World-wide Burden of Depression 1824–1825

National Institute on Aging

Aging—The Exercise and Nutrition Linkage 1955
AIDS 1963
Alzheimer's Disease and Ibuprofen 1941
Alzheimer's Disease 1915, 1934, 1935, 1948, 1954, 1960
Alzheimer's Disease Genetic Discoveries 1917
Biological Processes 1958
Biology of Aging 1920
Caloric Restriction 1949
Collaborative Activities 1959
Demographic Research 1934
Demography of Aging 1921
Disability Research 1933, 1956
Embryo Research 1936
Falls in the Elderly 1939
Genetic Research 1943
Health Care Savings 1937
Health Status and Clinical Trial Participation 1861
Hypertension 1952
Immune System 1963
Long Term Care 1943, 1965
Managed Care 1955
Menopause 1964
Number of Chronically Disabled Americans Age 65 and Over 1924
Nursing Homes—Individualized Care 1950
Opening Statement 1915, 1926
Osteoporosis 1937
Predictive Testing 1944
Projected Population Age 100 Years and Over 1931
Prolonging Independence—Delaying Disability 1956
Prostrate Cancer 1940
Protective and Risk Factors for Alzheimer's Disease 1919
Quality of Life 1936
Research Centers 1946
U.S. Life Expectancy at Age 85, 1900–1995 1932
Unraveling Longevity 1963
World Population by Age 1922

National Institute of Neurological Disorders and Stroke

Accident Prevention 2048
Alzheimer's Disease 2039
Amyotrophic Lateral Sclerosis 2022
Brain Diseases in Children 2039
Childhood Diseases 2035
Clinical Research 2041
Clinical Trials 2044
Cloning 2043
Congressional Justification 2051
Diseases of Aging 2010

Page
Epilepsy Research 2033, 2040
Estrogen and Stroke 2020
Future of Brain Research 2011
Human Embryo Research 2023
Introduction of Witnesses 2001
Knowledge Bottleneck 2042
Mad Cow Disease and Prion Hypothesis 2021
Minority Research Investigators 2037
Multiple Sclerosis 2034
Neurodegenerative Disease Initiative 2018, 2019
New Treatments and Discoveries 2038
Nicotine, Possible Therapeutic Effects of 2020
NINDS Budget Increases 2012
Opening Statement 2001
Parkinson's Disease 2016, 2028
Prion Hypothesis and Mad Cow Disease 2021
Research Centers Grants, NINDS 2026
Specific Disease Funding 2026
Spinal Cord Injury Research 2012, 2016, 2024, 2049
Statement of Director 2005
Stroke Research 2010, 2020, 2031, 2036, 2047, 2049
Targeted Research 2018

National Institute of General Medical Sciences

Biology of the Brain Initiative 2121
Budget Policy 2142
Budget Tables 2144
Cell Biology and Biophysics 2130
Compliance with NRSA Payback Requirement 2112
Employment Prospects for Research Trainees 2110
Evaluation of National Research Service Award Training 2112
Gender Differences in Response to Trauma 2115
Genetics and Developmental Biology 2133
Goals of the Director 2108
Goals to be Accomplished and Priority-Setting Process 2140
High Risk Research 2109
Inclusion of Underrepresented Minorities 2118
Innovations in Management and Administration 2141
Interim Funding 2108
Introduction 2123
Justification of Budget Estimates 2124
MARC Program 2122, 2136
MBRS and HBCU Participation 2120
MBRS Program 2119, 2137
Medical Scientist Training Program 2112
Minority Opportunities in Research 2117, 2137
New Approaches to Pathogenesis 2132, 2133, 2134, 2135
New Investigators 2110
NIGMS Organizational Chart 2125
Opening Statement 2095
Other Areas of Interest 2141
Percentage of Ph.D's Awarded to Minorities 2114
Pharmacology Research Associate Program 2140
Pharmacology, Physiology, and Biological Chemistry 2135

Page
Protease Inhibitors 2118
Rationale for Stipend Increases 2112
Research Advances 2130
Research Areas Pursued by Young Investigators 2113
Research in Chemistry and Physical Sciences 2108
Research Training Collaborations with Industry 2111
Scientists Employed as Temporary Workers 2111
Special Initiatives 2138
Special Programs 2137
Stimulation of Research Fields 2110
Stipend Levels 2116
Story of Discovery: From Chemistry to Gene Therapy 2129
Training Programs of the Howard Hughes Medical Institute 2114

Office of AIDS Research

AIDS Statistics 2163
AIDS in Minority Populations 2170
AIDS in Minority Populations 2203
AIDS Research Proportion of NIH Funding 2171
AIDS Research Addressing Minorities 2170
AIDS Research Proportion of Total NIH Request 2167
Benefits of AIDS Research to Other Diseases 2164
Changing Faces and Scientific Priorities 2190
Clinical Trials of New Therapeutic Agents 2188
Cooperation with Industry 2183
Demographic Groups With Increasing AIDS Cases 2163
Direct Support for OAR 2174
Federal Biomedical Research Plan 2175
Flexibility for OAR to Change ICD Distributions 2165
Inclusion of Minorities in AIDS Research 2193
Justification 2205, 2248
Latest Advances in AIDS/HIV Therapies 2202
Minorities on Research Training Grants 2168
Minority Participation in Clinical Trials 2197
Needle Exchange 2187
NIH Panel on Principles of Therapy for HIV Infection 2181
OAR Discretionary Fund 2176
OAR Collaboration with ORMH and ORWH 2192
Opening Statement 2155
Pediatric AIDS 2178
Prevention Science Working Group 2172
Projected AIDS Deaths Without a Vaccine 2164
Proportional Increases for NIH Institutes 2171
Prospects for International Availability of an AIDS Vaccine 2163
Recipients of AIDS Research Funds 2177
Reluctance of Monitories to Participate in Clinical Trials 2171
Research Plan 2186
Role of the Office of the Director 2167
Small Business Innovation Research Grants (SBIR) 2196
Social and Behavioral Factors of AIDS 2192
Status of Minority and Women's Health 2167
Status of the Development of an AIDS Vaccine 2186
The Investment in Minority Research Programs 2196
The New Generation of AIDS Researchers 2172

Page
Three Percent Transfer Authority 2166
Total AIDS Research Funding 2166
Training for HIV Researchers 2184
Witnesses, Introduction of 2155

Office of the Director and Buildings and Facilities

Administrative Cost Study 2264
Area Program 2301
Behavioral Research 2335
Budget Request for ORMH 2338
Building and Facilities 2257
Child Abuse and Neglect 2324
Cholestin 2262
Clinical Research Issues 2304
Concluding Remarks 2292
CRC Advanced Appropriations 2262
CRC Cost Estimates 2263
Credit Card Purchases 2303
Decrease in OD Funding Level 2323
Electronic Grant Submissions 2311
Employment Separation Rates 2345
Enrollment for Women's Health Initiative 2308
Extramural Associates Research Development Awards Program 2328
Extramural Biomedical Facility Construction Research Infrastructure 2344
Grant Scoring 2310
Herbal Medications 2266
Inclusion of Women and Minorities in Clinical Trials 2309, 2332, 2347
Institute of Medicine 2343
Introduction of Witness 2249
Justification of Budget Estimates 2358
Listing of NIH Facilities 2290
MARC and MBRS Programs 2270, 2334
Medical Nutrition Therapy 2266
Minority Health Initiative 2300
Minority Programs 2336
- Funding for Minority Programs 2338, 2345
- Funding for Minority Researchers 2271
- Inclusion of Minorities in Research 2330
- Increasing Minority Participation 2327
- Minorities in Clinical Trials 2351
- Minority Funding 2270, 2291
- Minority Research Grants 2272
- Minority Researchers 2337
- Recruitment and Retention of Minorities 2350
- Representation of Minorities in Research Protocols 2349
- Underrepresented Minorities 2326, 2352

National Agenda on Research on Women's Health 2269
National Biomedical Research Service Positions 2298
National Foundation for Biomedical Center 2315
New Component for Women's Health Initiative 2308
NIH Organizational Structure 2289
Office of Alternative Medicine 2265, 2318, 2323
- Alternative Medicine Research 2316
- Office of Alternative Medicine Budget 2301

Page

Office of Alternative Medicine—Continued
Office of Alternative Medicine Clearinghouse 2302
Office of Behavioral and Social Sciences Research 2315
Office of Dietary Supplements 2266
Office of Research on Minority Health and NIEHS Collaborations 2293
Opening Statement 2249
Opening Statement—Dr. Kirschstein 2251
ORMH—Standing Advisory Committee 2341
ORWH's Budget Level 2268
Pediatric and Neurodegenerative Initiatives 2306
Plans for New Institutes 2290
Progress of Minority and Women's Health 2326
Quotas 2274
Radioisotope Contamination 2295
Radiology and Imaging 2262
Recombinant DNA Advisory Committee 2314
Renovation of Clinical Center 2263
Research Needs of Children 2323
Research of Human Subjects 2313
Re-Submission of Unfunded Grant Applications 2313
SBIR Grants 2295
Science Education Activities at the NIH 2275
Senior Biomedical Research Service Positions 2295
Status of Minority and Women's Health 2326
The Ryan Commission 2316
Unified Information Technology System 2264
Women and Minorities in Biomedical Careers 2333
Women in Biomedical Careers 2269
Women's Health Initiative 2298
Adequacy of Spending on Diabetes 2484
Advice In Decision-Making 2435
AIDS:
Expenditures for AIDS and Other Diseases 2473
NIH Expenditures on AIDS Research 2494
Research Coordination 2482
Research Funding 2495
Scientific Opportunity 2471
Stabilizing Infections 2494
Vaccine Initiative 2500
AIDS and Scientific Opportunities 2471
AIDS Research Coordination 2482
AIDS Research Funding 2495
AIDS Vaccine Initiative 2500
Areas of Emphasis 2485
Biography, William E. Paul, M.D 2468
Biography, Harold E. Varmus, M.D 2459
Biography, Dennis Williams, Ph.D 2470
Budget:
Constraints 2436
Doubling NIH's 2497
NIH Budget for 1998 2508
Budgetary Constraints 2436
Cancer:
Mortality Rates 2488
Ovarian 2501

Page

Cancer—Continued
Ovarian 2503
Ovarian, Detection of 2490
Research Article 2489
Cancer Mortality Rates 2488
Cancer Research Article 2489
Clinical Research 2501, 2502
Clinical Research Report 2505
Coding for Parkinson's Research 2477
Commitment Base 2434, 2476
Committee Report Language 2472
Congressional Biomedical Research Caucus 2475
Congressional Support 2503
Cost Savings from Research 2500
Criteria For Decision-Making 2434
Curriculum Vitae, Phillip Gorden, M.D 2467
Curriculum Vitae, Richard Klausner, M.D 2460
Curriculum Vitae, Claude Lenfant, M.D 2465
Detection of Ovarian Cancer 2490
Disease:
Imprecision of Coding 2435
Trans-NIH Categories 2478
Doubling NIH's Budget 2497
Drug Rehabilitation 2506
Early Childhood Development 2506
Earmarks in DOD for Research 2507
Effect of Public and Congressional Input 2499
Expenditures for AIDS and Other Diseases 2473
Factors in Resource Allocation 2492
Factors In Resource Allocation 2472
Final Authority for Decision-Making 2486
Funding for Autism 2489
Funding for Population Research 2480
Genetics Research Opportunities 2496
Imprecision Of Disease Coding 2435
Information Dissemination 2503
Information Dissemination of Research Findings on Learning Disabilities 2507
Information Transfer 2499
Information Transfer in Prevention 2506
Information Transfer to Other Agencies 2506
Learning Disabilities:
Research on 2507
Information Dissemination of Research Findings on 2507
Limitations To Planning Science 2434
NIH Budget for 1998 2508
NIH Definitions of Selected Population Groups 2479
NIH Health Funding By Group 2481
NIH Expenditures on AIDS Research 2494
NIH Resource Allocation Procedures 2485
NIH Spending On Minority Initiatives 2479
Nobel Laureates 2474
Observations And Principles For Resource Allocation 2433
One Percent Transfer Authority 2486
Opening Statement of the Director NIH 2433
ORWH's Priority Setting Process 2504

Page
Ovarian Cancer 250, 2503
Pace Of Research 2437
Parkinson's Disease 2436
Parkinson's Disease And Related Research Awards, FY 96 2457
Politics and Research 2501
Prepared Statement Of Director, NIH 2439
Priority Setting 2493
Priority Setting Interaction of ORWH and NIH 2505
Public Relations for NIH 2482
Research on Learning Disabilities 2507
Resource Allocation By NIH 2437
Science Cannot Be Purchased 2436
Stabilizing AIDS Infections 2494
Statement of the Hon. George R. Nethercutt, Jr 2484
Statement of the Hon. George Gekas 2476
Statement of the Hon. Patsy Mink 2490
Statement of the Hon. Constance A. Morella 2498
Strategic Plan 2478
Technology Transfer 2502
Trans-NIH Disease Categories 2478
Unanticipated Research Results 2496

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