

**DEPARTMENTS OF LABOR, HEALTH AND
HUMAN SERVICES, AND EDUCATION, AND
RELATED AGENCIES APPROPRIATIONS FOR
FISCAL YEAR 2004**

TUESDAY, APRIL 8, 2003

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 10 a.m., in room SD-192, Dirksen Senate Office Building, Hon. Arlen Specter (chairman) presiding.
Present: Senators Specter, Cochran, Harkin, and Murray.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF ELIAS ZERHOUNI, M.D., DIRECTOR

ACCOMPANIED BY:

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JAMES F. BATTEY, JR., M.D., PH.D., DIRECTOR, NATIONAL INSTITUTE
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OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Good morning, ladies and gentlemen. The Ap-
propriations Subcommittee on Labor, Health and Human Services,
and Education will proceed.

Dr. Zerhouni, we now turn to this portion of the hearing on the
National Institutes of Health.

Dr. Gerberding, we thank you for your participation. If you
would like to be a director of the NIH or one of the institutes, you
may stay.

If you choose to retain your current position at CDC, you are free
to excuse yourself. Thank you very much for joining us.

Dr. GERBERDING. Thank you. I think I will keep to my present
job.

Dr. ZERHOUNI. We would not mind having her as a director at
NIH.

Dr. GERBERDING. Thank you.

Senator SPECTER. Dr. Zerhouni, we have already introduced you
with your impressive background and credentials coming from Al-
giers at a young age. We thank you for the work you are doing at
NIH. It is good to hear that you were in Mississippi with Senator
Cochran. Thank you for coming to Pennsylvania to a very inter-
esting forum we had a few months ago at the University of Penn-
sylvania. And now we look forward to your testimony.

SUMMARY STATEMENT OF DR. ELIAS ZERHOUNI

Dr. ZERHOUNI. Thank you, Senator Specter. And thank you,
members of the committee.

INTRODUCTION OF NEW INSTITUTE DIRECTORS

What I would like to do first and foremost is introduce to you four new directors of NIH who have joined us over the past year. Dr. Thomas Insel is the new Director of the National Institute of Mental Health. Thomas can say hi. Dr. Nora Volkow is going to assume the directorship of the National Institute of Drug Abuse. Dr. Rod Pettigrew is going to be, is the new Director of the National Institute of Bioimaging and Bioengineering. And T.K. Li is the new Director of the National Institute of Alcoholism and Alcohol Abuse.

To my right, I would like to introduce our new Deputy Director for NIH, Dr. Raynard Kington, who has replaced Dr. Ruth Kirschstein, who is now serving as the senior advisor to the directors, with us today as well and continues to help both Dr. Kington and I with her advice.

Senator SPECTER. Let me just pause for just a moment to thank Dr. Ruth Kirschstein for her outstanding service at NIH over many years, including serving as acting director. We salute you and are glad to see that you are still on board.

Dr. ZERHOUNI. Again, I would like to really extend our thanks to the full committee and to you, Mr. Chairman, and to you, Senator Harkin. We know that without your leadership, the doubling of NIH would not have occurred this year in the difficult economic and budgetary circumstances that we are facing. And we appreciate it very much.

RESEARCH PRIORITIES

I would like to quickly go over what NIH is planning to do with the doubling of the NIH budget and what our priorities are going to be. First and foremost, we want to make sure that the resources you have given us are invested with the best people and are invested on the best ideas that can promote the health of our people.

This is done in the context of, first of all, major priorities that continue to be priorities, but also evolving challenges. These evolving challenges are truly fundamental to the way biomedical research will need to be done in the future.

CHRONIC DISEASES

First and foremost, we have experienced over the past 40 years a tremendous shift in the landscape of disease in our country going from acute diseases that were very lethal to more chronic diseases. Seventy-five percent of the disease burden of the United States today is related to long-term chronic diseases. We have made great progress in cardiac diseases when we control acute myocardial infarction. But these patients are now surviving longer and have different kinds of problems.

AGING POPULATION

The second challenge is that of the aging population. And we need to tackle that proactively.

HEALTH DISPARITIES

The third is health disparities, as I mentioned before.

EMERGING DISEASES

The fourth, as you heard today, is emerging diseases. Not just infectious diseases, but also diseases that relate to the change in our environment, all conditions. For example, the rise in obesity and its implications on the incidence of diabetes in our country. Last, but not least, is the biodefense priorities, which we will continue to support.

STRATEGIC ROADMAP FOR NIH

Now to do so and to go forward, we wanted over the past year to work with all the directors of NIH and all the constituencies to define what we would call a strategic road map for NIH and how we will invest the resources you have placed in trust with us, and what are the priorities that we think will make the greatest difference in terms of advancing research, in terms of developing the best people, promoting the best ideas, and essentially translating them to real benefits. And there are three.

We will explore new pathways to discovery. And that is essentially to fully exploit the unprecedented opportunity of the genomic era. To us, this is the beginning, not the end, of an era. The genome is allowing us today to explore completely different ways of looking at disease than we had in the past.

Second, because of the scaling complexity of 21st century research, we understand now that the problems cannot be tackled by individual scientists alone. We need large multi-disciplinary teams that are going to work together to in fact do so.

Third, we need to re-engineer the clinical research enterprise of our country. We need to more quickly translate our discoveries into practice. And this will be a priority of the NIH in the future.

Last but not least, we are submitting to you a request for the fiscal year 2004 budget, which is a 2.6 percent change over the enacted 2003 level. When we worked—and Senator Specter and Senator Harkin and Senator Murray, I can tell you that we worked very, very hard, including myself and Dr. Gerberding and others to try to make sure that the impact on our programs in the new budget will be as limited as possible, in terms of critical mission areas. We did advocate internally, as you recommended in your statement.

Research will not be affected at the 2.6 percent level, but we will be able to maintain our research to the 7 percent level. Excluding biodefense, we will maintain a 4.3 percent level. And the number of grants will go 10,509.

At the bottom of the slide, you see why that is in 2004. And the reason is because many one-time expenditures that were related to building the infrastructure for biodefense, buildings and facilities that were needed in 2003 have been reinvested in the research portfolio in 2004. Now those are the main elements of the budget we are submitting. And as you said, Senator Specter, we are looking forward to your input in this process. And obviously, we will provide you with all the information that you may want us to provide you and answer all your questions in that regard.

PREPARED STATEMENTS

But rest assured that we will and are committed and will be committed to make sure that the return on investment of the NIH continues to be the same it was in the past. Thank you very much. [The statements follow:]

PREPARED STATEMENT OF DR. ELIAS ZERHOUNI

FISCAL YEAR 2004 PRESIDENT'S BUDGET REQUEST

Good morning, Mr. Chairman and members of the Committee. Let me begin by expressing my deepest appreciation for the generous and bipartisan support of the Congress, Secretary Thompson, President Bush, and the American people for the completion of the doubling of the NIH budget this year. I recognize and appreciate the extraordinary effort of this committee and, Mr. Chairman, your leadership as well as your efforts, Senator Harkin—without which the doubling would not have occurred. I thank you for it.

I also want to assure you that NIH fully understands and embraces its role as the steward of our Nation's investment in medical discovery. We must ensure that these precious resources are used wisely and lead to tangible benefits that touch the lives of everyone.

The year 2003 is truly a pivotal year for medical research. It is the year when we celebrate the 50th anniversary of the discovery of the structure of DNA and its direct consequence—the completed sequence of the Human Genome. We have witnessed nothing short of a revolution in science over the past 5 years. Some may see this year as the grand finale. I think of it more as the overture. As the 21st century begins to unfold, we are poised to make quantum leaps in our knowledge about how to improve people's health.

In my testimony, I will demonstrate what health benefits have resulted from the Nation's longstanding investment in the NIH, along with some of our most recent advances. Finally, I will outline emerging priorities and NIH's plans for responding to the health challenges before us.

THE NIH TRADITION

NIH-led progress in medical research is changing the landscape of disease. For example, NIH research led to a major reduction in mortality related to coronary heart disease and stroke. NIH contributed to this decline in a number of ways. First, we identified cardiovascular risk factors and the importance of behavior modification, such as smoking cessation, dietary changes, and exercise, to reduce risk and improve cardiovascular health. Second, we supported the basic science that led to the development of pharmaceuticals to control hypertension and high cholesterol levels. NIH-funded research also led to strategies as simple and inexpensive as taking aspirin to prevent heart disease and stroke, and life-saving procedures such as angioplasty and coronary artery bypass grafting. We also continue to evaluate best therapeutic strategies in medical practice, as in the recent ALLHAT trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) that showed that hypertension can be effectively managed with an initial choice of an inexpensive drug. Were it not for these advances and others, the expected death toll from coronary heart disease would have been over 1,300,000 in 2000 as compared to the actual death toll of 514,000.

Progress has been equally remarkable for Hepatitis B (HBV) and Hepatitis C (HCV) infections. New cases of these infections are on the decline, in part, because of improved vaccines and the reduced risk of infection from blood transfusion—both outcomes of NIH-funded research. Because of changes in the criteria for donor recruitment and new and improved approaches to testing blood, the risk of infection through transfusion has been virtually eliminated.

The ability to screen for HIV infection—made possible by NIH research serves as an important target for both prevention and treatment of AIDS. The mortality rate of this devastating disease is now one fifth of what it would have been without research on the fundamental biology of the HIV virus. Research on behavioral interventions to prevent HIV infection and improve its treatment also contributed to better control of the spread of this disease in our country.

One more dramatic example can be found in the development of the Haemophilus Influenza B vaccine. The results of this NIH research have led to a virtual elimination of this disease in our country and, the disease is in the process of being elimi-

nated worldwide. In the not too distant past, the complications of Hib made this disease the leading cause of acquired mental retardation in infants and children.

NEW CHALLENGES AND STRATEGIES

Due in part to research advances; the burden of disease is now shifting from more acute and lethal forms of disease to chronic illness. Our success in conditions like myocardial infarction and infectious diseases is leading to better survival rates. As the result of such prolonged survival and the aging of the population, the incidence of chronic and long-term diseases, such as congestive heart failure, cancer, Alzheimer's disease, Parkinson's Disease, diabetes, and obesity, among others, is increasing.

For example, although we have witnessed reductions in acute coronary heart disease, the burden of congestive heart failure has increased during the last 30 years of the 20th century. As another case in point, more people are living with cancer, as therapies transform this once acutely fatal disease into a more chronic and manageable condition.

Furthermore, rapid changes in our environment and lifestyle lead to disequilibrium between our genetic make-up and our ability to adapt to these changes. The most dramatic recent example is the rise in the incidence of obesity, due in part to the greatly increased availability of food and reduced daily physical energy requirements.

It is imperative that we develop more comprehensive strategies to address such emerging challenges. In all likelihood, these strategies will require a better understanding of: (1) the series of molecular events that lead to disease in the hope of affecting its course before the disease develops, so-called Molecular Prevention; (2) the interactions between genes, the environment, and lifestyle as they relate to the etiology and progression of disease; ways of delaying the onset of the disease and/or ways to reduce the severity of its course and its impact on quality of life.

All of these strategies will need to be explored simultaneously and it is this systematic approach, from most basic to applied research, that will produce much needed results. Several important examples of these strategies have already proved their value.

For example, a major cause of blindness, age-related macular degeneration (AMD), currently affects 1.75 million Americans. They have advanced degeneration in at least one eye. Over 7 million individuals are at substantial risk of developing AMD. Its prevalence increases dramatically with age; for more than 15 percent of white females over 80 years of age have AMD. By the year 2020, the number of people with AMD will increase by 50 percent to 2.95 million.

NIH is engaged in a major research program to understand the predisposing factors, the clinical course, and the prognostic factors of AMD. Researchers found that giving high levels of antioxidants and zinc reduce the risk of developing advanced AMD by about 25 percent. These nutrients also reduce the risk of advanced AMD-induced vision loss by about 19 percent. These findings may help people who are at high risk of developing advanced AMD keep their vision. Over the next five years, 329,000 people in the United States (66,000 per year) could be saved from advanced AMD. More remains to be done. We need to spread the word to change practices, and we need to continue work to identify the genes that control the risk of this devastating disease as well as to develop more interventions to prevent or delay the onset of blindness.

In another example, many doctors today who are treating patients with rheumatoid arthritis remember all too well how challenging treatment was not so long ago. In the early 1980s, treatment was initiated in what was known as a therapeutic pyramid. Patients would first be given a course of aspirin or another non-steroidal anti-inflammatory drug (NSAID), and would be followed to see if erosions occurred in the bone. If erosions did occur or if the patients did not respond to the NSAIDs, the next course was anti-rheumatic drugs that were added one-by-one as the disease progressed. Sadly, the disease-modifying therapy was initiated only after the patient was already on the road to disability. The root causes of the disease were not known, but the discovery, originally made through cancer research, of the role of Tumor Necrosis Factor (TNF), a naturally occurring protein in the body that mediates inflammation, dramatically changed the treatment landscape. By specifically targeting this protein with customised antibodies, entirely new drugs were developed and approved for the treatment of rheumatoid arthritis, including etanercept and infliximab. These were the first biological-response modifying antibody drugs that behave as antagonists—meaning that they work by specifically blocking the action and decreasing the availability of TNF.

These new-targeted therapies showed substantial effectiveness in people with rheumatoid arthritis who had not previously responded to other treatments. The treatments are generally well tolerated, although some concerns have been raised recently about the long-term effects of these agents. Other studies reported that infliximab and methotrexate used in combination not only reduced the symptoms of rheumatoid arthritis, but also halted the progression of joint damage when compared to the use of previous forms of therapy. Scientists involved in this study observed that in the last 2 years, rheumatoid arthritis research has moved further than in the previous 30 years, and that a wealth of new treatments is now available that have the potential to prevent and heal structural damage to the joints of people with this debilitating disease.

THE NEED FOR A STRATEGIC ROADMAP

The change in the landscape of disease requires us to adopt new approaches and accelerate the pace of our discoveries. The need has never been so pressing, the opportunities have never been greater, and challenges have never been more daunting. The NIH must simultaneously learn from the past, act in the present, and plan for the future. It must institute the changes necessary to improve the health of the American people. We need to proactively define enabling initiatives—how best to advance science as well as what science to advance. We need to map the terrain and over the past nine months we have been engaged in just such an effort.

Soon after I arrived at NIH, I convened a series of meetings to develop a “Roadmap.” My goal was to develop a short list of the most compelling initiatives that the NIH should pursue that would make the biggest impact on biomedical research.

This assessment was needed because powerful and unifying concepts of biology are emerging that hold the potential to lead to rapid progress. For example, in the past, cancer research was considered vastly different than heart or brain research. Today, with recent discoveries in molecular and cell biology, we know that biological systems obey common laws and follow similar pathways in both health and disease. Efforts to fully understand these complex molecular events are beyond the reach of any one laboratory or group of investigators. As we begin to decipher the tidal wave of knowledge we have amassed, the scope, the scale, and the complexity of 21st century science will require us to devise even newer ways to explore biology for the sake of improving health.

Three major themes emerged from these Roadmap meetings. First, we must uncover new pathways to scientific discovery. For example, we must develop a comprehensive understanding of the building blocks of the body’s cells and tissues and how complex biological systems operate. Also, structural biology will provide vital information about the proteins that make up the human body. Molecular libraries will give us new tools and targets for effective therapies. Overall, these examples, plus nanotechnology, computational biology and bioinformatics and molecular imaging will provide the foundation upon which new treatments, diagnostics and prevention strategies will emerge.

The second theme that emerged from our consultations is the changing dynamics of the research teams of the future. Because of the complexity and scope of today’s scientific problems, traditional “mentor-apprentice” models must be replaced by integrated teams of specialists from numerous disciplines that were considered unrelated in the past. Imaging research, for example, requires cell biologists, computer programmers, radiologists, and physicists to work collaboratively on new diagnostics and treatments.

The third theme that was voiced again and again by researchers is the need to re-engineer the national clinical research enterprise for optimal translation of our discoveries into clinical reality. The list of what is needed is long—it includes supporting multidisciplinary clinical research training career paths, introducing innovations in trial design, stimulating translational research, building clinical resources like tissue banks, developing large clinical research networks, and reducing regulatory hurdles. We must explore a standard clinical research informatics strategy, which will permit the formation of nation-wide “communities” of clinical researchers made up of academic researchers, qualified community physicians, and patient groups.

Our vision is to make sure that our citizens benefit from a vibrant clinical research system—a system that will allow us to more efficiently translate our breakthroughs in basic research with the goal of improving health.

The three thematic areas that I just described, that is, new pathways to discovery, multidisciplinary teams, and reengineering the clinical research enterprise, focus on technologies and systems that will enable researchers today and in the future to not only solve problems more quickly, but also to ask questions that we have not been

able to ask before—questions so complex that without the aid of these efforts they would be impossible to address.

Efforts to understand the building blocks of the body's cells and tissues and to understand how complex biological systems work can lead directly to new approaches to improving health or preventing disease. A recently discovered biological phenomenon called RNAi—or RNA interference—has led to the development of a new and potent research tool, which is being used to identify the function of specific genes in normal biological and disease processes.

A recent study, co-funded by NIH, used RNAi to identify genes involved in the regulation of fat metabolism in the roundworm experimental model in an effort to better understand obesity. One at a time, each of the 17,000 genes of the round worm was turned off using this novel method. Researchers found that inhibition of 305 genes decreased body fat, whereas inhibition of 112 genes increased fat storage. With this information, researchers identified new genes involved in fat metabolism, genes common in many organisms, including humans. These genes now give researchers multiple new opportunities for understanding obesity and new targets for the development of therapies. This is just one example of how these new approaches are beginning to transform medical research.

Finally and importantly, the NIH must communicate our research results both to the lay public and health professionals. NIH works in partnership with many different organizations to communicate scientific results and health information to the medical research community, health care providers, patients, the media and the general public across the nation. We conduct our education and outreach efforts in collaboration with other federal agencies, state agencies, private sector organizations and national health care organizations. We have made progress in this area. For example, the NIH Web site is now the most accessed of all government health and science web sites. This aspect of our mission will continue to be a priority for NIH.

BIODEFENSE

Civilian biodefense research has become a new core priority at NIH and a prominent component of our budget. Over the last year and a half, we responded to the most urgent needs of biodefense, namely the development of countermeasures such as vaccines, therapeutics, and diagnostic tests. These will allow us to respond to and control the intentional or unintentional release of agents of terrorism that affect human health, including infectious disease and microbial toxins. We are also now systematically reviewing our portfolio of biodefense research to include radiation and chemical exposures, and mental health preparedness research. Biodefense research will be the topic of a separate hearing.

Mr. Chairman, I am pleased to present the President's fiscal year 2004 request for the National Institutes of Health of \$27,663 million for the programs of NIH that fall under the purview of this Committee. This level will allow us to support our highest research priorities and continue the momentum we gained during the historic doubling of the NIH budget. In large part this is possible because of the very significant amount of one-time costs supported in fiscal year 2003 that will not be required in fiscal year 2004. Once these have been taken into account, NIH will be able to increase the amount available for research by 7.5 percent. Even after excluding increases for the Administration's highest priority—homeland defense—the research components of the NIH budget will still increase by 4.3 percent. The request will allow us to support the highest number of new and competing grants in history—10,509 new and competing grants. At this level, we will be able to continue to support approximately one-in-three of the research grant applications we receive. The final enacted fiscal year 2003 appropriation is very close to the President's request. In the coming weeks, NIH will work with appropriate staff to clarify discrepancies between the fiscal year 2003 request and the enacted level.

Special emphasis will be placed on areas of growing concern such as obesity and diabetes, the IDeA program, and the Best Pharmaceuticals for Children's Act. A total of \$35 million is requested through the Director's Discretionary Fund to support our important Roadmap activities. As the fiscal year 2004 budget is developed, NIH will work with appropriate staff to clarify discrepancies.

In sum, the plans I have outlined here today are ambitious and rightly so. They rise to the many scientific opportunities and significant health challenges that lie before us. Once again, my thanks to you and the American public for your continued investment in biomedical research to improve the health of everyone.

BUILDINGS AND FACILITIES PROGRAM

The Buildings and Facilities (B&F) program supports the physical infrastructure required to carry out the in-house component of the biomedical research mission of the National Institutes of Health (NIH). The fiscal year 2004 Buildings and Facilities budget request supports efforts to sustain a robust, modern, safe and secure physical infrastructure for the conduct of basic and clinical research and research support across the spectrum of biologic systems and diseases.

The B&F budget request is the product of a deliberate, corporate facilities planning process both within the NIH and the Office of the Secretary, Assistant Secretary for Administration and Management, HHS. At the NIH, the Facilities Planning Advisory Committee (FPAC) oversees this process and provides advice to the NIH leadership and Director. The FPAC is also instrumental in adjusting priorities as necessary to deal with unanticipated public health challenges and changes in national priorities. The goal of the planning process is to optimally meet the changing facility needs of the NIH research programs in the Washington, D.C., region and across the NIH field stations with a mix of owned and leased facilities. The fiscal year 2004 Buildings and Facilities (B&F) budget request supports the NIH's research infrastructure priorities. The request includes projects and programs to responsibly manage the repair and upkeep of the existing physical infrastructure, and to maintain our facilities at an optimal operating standard to meet mission as well as safety and regulatory requirements.

The NIH appreciates the support from Congress in fiscal year 2003 for NIH's Physical Security, Biodefense facilities, and the final phase of the construction of the Mark O. Hatfield Clinical Research Center.

The fiscal year 2004 request maintains responsible funding support for the ongoing safety, renovation and repair, and related projects that are vital to proper stewardship of the entire portfolio of real property assets and continues the functional integration of the clinical research components of the existing Building 10 with the new Mark O. Hatfield Clinical Research Center (CRC).

The fiscal year 2004 B&F budget request is organized among three broad Program Activities: Essential Safety and Regulatory Compliance, Repairs and Improvements, and Renovations. The fiscal year 2004 request provides funds for specific projects in each of the program areas. The projects and programs enumerated are the end result of the aforementioned NIH Strategic Facilities Planning process and are the NIH's capital facility priorities for fiscal year 2004.

FISCAL YEAR 2004 BUDGET SUMMARY

The fiscal year 2004 budget request for Buildings and Facilities is \$80 million. The B&F request includes a total of \$14 million for Essential Safety and Regulatory Compliance programs composed of \$2 million for the phased removal of asbestos from NIH buildings; \$5 million for the continuing upgrade of fire and life safety deficiencies of NIH buildings; \$1.5 million to systematically remove existing barriers to persons with disabilities from the interior of NIH buildings; \$0.5 million to address indoor air quality concerns and requirements at NIH facilities; and \$5 million for the continued support of the rehabilitation of animal research facilities. In addition, the fiscal year 2004 request includes \$60.5 million in Repairs and Improvements for the continuing program of repairs, improvements, and maintenance that is the vital means of maintaining the complex research facilities infrastructure of the NIH. Finally, the request includes \$5.5 million in Renovations for the Building 10 Transition Program.

My colleagues and I will be happy to respond to any questions you may have.

PREPARED STATEMENT OF DR. DUANE ALEXANDER

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2004 President's budget request for the National Institute of Child Health and Human Development (NICHD). The fiscal year 2004 budget includes \$1,245 million, an increase of \$41 million over the fiscal year 2003 enacted level of \$1,205 million comparable for transfers proposed in the President's request. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report which compares our fiscal year 2002 results to the goals in our fiscal year 2002 performance plan.

Forty years ago, the U.S. Congress charged the NICHD with a broad mandate. The Institute was asked to develop a research program to ensure that people are able to have children when they want them; that every child is born healthy; that

women suffer no adverse consequences from the reproductive processes; and that children experience healthy physical, cognitive, behavioral, and social development, reaching adulthood free of disease and disability, and able to lead productive lives.

We have made exceptional progress toward those goals during the last 40 years. Infant mortality has been cut by more than 70 percent, largely due to NICHD research that has led to new ways to treat and prevent respiratory distress syndrome, to manage premature infants, and to reduce Sudden Infant Death Syndrome. Mental retardation in the United States has been significantly reduced because we have conquered and controlled some of its leading causes: Hemophilus influenza type b (Hib) meningitis, phenylketonuria (PKU), measles encephalitis, and jaundice. Infertility that deprived millions of couples from conceiving children can now be diagnosed and in many cases treated. Transmission of HIV infection from mother to baby has been reduced from 27 percent to less than 2 percent in the U.S. as a result of research showing the effectiveness of administering antiretroviral drugs to the mother during pregnancy and to the infant just after birth.

We look forward to building on 40 years of scientific achievements and we would like to share with you recent achievements that are improving the health of the American people.

PREMATURE BIRTH: NEW RESEARCH MAY REVERSE A TREND

The number of infants who are born prematurely is increasing. While infant mortality rates have decreased significantly in recent years, the number of premature low birth weight babies born has increased by 11 percent over the last two decades. The number of premature very low birth weight infants, weighing less than 1,500 grams, has increased by 24 percent. Research supported by the NICHD has helped many premature infants to survive. But these infants can develop neurological, respiratory, or other conditions causing life-long disabilities. Recently, NICHD scientists discovered that weekly injections of progesterone, a readily available hormone, can lower premature birth by more than one-third among women who are at risk of premature delivery. In this study, like many clinical studies, some of the women received the progesterone and some received a placebo injection. The results were so dramatic that the scientists halted the study and administered progesterone to all women enrolled in the study.

ORAL CONTRACEPTIVES AND BREAST CANCER: NO ASSOCIATION

The NICHD research has also provided reassuring evidence to women and their physicians who may be concerned about a possible relationship between oral contraceptive use and breast cancer. About 80 percent of U.S. women born since 1945 have used oral contraceptives. Conflicting studies had caused concern about the possible effect of oral contraceptive use on breast cancer risk. The NICHD's Women's Contraceptive and Reproductive Experiences Study found that women between the ages of 35 and 64 who took oral contraceptives at some point in their lives were no more likely to develop breast cancer than other women the same age who never took oral contraceptives. Many women who took oral contraceptives during their reproductive years are now reaching the ages of greatest breast cancer risk. This study should resolve the long-standing concern that oral contraceptive use might be associated with an increased risk of breast cancer in later life.

VASECTOMY AND PROSTATE CANCER: NO ASSOCIATION

Another study supported by the NICHD answered an important question for men who have had vasectomies. About one out of six American men over the age of 35 has had a vasectomy. Some studies conducted in the United States in the early 1990s reported a moderately increased risk of prostate cancer among men who underwent vasectomy. Other studies found no such risk. Because of this conflicting evidence, many urologists have increased prostate cancer screening of men who had vasectomies and have discouraged vasectomies in men with a family history of prostate cancer. The NICHD study found that men who had a vasectomy were no more likely to develop prostate cancer than those who had not had a vasectomy. The study also found that men who had vasectomies as long as 25 years ago did not have an increased risk of prostate cancer. These results should reassure men who have had or who are considering a vasectomy.

STROKE PATIENTS IMPROVE FUNCTION OF IMPAIRED LIMB

The results of other NICHD-supported research provide encouraging news to some stroke victims. Until recently, therapy for stroke victims often involved teaching patients to strengthen their less impaired limb for several weeks after a stroke. The

prevailing view among rehabilitation professionals was that patients' motor ability reached a plateau at about six months after a stroke. They believed that additional therapy would provide little if any additional benefit. But new research has shown that the use of the impaired limb can improve significantly a year or more after a stroke. Using "Constraint Induced Therapy," researchers showed that constraining the good or less affected limb for 10 days can help restore a great deal of mobility to the impaired limb.

TRAUMATIC BRAIN INJURY NETWORK FOR BETTER TREATMENTS

Traumatic brain injury is one of the leading causes of death and disability in children and adults. An estimated two million head injuries occur in the United States each year. As a result of advances in emergency medicine at the accident scene and the hospital, many TBI victims are living longer. However, many will live with persistent physical, cognitive, behavioral and social deficits that compromise their quality of life. Research over the last two decades has demonstrated that not all neurologic damage occurs at the moment of injury, but evolves over the minutes, hours, and days after an accident. Research also has dramatically improved the immediate care, follow-on care, and rehabilitative process for TBI patients. Yet there are many unanswered questions about the underlying damage and the reasons for reduced functioning associated with TBI. In addition, to determine the most appropriate therapies for children and young adults with TBI, multiple sites are needed to evaluate various interventions with many patients. To address this need, the NICHD recently established the Traumatic Brain Injury Clinical Trials Network. The Network will evaluate medical, rehabilitative, and educational interventions to identify which ones most effectively improve the long-term outcomes of TBI patients.

NEW FRAGILE X CENTERS WILL DEVELOP TREATMENT OPTIONS

Fragile X syndrome is the most common genetically-inherited form of mental retardation currently known. The condition occurs in every 1 out of 2,000 males and in 1 in 4,000 females. The syndrome is caused by a mutation in a specific gene (FMR1) on the X chromosome. In its fully-mutated form, the FMR1 gene interferes with normal development. In a partially mutated (premutation) form, the FMR1 gene can cause fragile X syndrome in the children of a carrier (a person who has the premutation gene). Until recently, however, the premutation form was not thought to cause symptoms in carriers. Scientists have now identified a subgroup of premutation FMR1 carriers with symptoms that appear to be associated with the gene. Symptoms included mild cognitive and emotional problems and, in female carriers, premature menopause. In older male carriers, the premutation gene is associated with a neurological syndrome. Identifying a genetic basis could be a first step toward accurate diagnosis and, possibly, development of new treatments for these often overlooked symptoms. In addition, to develop improved diagnostic techniques and treatment options, the NICHD will begin funding three new Fragile X research centers in fiscal year 2003. Each center will call upon the combined expertise of several researchers working in diverse fields to investigate different aspects of the disorder. The new Fragile X Research Centers will study issues such as how the fragile X affects the developing brain and nervous system, how the disorder progresses throughout an individual's life span, and effective treatments that can improve the behavior and mental functioning of people with fragile X syndrome.

STRATEGIC ALLIANCES WITH MINORITY GROUPS TO REDUCE SIDS

Less than ten years ago, the NICHD initiated a campaign urging parents and caretakers to place infants on their backs to sleep to reduce the risk of Sudden Infant Death Syndrome (SIDS). Since that time, the SIDS rate in the U.S. has declined by more than 50 percent. This dramatic decline represents a significant public health achievement because the SIDS rates had remained tenaciously steady prior to the NICHD campaign. Although the SIDS rates have declined in all populations since the campaign began, the SIDS rate among African American infants remains double that of white infants. Among Alaska Natives and many American Indian tribes, the rates are higher still. To begin closing this gap, the NICHD has formed strategic alliances with the Alpha Kappa Alpha sorority, The National Coalition of 100 Black Women, and The Women in the NAACP. In collaboration with these organizations, the NICHD has planned and will support a series of "summit" meetings in three U.S. cities with high rates of African American SIDS deaths. These summits will enlist the resources of faith-based and community organizations, public health officials, and service organizations to help establish an infrastructure that will provide information, material, and support for reducing SIDS among African American infants. Each organization will take the lead in organizing one of the sum-

mit meetings and will continue to serve as the catalyst for SIDS risk reduction activity in that city and its surrounding region.

The NICHD has also initiated a project with American Indian and Alaska Native groups to reduce SIDS and infant mortality in these populations. At NICHD-sponsored meetings in Minneapolis, MN and Rapid City, SD, representatives of Tribal Chairman's Health Boards and Alaska Native health organizations provided the NICHD with a blueprint to support the activities of community health workers involved in SIDS risk reduction education. The NICHD will develop and disseminate the materials for this effort during the current year.

TESTING DRUGS TO IMPROVE HEALTH OF CHILDREN AND PREGNANT WOMEN

In fiscal year 2004, the NICHD will continue to invest in research and programs that benefit the American people. One such investment is the fulfillment of the Best Pharmaceuticals for Children Act (BPCA). The immature physiology of children means that drugs approved to prevent or treat illness in adults may have different effects in younger patients, requiring children's physicians to prescribe different doses and make other adjustments in drug therapies. However, for approximately seventy-five percent of the pharmaceuticals approved by the Food and Drug Administration (FDA) for adults, there are inadequate safety and efficacy data to allow approval for pediatric uses, or to guide physicians in prescribing these drugs for children. The BPCA, signed into law in January 2002, directs the NIH to issue contracts to test in children off-patent prescription drugs already approved for adults. Working with the FDA and other experts, the NICHD identified a priority list of drugs to be tested through the Institute's Pediatric Pharmacology Research Units (PPRUs) and at other sites. The fiscal year 2004 budget request includes an increase of \$25 million, across all of the NIH Institutes and Centers (ICs), for these studies.

Drugs prescribed to pregnant women are also a concern. Although nearly two-thirds of all pregnant women take at least four to five drugs during pregnancy and labor, the effects of these prescribed drugs on a pregnant woman and her fetus remain largely unstudied. In addition, little is known about how pregnancy-related changes in cardiac output, blood volume, intestinal absorption, and kidney function may influence drug absorption, distribution, utilization, and elimination. Therefore, the NICHD will establish a new network of Obstetric-fetal Pharmacology Research Units that will allow investigators to conduct key pharmacologic studies of drug disposition and effect during normal and abnormal pregnancies.

EXPANSION OF NEWBORN SCREENING THROUGH MICROARRAY TECHNOLOGY

At present, all states routinely screen all newborns for only two disorders: phenylketonuria (PKU) and congenital hypothyroidism. These are conditions for which effective treatments are available. In addition, most states screen for a mix of 1 to 15 other disorders, but some commercially available tests can screen for up to 50 conditions. A Secretarial-level panel and the American Academy of Pediatrics have recommended that an expanded and standardized approach to newborn screening be developed. To address this need, the NICHD proposes to apply the knowledge and techniques garnered from the Human Genome Project. Using cord blood and microarray technology, there is the potential to identify disease genes at birth for more than 200 single gene defects associated with mental retardation, nearly 100 associated with immunodeficiency disorders, approximately 10 causes of muscular dystrophy, and cystic fibrosis. Although treatments are available for many of these conditions, effective study of potential new treatments for others requires a population who has not yet developed symptoms of the condition. Screening of newborn infants can provide this population. This testing could be done in one procedure so that economies of scale and simplicity may overcome one of the major obstacles to widespread acceptance of expanded newborn screening: cost.

The NICHD will collaborate with several other ICs, research institutions, and industry to develop the appropriate microarray chip and associated technology for mass screening and pilot test the new screening technology. This approach would maximize the use of newborn screening for preventive purposes. Moreover, by developing this translational research, NICHD will fulfill one of the objectives of the NIH road map activities.

Mr. Chairman, I will be happy to provide answers to any questions you have.

PREPARED STATEMENT OF DR. JAMES F. BATTEY, JR.

Mr. Chairman and Members of the Committee, I am pleased to present the President's budget request for the National Institute on Deafness and Other Communica-

tion Disorders (NIDCD). The fiscal year 2004 budget includes \$380,377,000, which reflects an increase of \$10,190,000 over the fiscal year 2003 enacted level of \$370,187,000 comparable for transfers proposed in the President's request. Disorders of human communication exact a significant economic, social, and personal cost for many individuals. The NIDCD supports research and research training in the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. Results of NIDCD's research investment will foster the development of more precise diagnostic techniques, novel intervention and prevention strategies, and more effective treatment methods for the millions of Americans with communication disorders. My testimony will highlight some examples of research progress in human communication sciences.

Cochlear Implants.—If Ludwig van Beethoven were able to reverse his deafness and regain his hearing again as he reached the climax of his career as a composer, would the world have been blessed with even more of his music? Scientific technology has advanced significantly since the 18th century, and assistive hearing devices are now able to restore sound perception to deaf individuals. One such device, the cochlear implant, has provided hope to thousands of deaf individuals worldwide. A cochlear implant converts sound into electrical impulses, bypassing the damaged sensory hair cells that detect sound, stimulating the auditory nerve directly and restoring sound perception. According to the Food and Drug Administration 2002 data, approximately 59,000 people worldwide have received cochlear implants. In the U.S., about 13,000 adults and nearly 10,000 children have received them. With over 30 years of NIH research investment, the cochlear implant has evolved from an experimental device to a commercially available treatment to assist those who are profoundly deaf or severely hearing impaired.

Hereditary Deafness Gene Discovery.—Within the last seven years, over 70 different genes for hearing loss that is not associated with other inherited characteristics (nonsyndromic hereditary hearing impairment) have been mapped and over 25 identified. In addition, several genes essential for normal auditory development and/or function have been identified using mouse models. Recently, scientists have discovered a new gene of unknown function, TMC1, in which mutations cause deafness. NIDCD intramural scientists have identified a mutation in the mouse Tmc1 gene which causes similar types of dominant and recessive hearing loss found in large human family studies. In mice, mutations in the Tmc1 gene causes defects in the function of the specialized sensory hair cells of the inner ear. Hair cells detect and convert the physical stimulus of sound into electrical impulses sent to the brain via the auditory nerve. This research contributes to new models for studying specific forms of human deafness.

Sensory Stereocilia Renewal Aid Recovery to Hearing Loss.—Stereocilia, or hair cell bundles, are fine projections in the inner ear that vibrate when stimulated by sound. The movement of the stereocilia activates a molecular pathway that generates an electrical signal from the auditory nerve to the brain, which is interpreted to be sound. Stereocilia are located in the surface of the inner ear and are supported by a rigid and dense core of filaments. Until recently, this core was thought of as a stable structure whose sole function was to serve as rigid supports for changes in the mechanical property of the hair cells. NIDCD intramural scientists have discovered that there is a continuous renewal of the stereocilia core every 48 hours. This process occurs in the mature bundles during recovery from temporary noise-induced hearing loss and suggests that the stereocilia core structure plays an unforeseen role in this recovery process. Such a renewal mechanism could also provide more information on the molecular basis of genetic, environmental, and age-related inner ear disorders that involve malformation or disruption of stereocilia.

Motor Protein Facilitates the Speed of Sound.—One important component in the mechanical transmission of sound from the ear to the brain is Myosin-1C, a major motor protein involved in the movement of the stereocilia in the inner ear. It is hypothesized that motor proteins serve as the link between the stereocilia's membrane and cell core thereby changing the polarity of hair cells following sound vibration. NIDCD-supported scientists are in the process of deciphering how Myosin-1C works. Specifically, they used a chemical-genetic approach to inhibit Myosin-1C motor protein activity in mice by introducing a custom designed amino acid that alters the protein's function. The designer amino acid rendered the protein susceptible to a controllable inhibitor, thus allowing regulation of the protein's motor function. These results demonstrate the importance of Myosin-1C in transmitting sound to the brain, allows observation of protein function in a controllable native environment and permits assessment of protein function in a biological process.

Antibiotic Controls the Vertigo of Ménière's Disease.—Ménière's disease is a distressing and often disabling disorder of inner ear function, characterized by spontaneous attacks of vertigo, fluctuating hearing loss, tinnitus and fullness in the ear.

When vertigo cannot be controlled by diet or medication, severing of a vestibular nerve from the affected ear usually controls vertigo while preserving hearing. NIDCD-supported scientists have demonstrated that a single injection of the antibiotic, gentamycin, through the eardrum into the middle ear space, is an alternative to surgery and is effective in diminishing vestibular response and in controlling vertigo in individuals with Ménière's disease. Experimental studies suggest that gentamycin reduces vestibular responsiveness, and hence, vertigo, by causing a toxic effect on the vestibular hair cells, the sensory receptors that detect head motion stimuli and orientation.

Odorant Receptors Help Mosquitoes Smell Their Prey.—The sense of smell (olfaction) plays an important role for blood-feeding female mosquitoes in finding a host. Mosquito-borne disease is a serious world health concern, and the mosquito is known to transmit a variety of deadly diseases, including malaria, West Nile virus, dengue and yellow fever. Host preference, especially to humans, in the female mosquito is a critical component of disease transmission. NIDCD-supported scientists are characterizing the genes that play a role in the function of the olfactory system of *Anopheles gambiae* and have identified odorant receptor-encoding genes selectively expressed in the olfactory organs of this malaria-transmitting mosquito. Blood-feeding and host preference selection involve only the female mosquito, so the scientists studied the expression of odorant receptor genes, AgOr, in the female mosquito's primary olfactory organ—its antennae. It was observed that AgOr1 is turned off in the olfactory tissue of the female mosquito 12 hours after a blood meal, which is consistent with decreased host-seeking behavior. These findings suggest that AgOr1 may detect an olfactory signal that is active in female mosquitoes before but not after a blood meal. Developing selective antagonists to AgOr1 may help to control the transmission of malaria and other mosquito-borne diseases, and may also represent a novel disease prevention approach that is based on an understanding of olfactory receptor genes. In addition, these findings may ultimately be useful in developing new repellants and attractants that are more effective, economical and ecologically friendly.

Discovery of an Amino Acid Taste Receptor.—Taste is responsible not only for attraction and repulsion to various foods but is also responsible for providing important information about the chemical environment. The basic taste qualities are sweet, sour, salty, bitter and umami (the taste of monosodium glutamate or the taste associated with protein-rich foods). A major challenge in taste research is identifying the various types of taste receptors on the tongue that respond to different structurally diverse compounds. Recently, scientists have identified a taste receptor dedicated to tasting amino acids, the building blocks of proteins that are involved in the biological processes in the body. It has been known that sweet-, bitter- and umami-tasting substances activate G-protein-coupled receptors in the tongue. NIDCD-supported scientists discovered that two subunits in the T1R receptor family, T1R1 and T1R3, can combine to form an amino acid receptor, T1R1+3, that responds to most of the 20 standard amino acids. Identification of an amino acid taste receptor provides a new tool to help scientists decode the molecular basis for detecting different taste qualities in mammals.

Do Stutterers Have Different Brains?—To study the brain activity patterns in the cortical speech-language areas of the brain of individuals who stutter, NIDCD-supported scientists performed brain imaging studies on two groups of adults; those with or without persistent developmental stuttering (PDS). Results of the analysis showed that differences in the speech-language areas of the brain are more common in adults with PDS, although no one anatomic feature accounted for the group differences. The major anatomic finding was that the size of the right and left planum temporale (PT) of the brain were significantly larger in the adults with PDS. The PT is important for higher order processing of language information. The results about the PT size and other findings, such as variations of infolding patterns of the brain, demonstrate that atypical size or shape of the speech-language area may put individuals at risk for stuttering.

Speech-Sound Disorders are Risk for Later Academic Impairments.—Children with speech-sound disorders often have difficulties in other areas of language as well. These disorders are characterized by the inability to use speech sounds that are normal for the individual's age and dialect. Speech-sound disorders involve language difficulty affecting an individual's ability to learn and organize speech sounds into a system of sound patterns. Poor awareness of speech skills and a weakness in vocal sound classification in verbal memory may put children of preschool age with speech-sound disorders at risk for later spelling difficulties. In a recent NIDCD-supported study, the spelling errors of children with history of speech-sound disorders were analyzed to predict the association between weaknesses in spoken language skill in early childhood and school-age spelling abilities. The findings of this study

support previous research indicating that children with early speech-sound disorders are at risk for later spelling difficulties. Evidence from studying these families raises the possibility of a common genetic cause for speech/language and written language disorders. Although the genetic cause for these disorders is not known, specific signs of the disorder suggest a male gender bias since brothers were also more likely to have the disorder than sisters. The findings of this study reveal that preschool children with speech-sound disorders are at risk for later spelling impairments even after productive speech disorders have resolved.

A Possible Gene for Childhood Language Disorders.—Children who fail to develop language normally (in the absence of factors such as neurological disorders, hearing impairments, or lack of adequate opportunity) have specific language impairment (SLI). SLI has a prevalence of approximately 7 percent in children entering school and is associated with later difficulties in learning to read. Research studies have consistently demonstrated that SLI clusters in families, suggesting that genetic factors may be an important cause of SLI. NIDCD-supported scientists are scanning the genome for the location of the gene suspected of causing SLI, by studying families where multiple members have with language/reading disorders. The study showed significant evidence of a link between a region of chromosome 13 and susceptibility to SLI. Further analysis also suggests two additional gene locations on chromosomes 2 and 17 that may play a role in SLI. In addition, mutations in the same region in chromosome 13 is implicated in autism, and some children with autism show language deficits that are very similar to SLI.

Mr. Chairman and Members of the Committee, these are just a few examples of NIDCD's research advances. I would be pleased to answer any questions you may have.

PREPARED STATEMENT OF DR. FRANCIS S. COLLINS

Mr. Chairman and Members of the Committee: Due in great part to the visionary leadership and commitment of Congress, this month the International Human Genome Project (HGP), led by the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH), will have accomplished all of its original goals, ahead of schedule and under budget. This historic achievement, in the month of the 50th anniversary of Watson and Crick's seminal publication of the structure of DNA, opens the genomic era of medicine. April will also witness the publication of a bold vision for the future of genomics research, developed by the NHGRI. This vision, the outcome of almost two years of intense discussions with hundreds of scientists and members of the public, has three major areas of focus: Genomics to Biology, Genomics to Health, and Genomics to Society.

Genomics to Biology.—The human genome sequence provides foundational information that allows development of a comprehensive catalog of all of the genome's components, determination of the function of all human genes, and deciphering of how genes and proteins work together in pathways and networks.

Genomics to Health.—Completion of the human genome sequence offers a unique opportunity to understand the role of genetic factors in health and disease, and to apply that understanding rapidly to prevention, diagnosis, and treatment. This opportunity will be realized through such genomics-based approaches as identification of genes and pathways and determining how they interact with environmental factors in health and disease, more precise prediction of disease susceptibility and drug response, early detection of illness, and development of entirely new therapeutic approaches.

Genomics to Society.—Just as the HGP has spawned new areas of research in basic biology and in health, it has created new opportunities in exploring societal issues. These include analysis of the impact of genomics on concepts of race, ethnicity, kinship, individual and group identity, health, disease, and "normality" for traits and behaviors, and defining policy options regarding the use of genomic information in both medical and non-medical settings.

NEW NHGRI INITIATIVES

The NHGRI has already begun several new initiatives, and is planning others, to meet the challenge of this new vision for the future of genomics. Below are examples of these cutting edge programs.

The Creation of a Human Haplotype Map

Multiple genetic and environmental factors influence many common diseases, such as diabetes, cancer, stroke, psychiatric disorders, heart disease, and arthritis; however, relatively little is known about the genetic basis of common diseases. The

NHGRI has begun to create a “haplotype map” of the human genome to enable scientists to find the genes that affect common diseases more quickly and efficiently. The power of this map stems from the fact that each DNA variation is not inherited independently; rather, sets of variations are inherited in blocks. The specific pattern of particular genetic variations in a block is called a haplotype. This new initiative, an international public/private partnership led and managed by NHGRI, will develop a catalog of haplotype blocks, the “HapMap.” The HapMap will provide a new tool to identify genetic variations associated with disease risk or response to environmental factors, drugs, or vaccines. Ultimately, this powerful tool will lead to more complete understanding of, and improved treatments for, many common diseases.

The ENCODE Project: ENCyclopedia Of DNA Elements

To utilize fully the information that the human genome sequence contains, a comprehensive encyclopedia of all of its functional genetic elements is needed. The identity and precise location of all transcribed sequences, including both protein-coding and non-protein coding genes, with their structure, transcription start sites, polyadenylation sites, and alternative splicing variants must be determined. The identity of other functional elements encoded in the DNA sequence, including promoters, enhancers, and other transcriptional regulatory sequences, and determinants of chromosome structure and function, such as origins of replication and hot spots for recombination, also is needed. The NHGRI has developed a public research consortium to carry out a pilot project, focusing on a carefully chosen set of regions of the human genome, to compare existing and new methods for identifying functional genetic elements. This ENCyclopedia Of DNA Elements (ENCODE) consortium, which welcomes all academic, government, and private sector scientists interested in facilitating the comprehensive interpretation of the human genome, will greatly enhance use of the human genome sequence to understand the genetic basis of human health and to stimulate the development of new therapies to prevent and treat disease.

Chemical Genomics

One novel way that the NHGRI plans to pursue translating genomics to human health is the development and deployment to the biomedical research community of libraries of small organic compounds. This is a fundamentally new approach for research in the public sector, and will accelerate understanding of the function of the human genome and the development of new treatments. The NHGRI proposes to use the types of organic molecules in most marketed pharmaceuticals, “drug-like,” or “small” molecules, as a core of this resource. In collaboration with other NIH institutes, the NHGRI is planning for a resource that includes: (a) large libraries of chemical compounds of appropriate structural diversity and properties; (b) assay development capacity; (c) robotic assay capacity, also termed high throughput screening (HTS); (d) medicinal chemistry capacity to transform “hits” identified by HTS into workable chemical probes; and (e) distribution capacity to disseminate the reagents to the biomedical research community efficiently.

Genome Technology Development

The NHGRI continues to invest in technology development that furthers the uses of genomics. Technical advances have caused the cost of sequencing to decline dramatically, from \$10 to less than \$0.09 per base pair, but this cost must decline even further for all to benefit from genomic advances. The NHGRI, along with many partners, will actively pursue the development of new technologies to sequence any individual’s genome for \$1,000 or less. Other areas of technology development are also ripe for expansion and the NHGRI plans to pursue them vigorously.

Studying the Genetic Basis of Health

Analytic methods to find genetic variants that contribute to disease can also help find genes and genetic variants that contribute to health. The NHGRI plans to support development of new tools and analytical methods to discover the genetic components of resistance to diseases, disorders, toxins, and drug reactions. By finding genetic variants that convey reduced susceptibility, researchers will better understand disease processes and how to slow, or even prevent, them. Promising approaches for identifying disease-resistant gene variants include studying people at high risk for a disease who do not develop it, relatives of people with disease who do not themselves have the disease, or individuals who reach extreme old age without serious illness.

RECENT SCIENTIFIC ADVANCES IN GENOMICS

Progress in Sequencing Model Organisms

From the Human Genome Project's outset, the NHGRI and its partners have included, among their research goals, mapping and sequencing the genomes of several non-human organisms, since they would be of great value in understanding the biological data encoded in the human DNA sequence and, thus, in combating human disease. Genomic sequences for a number of important organisms, beyond those initially identified by the HGP, have been determined. Primary among these is the laboratory mouse. In December 2002, an analysis of an advanced draft of the mouse genome was published and provided a key tool for interpreting the human sequence. The first assembly of the rat genome sequence was announced in the same month by the Rat Genome Sequencing Project. A peer review process now selects new genomes to sequence. To champion an organism, scientists write a "white paper" that presents arguments for prioritizing their proposed target for sequencing. After two rounds of white papers, this process determined the highest priority as: chicken, chimpanzee, cow, dog, a set of fifteen fungi, honeybee, sea urchin, and two protozoans. Sequencing of the chicken, chimpanzee, and honeybee has already begun.

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS OF GENETIC RESEARCH

The NHGRI devotes five percent of its annual budget to research involving the ethical, legal and social implications (ELSI) of genetics and genomics. Below are examples of this program's important work.

Genetic Discrimination

Most Americans are optimistic about the use of genetic information to improve health, but many are also concerned that insurers and employers will misuse genetic information. These concerns deter participation in important biomedical research and the clinical use of genetic information. The NHGRI has supported research efforts to elucidate this issue. Such research has helped inform legislative activity; over 40 states have passed genetic nondiscrimination bills.

Reducing Health Disparities

The NHGRI recognizes the critical importance of ensuring that the potential of genomic research benefits all racial and ethnic groups. The NHGRI has taken steps to engage and empower minority communities in genomic research. The rewards of genomic research will be realized only with active participation of all racial and ethnic groups. An important area of genomic research is investigating how DNA sequence variation affects differing susceptibility to disease among various populations. The significant societal ramifications of this research also need attention. Genomic research affects all populations; thus, all groups need to set the research agenda and examine the broader issues it raises. The NHGRI has intensified its efforts to address health disparities by developing a strategic plan that identifies goals in areas such as research projects, information sharing, development of partnerships, and increasing diversity of the research workforce.

Effects of Gene Patents and Licenses on Genetic Testing and Research

The NHGRI continues to be concerned about the issues of gene patenting and licensing. To gain a better understanding of these issues, it has funded case studies and surveys to describe and analyze the effects of patents that award proprietary claims to the use of DNA sequences. The NHGRI held a roundtable discussion in December 2002 with outside experts in gene patenting to explore the ramifications on healthcare delivery and research of patenting and licensing genetic sequence data and single nucleotide polymorphisms. The NHGRI will utilize the insights provided at this roundtable to define further research to inform the policy process.

CONCLUSION

This year marks a very exciting transition in the field of genomics, with the full sequencing of the human genome marking the successful achievement of all of the HGP's original goals, and thus the advent of the genomics era. When Congress decided to fund the HGP it did so with the justifiable belief that this work would lead to improved health for all. The ability to accelerate the realization of this vision now lies before us. At the same time, we must be sure that all our citizens have access to these technological advances and that this information is not misused. It is our sincere belief that the newly created discipline of genomics will make a profound difference on the health and well being of the people of this world. We are profoundly grateful for the support the Congress has given to this program.

Mr. Chairman, I am pleased to present the President's budget request for the National Human Genome Research Institute. The fiscal year 2004 budget includes \$478,072,000, an increase of \$13,467,000 over the fiscal year 2003 enacted level of \$464,605,000 comparable for transfers proposed in the President's request.

PREPARED STATEMENT OF DR. ANDREW C. VON ESCHENBACH

The early part of the 21st century promises to be a period of unprecedented progress in conquering our most debilitating diseases especially cancer. The nation's unwavering support of the biomedical research enterprise, in particular, the unified effort by this committee, all of Congress, and the President to double the NIH budget over the past five years, has positioned us to attack this devastating disease more effectively. Cancer affects nearly every family in America. In 2003, 1.4 million of our citizens will face a diagnosis of cancer—and over 560,000 of our citizens will die from their disease this year. Every day, 1,500 Americans lose their own battle with cancer. These are daunting statistics, and the aging of the baby boomer population and shifting demographics of America during the next 15–20 years represent enormous healthcare and economic challenges that we must begin to prepare for now.

But, there is reason for optimism! Our nation's investment in basic research has fueled the engine of discovery, thereby enabling unparalleled advances in illuminating the genetic changes and molecular mechanisms that ultimately produce cancer. The sequencing of the human genome and associated progress in new areas such as functional genomics, animal models of cancer, and proteomics, provide us with a clearer picture of the disturbances that cause cancer to develop and ravage the human body. For the first time, we have within our grasp the ability to design target-specific interventions to preempt this process. We must enrich these extraordinary advances in basic science with equally extraordinary efforts to develop new agents and technologies to actualize these interventions at key steps in cancer progression. We now understand that cancer is a process—a process with multiple opportunities to develop new, more effective interventions to prevent, detect and treat cancer.

To capitalize on this knowledge, we must significantly accelerate the pace of progress across the entire research continuum. The pathway begins with discovery of knowledge that underpins the development of new molecules and tools and ends with the delivery of diagnostics and therapeutics to patients. Discovery, development and delivery are interlinked, and it is crucial that we take the steps needed to ensure that all phases of the research enterprise are functioning optimally.

I believe that we stand at an “inflection point” in our nation's effort to conquer cancer. The research enterprise has delivered remarkable scientific achievements in biomedical research over the past decades, and we now are positioned to experience a rapid increase in the trajectory of this research. This affords us an unprecedented opportunity to harness strategically these achievements to confront the challenges of cancer today and tomorrow.

We now envision a time when the suffering and the death that are caused by cancer will be eliminated; and we believe that it is realistic to set ourselves a challenge goal to achieve this vision by the year 2015. I have presented the cancer research community with this challenge and am confident that they will achieve the goal. I want to be clear what we mean by “reduce suffering and death from cancer,” and to explain why I believe that this vision is achievable.

We are not saying that all cancer will be cured or eliminated. What we are saying is that in this 12-year time-frame, many cancers will be cured, but many more will be transformed into chronic, manageable diseases that patients can live with—not die from. There is precedent for this paradigm shift. In a single generation, we made enormous strides in reducing deaths from coronary artery disease and converting this disorder into a condition that people live with and manage. Likewise, using our knowledge of the AIDS virus, molecular biology, and skills in developing target-based therapy, we have developed treatments for AIDS patients that both save lives and preserve quality of life. I think we can do the same for cancer.

This vision presents new challenges for the NCI and for everyone working to conquer this devastating disease. We will meet those challenges by further strengthening basic research, especially in advancing our understandings about the mechanisms of cancer progression. In parallel, we will intensify our focus on developing the clinical research and delivery systems needed to provide the promise of every-thing that science can provide to everyone in need.

I discovery, we will establish a national effort to “map” the critical events of the complex of integrated cancer disease pathways at the cellular level. This “systems biology approach” will allow us to dissect strategically the complex and redundant

reactions and interactions within cells, and will enhance our technical capabilities to identify molecular targets and create new therapies. We will also focus on the exploration of new technologies, in areas such as molecular imaging, proteomics and genomics, and nanotechnology. These new technologies offer the promise of developing new platforms to monitor cells, identifying intricate molecular changes, and delivering therapeutics to specific targets within the cell. The application of these advanced technologies is no longer a dream. Advances in positron emission tomography, coupled with new molecular imaging agents, now make functional monitoring possible, permitting clinicians to “visualize” the biologic progress of cancer. Scientists and engineers are working to achieve this goal through NCI’s unique programs that foster the development of innovative technologies for cancer diagnosis and treatment.

The NCI will also place new emphasis on the development process—the translation of basic research advances into new products that are ultimately delivered to cancer patients. This is especially true in the area of cancer therapeutics. It currently takes 15–20 years for a promising new molecule to reach patients. That is just unacceptable in the 21st century. Genomics and proteomics are providing us with hundreds, potentially thousands, of new therapeutic targets for cancer; but the enterprise is not optimized to develop and deliver these “new paradigm” drugs. This is a systems problem and it can be solved. In collaboration with the NIH, the Food and Drug Administration (FDA) and other partners, we will work to “re-engineer” the clinical trials infrastructure for the evaluation of new cancer interventions. Underpinning all of these initiatives will be the deployment of a bioinformatics infrastructure that will allow us to use artificial intelligence to convert massive amounts of data into new knowledge that will inform discovery, development, and delivery to benefit patients.

The NCI will undertake programs to optimize the process of developing new drugs through an emphasis on validating new cancer targets. We will also work more closely with the FDA to facilitate the science necessary to create a seamless system of drug discovery, development, and delivery. To achieve these goals, the NCI will create novel partnerships with all of the sectors involved in developing and delivering these new drugs. In all that we do, we will encourage the removal of barriers that separate us by creating a new environment that encourages and rewards multi-disciplinary research.

The emerging field of proteomics provides us with unimagined opportunities to apply these new targeted therapies and preventive strategies by detecting cancer early enough to stop, slow, or possibly reverse disease progression. Novel disease biomarkers are finally providing us with new screening tools to detect early-stage cancer in populations and individuals; and the NCI will utilize its enormous strength in molecular epidemiology to provide rational strategies for cancer prevention and disruption of progression within populations.

All of these tactics will be directed to reducing suffering and death from cancer. That does not mean that we will lessen our emphasis on curing cancer—quite the opposite—but that will no longer be our only defining goal. We will also embrace the vision of changing the course of cancer by reducing its morbidity and mortality through the application of technologies and knowledge that were only a dream just a few short years ago. Those dreams can become reality.

Finally, I believe we stand at a pivotal crossroads—a defining moment in the history of this nation’s effort to prevent and cure cancer. We now embark on a new course that will enable patients to live with cancer as a chronic, non-debilitating disease that doesn’t threaten their vitality, careers, and families. An ever increasing body of scientific knowledge and an array of advanced technologies provide us with the opportunity to detect cancer early and preempt the progression of the disease. We will be able to remove the fear of cancer for many more people, but more importantly for those who must live with their disease, life will take on new meaning. We have within our grasp the power to eliminate the suffering and death from cancer—and we will succeed.

BUDGET STATEMENT

The fiscal year 2004 budget includes \$4,770 million, an increase of \$183 million over the fiscal year 2003 enacted level of \$4,587 million comparable for transfers proposed in the President’s request.

PREPARED STATEMENT OF DR. ANTHONY S. FAUCI

Mr. Chairman and Members of the Committee: I am pleased to present the President’s budget request for the National Institute of Allergy and Infectious Diseases

(NIAID) of the National Institutes of Health (NIH). The fiscal year 2004 budget includes \$4,335,255,000, an increase of \$631,126,000 over the fiscal year 2003 enacted level of \$3,704,129,000 comparable for transfers proposed in the President's request. The NIAID budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIAID's third annual performance report, which compares our fiscal year 2002 results to the goals in our fiscal year 2002 performance plan.

NIAID: AN OVERVIEW

Since 1948, NIAID has conducted and supported basic research into the etiology and pathogenesis of allergic, immunologic, and infectious diseases, as well as targeted research to develop new and improved interventions to prevent, diagnose, and treat these illnesses. Over the past half century, and in the past decade in particular, progress in the core disciplines of the Institute—immunology, microbiology, and infectious diseases—has been extraordinary. The rapid growth in scientific knowledge and the availability of new research tools has facilitated the development of numerous vaccines, therapies and other interventions that have saved or improved the lives of millions of individuals. For example, NIAID-supported scientists helped develop many of our most useful vaccines, including new or improved vaccines that protect against invasive *Haemophilus influenzae* type b (Hib) disease, pneumonia and meningitis caused by pneumococcal bacteria, pertussis, influenza, measles, mumps, rubella, chickenpox, and hepatitis A and B. These and other vaccines helped reduce infectious disease mortality in the United States more than 14-fold in the 20th century.

The scientific advances realized during 55 years of NIAID research have been applied to long-standing global health problems such as asthma, autoimmune diseases, diarrheal diseases, malaria, and tuberculosis, as well as to diseases and pathogens that have recently emerged or re-emerged. Examples of the latter include the acquired immunodeficiency syndrome (AIDS), highly virulent influenza viruses, West Nile virus, drug-resistant microbes, severe acute respiratory syndrome (SARS), and a new kind of emerging disease—one spread deliberately by bioterrorists. As has been the case with AIDS and other emerging health crises, the NIAID response to the threat of bioterrorism has been swift and comprehensive, resulting already in important progress both in basic science and in the development of biodefense countermeasures.

NIAID BIODEFENSE RESEARCH

The anthrax attacks in the fall of 2001, which occurred soon after the horror of the September 11 terrorist assaults on the World Trade Center and the Pentagon, starkly exposed the vulnerability of the United States and the rest of the world to bioterrorism. Since the fall of 2001, NIAID has rapidly accelerated basic and clinical research devoted to the prevention, diagnosis, and treatment of diseases caused by potential agents of bioterrorism. Indeed, biodefense research spending now accounts for approximately one-third of the NIAID research portfolio. Our efforts have focused both on "Category A" agents considered to be the worst bioterror threats (smallpox, anthrax, botulinum toxin, plague, tularemia, and hemorrhagic fever viruses such as Ebola), as well as on a longer list of Category B and C priority pathogens agents that also pose significant threats to human health. The NIAID biodefense program is guided by the NIAID Strategic Plan for Biodefense Research, as well as by detailed research agendas for Category A agents and Category B and C priority pathogens. Each of these documents was prepared in consultation with blue-ribbon panels of experts, and delineates immediate, intermediate, and long-range NIAID plans for biodefense research and countermeasures development. Using the roadmap outlined in these agendas, NIAID has developed a total of 46 biodefense initiatives to stimulate research in fiscal years 2002 and 2003: 30 are new initiatives and 16 are significant expansions. During this same time period, NIAID has seen a 30 percent increase in the number of grant applications; the vast majority of these are in response to our biodefense initiatives.

The NIAID biodefense research program is anchored in the traditional NIH processes of basic biomedical research; concurrently, we are aggressively pursuing the goal of translating the findings of basic research into definable and quantifiable endpoints such as diagnostics, therapeutics, and vaccines. NIAID historically has sought to translate basic research findings into "real-world" interventions, as with the vaccines noted above. Until now, however, the path to product development has not been central to our research strategy. The attacks of September 11, 2001, and the subsequent anthrax incidents have compelled us to modify somewhat the way we do business, with an increased focus on translational research and product devel-

opment. This applied research is based on the strongest possible foundation of fundamental knowledge of pathogenic microbes and the host immune response.

As we pursue innovative biodefense countermeasures, we have strengthened our interactions with the private sector, including biotechnology companies and pharmaceutical manufacturers. Many biodefense products do not provide sufficient incentives for industry to develop them on their own, because a profitable market for these products cannot be guaranteed. Therefore, NIAID has developed public-private partnerships with industry to overcome such obstacles so that new and improved interventions against bioterror threats can quickly be developed.

A number of significant advances in understanding, treating, and preventing potential agents of bioterror already have been realized. For example, NIAID-supported scientists have identified antivirals that may play a role in treating smallpox or the complications of smallpox vaccination, as well as new antibiotics and antitoxins against other major bioterror threats. Investigators have demonstrated that existing stores of smallpox vaccine can be diluted five-fold and still retain their potency, greatly increasing the Nation's available stock of smallpox vaccine. These studies of diluted smallpox vaccine helped fulfill an immediate goal delineated in our strategic plan for biodefense. In the intermediate-term, new and improved vaccines against smallpox, anthrax, and other potential bioterror agents are being developed and evaluated at NIAID intramural facilities, as well as by our grantees and contractors in academia and industry. One of these is a smallpox vaccine based on a strain of the vaccinia virus that replicates less robustly than the traditional smallpox vaccine virus, and is known to be less reactogenic than the current smallpox vaccine. In the long-term, we will develop even safer vaccines against smallpox virus and other pathogens.

Advances in biodefense, as well in other areas of infectious diseases research, are being facilitated by the detailed information about pathogens that now can be rapidly gleaned by determining their genomic sequence. The field of pathogen genomics has made remarkable progress: sequencing of the genomes of more than 100 pathogens is complete or nearing completion. Among them are approximately 30 different Category A, B and C agents, including multiple strains of the anthrax bacterium. This genomic information is being used to inform the development of new antimicrobials, vaccines, and diagnostics.

Progress in biodefense research depends on the availability of research resources, such as animal models, standardized reagents, and appropriate laboratory facilities, as well as on human capital, that is, well-trained investigators. Among many initiatives to improve the biodefense research infrastructure, NIAID will establish in fiscal year 2003 a nationwide network of Regional Centers of Excellence for Biodefense and Emerging Infectious Disease Research, and design, build, and renovate a system of Regional and National Biocontainment Laboratories. These facilities will include a small number of Biosafety Level-4 (BSL-4) laboratories, which have the containment safeguards necessary to study highly pathogenic organisms. The new Centers and laboratories will serve as national resources for biodefense research and product development, as well as for the study of other emerging diseases such as influenza and West Nile virus.

The many new NIAID initiatives in biodefense research will provide benefits far beyond protection from deliberate acts of bioterrorism. After all, the general philosophy and strategy of biodefense is essentially the same as that for defense against naturally emerging and re-emerging infectious diseases that threaten global public health. With the careful NIAID planning process, new biodefense resources will unquestionably have enormous benefits in our struggle against other diseases, endemic and emerging, that far transcend the specter of bioterrorism.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Another major focus of the Institute, accounting for approximately one-third of NIAID spending, is research devoted to finding interventions to slow the pandemic of the human immunodeficiency virus (HIV), the cause of AIDS. HIV/AIDS is the defining health crisis of our generation, having claimed well over 20 million lives since the beginning of the pandemic. Another 42 million people worldwide are living with the virus. Most of the world's HIV-infected people live in resource-poor countries, where HIV frequently is superimposed on other significant health challenges, including endemic diseases such as malaria and tuberculosis, and malnutrition. By 2010, more than 45 million new infections will occur, for a cumulative total of 105 million infections, according to estimates of the Joint United Nations Programme on HIV/AIDS.

Despite these grim numbers, significant progress has been made against the HIV/AIDS, much of it due to the research and prevention efforts of NIAID and other

NIH Institutes, the Centers for Diseases Control and Prevention, and other agencies of the Department of Health and Human Services. In this country, prevention efforts have reduced the annual number of new HIV infections in the United States from approximately 150,000 per year to about 40,000 annually. In recent years, we have seen the positive impact of advances in HIV therapeutics for many living with HIV/AIDS in the United States and other western countries, and more recently the promise these medicines offer for those in the developing world. All but one of the 19 antiretroviral drugs licensed in the United States target one of two viral targets: the HIV protease enzyme or the HIV reverse transcriptase enzyme. Over the past few years, NIAID-supported scientists and their collaborators have identified new targets for HIV therapy and novel drugs that block other stages of the virus replication cycle. Among them are agents that block viral genes from entering the host cell nucleus, and drugs that keep the virus from attaching to or entering the cell in the first place. In the latter category, a drug known as Fuzeon or T-20 that blocks the fusion of HIV to the host cell membrane was recently approved and holds great promise for the many HIV-infected patients who harbor HIV that is resistant to current therapies.

To help turn the tide of the global HIV/AIDS pandemic, NIAID has established research collaborations with international colleagues to develop comprehensive approaches to the HIV pandemic in poor countries, encompassing prevention activities, antiretroviral therapy when feasible, and care of the HIV-infected person. These collaborations have yielded extraordinary results, notably in developing methods to reduce mother-to-child transmission of HIV. However, a rate-limiting factor in HIV/AIDS research efforts in developing countries has been a lack of funds for the purchase of antiretroviral drugs and for improving existing healthcare infrastructure. In January 2003, the Institute's international AIDS program received a substantial boost with the announcement of the President's Emergency Plan for AIDS Relief. This plan commits \$15 billion over 5 years (\$10 billion of which is new money), starting with \$2 billion in fiscal year 2004, for HIV/AIDS prevention, treatment, and care in 14 of the hardest-hit countries in sub-Saharan Africa and the Caribbean. This lifesaving effort will not only reduce the suffering caused by HIV/AIDS in countries that account for 50 percent of the world's HIV infections, but will provide a framework that will facilitate NIAID research efforts to develop new and improved tools of treatment and prevention.

Many approaches to HIV prevention are being developed or refined, but the "holy grail" of HIV prevention remains the development of a safe and effective HIV vaccine. Numerous vaccine candidates have shown promise in monkey models of HIV infection, and the most promising ones are rapidly being moved into human trials on the NIH campus and in the domestic and international sites of the NIAID HIV Vaccine Trials Network.

OTHER VACCINES

In addition to developing HIV and biodefense vaccines, NIAID continues to make significant progress in the quest for new and improved vaccines for other diseases of global health importance. The NIH has three broad goals in vaccine research: identifying new vaccine candidates to prevent diseases for which no vaccines currently exist; improving the safety and efficacy of existing vaccines; and designing novel vaccine approaches, such as new vectors and adjuvants, substances that improve vaccine performance.

More than 100 vaccines currently are being developed by NIAID-funded researchers, including promising candidates against emerging diseases such as Ebola virus, West Nile virus, dengue, and dangerous strains of influenza virus. Of particular note are novel tuberculosis vaccines, which soon will enter clinical trials. These trials will mark the first time in more than 60 years that new approaches to TB vaccination have been assessed in humans. These vaccines are a tangible "payoff" of research funded by NIAID and others that led to the availability of the complete genomic sequence of the tuberculosis bacterium. The quest for a malaria vaccine received a significant boost in 2002 when researchers funded by NIAID and others published the genomic sequences of the malaria parasite *Plasmodium falciparum*, and one of its main mosquito vectors, *Anopheles gambiae*. Together, these projects are probably the most significant pathogen genome sequencing effort to date. With the availability of the human genome sequence, scientists now have detailed genomic information for each of the organisms involved in human malaria: the human host, the mosquito vector and the malaria parasite itself. This groundbreaking malaria research promises to provide new targets for vaccine development and other interventions against a disease that claims the lives of more than a million people each year, most of them children in sub-Saharan Africa.

IMMUNE-MEDIATED DISEASES

Immune-mediated diseases such as autoimmune diseases, allergic diseases, and asthma are important health challenges here and abroad. Autoimmune diseases, for instance, afflict 5 to 8 percent of the U.S. population; asthma and allergic diseases combined represent the sixth leading cause of chronic illness and disability in the United States. The past two decades of fundamental research in immunology have resulted in a wealth of new information and extraordinary growth in our conceptual understanding of the immune system and the pathogenesis of immune-mediated diseases. Researchers now know a great deal about the effector molecules that contribute to many immunological conditions, knowledge that has led to the design and discovery of drugs to block those molecules. For instance, we now have powerful treatments that selectively target several of the immune system molecules that cause inflammation, a hallmark of many autoimmune diseases. Blockers of an immune system molecule called tumor necrosis factor-alpha are now routinely used in patients with rheumatoid arthritis and other immunologic conditions.

A relatively new avenue of research suggests that it may be possible to interrupt deleterious immune responses, without dampening protective ones, and provide patients with long-term clinical benefit. The ability to induce "immune tolerance" by selectively blocking deleterious immune response holds great promise for treatment of many immune-mediated conditions, including type 1 diabetes, rheumatoid arthritis and multiple sclerosis, as well as asthma and allergic diseases. For example, researchers have shown in a small trial conducted by the NIAID-sponsored Immune Tolerance Network (ITN) that antibodies to the CD3 molecule on T-cells, given for two weeks soon after patients were diagnosed with type 1 diabetes, appeared to halt the destruction of the patients' insulin-producing cells for at least a year, preserving their ability to produce some of their own insulin. Further follow-up is underway to determine the long-term benefits of this experimental therapy; a larger trial is currently recruiting patients.

Induction of immune tolerance is also one of our highest priorities in organ transplantation research. The ability to selectively block the immune response to a transplanted organ would diminish or eradicate the risk of rejection, as well as the risks and morbidities associated with current methods of immunosuppression. A trial currently underway in the ITN is using a unique approach involving simultaneous bone marrow and kidney transplantation in patients with multiple myeloma. Although only a very small number of patients have undergone the procedure, early results are encouraging, as they have tolerated their transplanted kidneys without immunosuppressive medications for up to 3 years.

Another important NIAID research focus is the development of new interventions to reduce the burden of asthma. NIAID has long been at the forefront of discoveries leading to the characterization of asthma and allergic diseases and is now vigorously pursuing the translation of basic knowledge into more effective treatment and prevention strategies. The NIAID-sponsored Inner-City Asthma Study, completed in 2002, evaluated the effects of a home-based environmental intervention on asthma symptoms and health care utilization in inner-city children with moderate to severe asthma. The intervention led to an additional three weeks of symptom-free days and a 14 percent reduction in unscheduled emergency room or clinic visits in the first year of the intervention; these effects largely persisted for a year following the intervention phase. The improvement in symptoms was correlated with a reduction in levels of key allergens in the home. Building on these results, the NIAID in 2002 launched the Inner-City Asthma Consortium, to conduct clinical trials of novel immune-based agents to treat or prevent asthma.

CONCLUSION

The role of NIAID in fighting infectious and immunologic diseases has never been more important, particularly in the post 9-11 world. Working with our many collaborators in the public and private sectors, we hope to further reduce the burden of diseases endemic in the United States and abroad, to enhance our preparedness against bioterrorism, and to continue to prepare for new threats to public health that will inevitably emerge in the future.

PREPARED STATEMENT OF DR. PATRICIA A. GRADY

Mr. Chairman and Members of the Committee: The fiscal year 2004 budget includes \$134,579 million, an increase of \$4,060 million over the fiscal year 2003 enacted level of \$130,584 million comparable for transfers proposed in the President's request.

Nursing research and nursing practice are converging to address the challenges of maintaining and improving health and healthcare in our country. During this time of heightened uncertainty in many aspects of our lives, nursing research, which informs the practice of the nation's largest number of healthcare professionals—2.7 million nurses—is critical to developing and testing interventions that improve health. Increasingly there is a need for health promotion research, which is a special strength of nursing research. This need is reflected in a recent Department of Health and Human Services (DHHS) Fact Sheet that attributes 40 percent of premature deaths to unhealthy behaviors, such as smoking and poor eating habits. Conversely, of the 30-year average gain in life expectancy in the last century, the DHHS report states that 25 of those years came from advances in public health, principally from health promotion. Consistent with the NIH Research Roadmap for the future, nursing research also focuses on multidisciplinary and clinical research. The goal is to help healthcare professionals work smarter by capitalizing on new technologies and research-tested methodologies that extend the reach and quality of their practice in promoting health, managing illness, and improving care. Now let me discuss some findings.

REDUCING POSTMENOPAUSAL WOMEN'S RISKS FOR CARDIOVASCULAR DISEASE

Heart disease is the leading cause of death in women in the United States. Even though the death rate has decreased in recent years, the benefit is less for women than men. More needs to be known about the effects of preventive strategies, such as exercise and diet, in reducing risks of the disease. We know lowering total and low density lipoprotein cholesterol (LDL-C) and raising high-density lipoprotein cholesterol (HDL-C) reduces risk of cardiovascular disease in women. Nurse researchers did a study that asked the question of why HDL-C, the "good cholesterol," drops when post-menopausal, obese women adhere to a low-fat diet. On a low-fat diet, weight loss occurs and the deleterious LDL-C decreases, but the weight loss is accompanied by a reduction of the good HDL-C. Findings of the study indicate that the causal factor for the HDL-C reduction was not the type or amount of fat the women consumed, but rather that they substituted simple sugars, such as syrups and refined sugar, for fat in their diets. What the women should have done was substitute complex sugars, such as high fiber vegetables and starches. The current American Heart Association guidelines recommend consuming 55 percent of energy from carbohydrates, without specifying complex or simple. This study points out the need to write more specific dietary guidelines that differentiate between types of carbohydrates, in addition to types of fat. This study is especially timely in an age where low-fat and fat-free foods often depend on simple sugars to improve taste.

REDUCING RISK FACTORS FOR OBESITY AND HYPERTENSION IN ADOLESCENTS

Obesity continues to be a major health problem in the United States. The Centers for Disease Control and Prevention states that about 15 percent of children and adolescents are overweight, a 4 percent increase since the last survey in 1994. The U.S. prevalence of obesity increased by 61 percent in the 9 years prior to 2001. Habits formed in childhood become the lifestyles that drive this upswing. Researchers testing an intervention in children and adolescents have been able to decrease risk factors for hypertension and obesity. As part of the Cardiovascular Health in Children and Youth study, researchers tested rural, mostly African-American middle school students in an eight-week physical activities program combining exercise and health education. Subjects were divided into four groups—exercise, education, or both, and controls. Those in the two exercise groups had a lower increase in body fat, and the blood pressure of the three intervention groups decreased compared to controls. These results demonstrate the effectiveness of regular aerobic exercise and health education programs for school-aged children to help reduce their risks for cardiovascular disease later in life.

COPING WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

People with Chronic Obstructive Pulmonary Disease (COPD), which causes discomfort at best and severe, life-altering changes at worst, report that there is little available to help improve their breathing. Shortness of breath often results in inability to work, limited social activities, and even difficulty in dressing themselves. As the nation's fourth leading cause of death, COPD affects over 22 million people. In confronting this issue, nurse investigators tested a "self management" inspiratory muscle training technique to assist patients in improving their own breathing and respiratory muscle strength. For 30 minutes, 5 days a week, over a 16-week period, patients used a mouthpiece attached to a tube with openings that gradually decreased in size to make inhalation more challenging. Following training, these sub-

jects' breathing, respiratory muscle strength, and endurance were considerably improved compared to a control group, and they could once again perform daily activities. The study also showed that subjects were able to self-manage by performing inspiratory muscle training at home without direct professional assistance.

IMPROVING CARE AT THE END-OF-LIFE CARE

Another important healthcare issue involves end-of-life and palliative care. As the lead Institute at NIH for coordinating this research, NINR supports research to improve the way the healthcare system addresses end-of-life issues. A recent study commissioned by Last Acts contributed more evidence of the need for change, concluding that the United States does only a mediocre job of caring for seriously ill and dying patients. The study also indicated that although many would prefer to die at home or in a hospice, most die in the hospital, where high tech efforts to prolong life and where patients' diminished control over decisions are common.

Nurse researchers studied the outcomes for patients enrolled in the Program for All-inclusive Care for the Elderly (PACE), a managed care program for people 55 and older. Results showed that unlike the general population, where 44 percent die in the hospital and 20 percent die at home, the numbers are almost reversed in PACE, with 45 percent dying at home and 21 percent in the hospital. Another outcome was improved consistency and predictability of care. End-of-life care is often fragmented, and in the case of advance directives, written instructions may not be honored in the hospital, since staff may not have immediate access to patient records from other care facilities. The PACE program, however, offers consistent care, thus increasing the likelihood that advance directives will be followed. PACE also helps older people develop advance directives.

NEW AND EXPANDED INITIATIVES

For fiscal year 2004, NINR plans include launching a new pediatric end-of-life initiative, stimulated by the Institute of Medicine's report: *When Children Die: Improving Palliative and End-of-Life Care for Children and Their Families*. This report concluded that pediatric end-of-life issues have received insufficient research attention. We will also support the development of ethnically and culturally sensitive interventions for those near the end of life and approaches to improve communications between care providers, patients and families.

Research on strategies for self-management of chronic illness will be expanded to include reducing symptoms related to high blood pressure, diabetes, dementia and developmental disabilities. These strategies will incorporate age, gender, and ethnic and cultural factors.

Minority men will be targeted for interventions that promote healthy lifestyles, since they have a shorter life span and a higher mortality rate than Caucasian men and all subgroups of women. NINR will stimulate research on factors that influence decision-making for healthy choices, such as nonsmoking, exercise, and proper nutrition. Other issues to be addressed include: How can these men improve management of stress? How do their families and their communities influence their health-related behaviors? Because young minority men are often underserved, studies in this area could create an important strategy for effective public health interventions to follow.

We continue to have a strong interest in the significant health disparities for minority women. NINR will expand research that targets prevention of low birthweight babies, since according to Healthy People 2010, of the Department of Health and Human Services, the incidence rate for low birthweight African-American women is twice that of Caucasian women. Puerto Rican women are also especially likely to have low birthweight infants. Issues include improving early identification and management of complications during pregnancy, such as infection, hypertension, and diabetes.

TRAINING NURSE RESEARCHERS FOR THE FUTURE

NINR is addressing the future of nursing science—how to ensure that sufficient, high-quality research continues to grow and play a fundamental role in health care. In the early 90's, and again in 2000, the National Academy of Science's National Research Council stated that the number of nurse researchers must increase. Over the next four to six years, our Nation is facing a critical nursing faculty shortage. Nurse researchers form the backbone of university faculty in schools of nursing. In rising to this workforce challenge, NINR emphasizes early entry into research careers, including fast-track baccalaureate-to-doctoral programs, to increase the number of nurse investigators. Other opportunities are made available through the

NINR Centers programs and NINR/NIH research training mechanisms and career development awards.

Our centers provide an environment and infrastructure to promote early entry into and sustained participation in research programs. NINR funds nine Core Centers, each of which offers research and research training opportunities to those in their geographic areas. We also fund nine Developmental Centers that enhance emerging research programs. Our recently-launched Nursing Partnership Centers to Reduce Health Disparities funded 17 Centers which pair research-intensive nursing schools with minority-serving schools of nursing. These Partnerships are expected to expand research on health disparities and increase the number of minority nurse investigators.

NINR is focusing on ways to integrate genetic science into nursing research, education, and practice. Strategies include facilitating lifestyle changes for those at risk, genetic counseling, and selecting optimal therapeutic interventions based on genotype. The fourth NINR Summer Genetics Institute will be offered this year. This is an intensive, eight-week genetics training program held on the NIH campus. Its goal is to produce graduates who develop successful research careers and help integrate genetic information into research and educational programs across the country.

Mr. Chairman, this concludes my remarks. I would be pleased to answer any questions you and other members of the Committee may have.

PREPARED STATEMENT OF DR. JUDITH H. GREENBERG

Mr. Chairman and Members of the Committee, good morning. I am pleased to present the President's budget request for the National Institute of General Medical Sciences (NIGMS). The fiscal year 2004 budget includes \$1,923 million, an increase of \$76 million over the fiscal year 2003 enacted level of \$1,847 million comparable for transfers proposed in the President's request.

The NIH budget request includes the performance information required by the Government Performance and Results Act of 1993. Prominent in this data is NIH's fourth annual performance report, which compared our fiscal year 2002 results to our fiscal year 2002 performance plan goals.

AN IMPRESSIVE TRACK RECORD

Since its creation more than 40 years ago, the National Institute of General Medical Sciences has built an impressive track record as a strategic investor in the future of basic biomedical research. Though not a household name, NIGMS is highly respected in the scientific community as an Institute that nurtures the nation's brightest minds in biomedicine. Through its forward-thinking funding programs, NIGMS supports thousands of scientists nationwide whose fundamental research is laying the foundation for promising new advances in disease diagnosis, treatment, and prevention.

Perhaps the most notable indicator of that track record is the number of NIGMS-supported scientists who have won Nobel Prizes—a remarkable 53 to date. In 2002, both the Nobel Prize in Physiology or Medicine and the Nobel Prize in Chemistry went to long-time NIGMS grantees, Dr. H. Robert Horvitz of the Massachusetts Institute of Technology and Dr. John B. Fenn of Virginia Commonwealth University, respectively. Dr. Horvitz's discovery of key genes controlling cell death shed new light on illnesses such as AIDS, Parkinson's disease, stroke, and cancer. And Dr. Fenn's refinement of a technique called mass spectrometry has made it possible to analyze large molecules in biological samples, an advance now widely used for blood testing.

Our Institute's leadership in supporting biomedical science was also recognized in 2002 with the prestigious Albert Lasker Award for Basic Medical Research. NIGMS grantees Dr. James E. Rothman of the Memorial Sloan-Kettering Cancer Center and Dr. Randy W. Schekman of the University of California, Berkeley, were honored for discovering the universal molecular machinery that drives "cellular trafficking." Their work helped explain vital processes such as how insulin is released in pancreatic cells, how organs develop inside embryos, and how viruses infect their hosts.

Yet another acknowledgment of NIGMS' contributions to biomedical research came late last year when the journal *Science* declared the discovery of how small RNA molecules control the behavior of genes to be the top scientific achievement of 2002. Funded in large part by grants from NIGMS, this "Breakthrough of the Year" research shows promise as the basis for new therapies to treat cancer, AIDS, and other diseases.

As we look ahead to fiscal year 2004 and beyond, NIGMS is poised to help make possible even more ground-breaking advances in biomedical science. I would like to share with you some of our strategies for accomplishing this important mission.

UNRAVELING THE 3-D STRUCTURES OF PROTEINS

Fifty years ago, Drs. James Watson and Francis Crick made their famous discovery of the double-helix structure of DNA. This year, scientists will reach another milestone: the completion of a highly accurate sequence representing the entire set of genetic instructions encoded in human DNA. As the Human Genome Project achieves this landmark goal, its promise to usher in a new era of molecular-based medicine will depend on another, equally important undertaking: discovering all the proteins our genes make and the functions these cellular “workhorses” play in health and disease.

Key to this ambitious effort is the unraveling of the complex, three-dimensional structures of proteins. Determining these structures can in turn reveal how proteins function and help scientists tailor the design of new drugs to treat diseases. NIGMS is the world’s single largest supporter of research in structural genomics, a field dedicated to discovering the structures of proteins using sophisticated computer-based methods.

In fiscal year 2000, NIGMS launched the Protein Structure Initiative (PSI), with the goal of determining 10,000 protein structures in 10 years. The nine pilot research centers we currently support have made significant progress in developing tools for the high-throughput determination of protein structures and have begun to yield some promising results, with potential applications in biomedicine and beyond.

In November 2002, for example, NIGMS-funded researchers at Argonne National Laboratory determined the structure of a protein knot—one of only a few such structures seen in nature, and the first found in a protein from the most ancient type of single-celled organism, an archaeobacterium. The microbe that the newly discovered protein comes from is of interest to industry for its ability to break down waste products and produce methane gas.

NIGMS is considering additional activities to help the centers reach their full capability, including a materials storage bank and a database for protein production and crystallization experiments. The production phase of the PSI, during which researchers will be rapidly deriving protein structures, will begin in fiscal year 2005.

HARNESSING MATH & COMPUTERS TO SOLVE BIOLOGICAL PROBLEMS

In addition to leading the way in structural genomics, NIGMS is also at another forefront: a shift in biomedical science often called the “mathematization” of biology. This shift represents a broadening of biologists’ research focus from studying how individual biological molecules behave to investigating how a large number of molecules interact with one another. In order to model and predict these complex interactions, biomedical scientists are increasingly partnering with quantitative scientists, including mathematicians, physicists, computer scientists, and engineers. Together, they are applying their combined expertise to solve particularly challenging problems in biomedicine, such as understanding embryonic development, metabolism, cell growth, and cell death.

To encourage more quantitative approaches in biological studies, NIGMS established Centers of Excellence in Complex Biomedical Systems Research. The first awards were for two center grants and seven planning grants to lay the groundwork for future centers, designed to foster a multidisciplinary research environment for developing innovative methods to solve biomedical problems. These centers will also lead the way in training the next generation of computational biologists.

A good example of this teamwork is the recent work by NIGMS-funded researchers who have produced the first comprehensive “script of life,” describing the regulation of all the genes in yeast. Reporting in the journal *Science* in October 2002, Dr. Richard Young, a biologist at the Whitehead Institute for Biomedical Research, and Dr. David Gifford, a computer scientist at the Massachusetts Institute of Technology, detailed how they used advanced, high-throughput biological and computing technologies to do in weeks what would have taken years to achieve using traditional techniques.

The mathematization of biology and its importance in modeling complex biological systems were also major themes at our Institute’s “Visions of the Future” meeting, held in September 2002. NIGMS invited visionary scientific leaders to identify the most important and emerging areas of biomedical research. A recurring topic of discussion was the need to develop mechanisms that encourage cooperative interactions among mathematicians, physicists, computer scientists, engineers, and biolo-

gists. Moreover, meeting participants stressed the need for more rigorous quantitative training of undergraduate and graduate students who are pursuing research careers in the life sciences.

Such interaction and training were cited as keys to realizing some of science's grandest visions. These include the development of "virtual" models—of cells, tissues, disease states, and ultimately entire organisms—as well as new imaging tools and methods for making "molecular movies" of cellular machinery. Such technologies will help fill enormous gaps in our understanding of how molecules move in three dimensions and how they interact inside living cells in real time. Through its support of research and training in computational biology and other areas that cross traditional academic boundaries, NIGMS is uniquely positioned to help turn these visions into reality.

GUARDING AGAINST INFECTIOUS DISEASES & BIOTERRORISM

As concern grows over bioterrorism and the emergence of new infectious diseases, NIGMS is designing an initiative to address this threat using computational approaches and mathematical modeling. Such models will help predict the spread of microbes, the rate of disease progression in individuals, the effectiveness of different treatment or prevention strategies, and the community response to new infectious diseases. These predictions will, in turn, provide policymakers with critical information that will help them respond quickly to the threat of a new disease or bioterrorism attack.

This new initiative follows on the footsteps of another successful NIGMS program—one dealing with the evolution of infectious diseases. Deadly viruses and bacteria can adapt to seemingly limitless environmental conditions by making rapid genetic changes, far outpacing our own ability to adapt. This microbial evolution renders previously effective drugs useless and creates a moving target for drug designers. However, by analyzing the evolution of infectious organisms, researchers now have a leg up on how to outwit potentially dangerous microbes.

One application of this area of study is antibiotic resistance, an increasing problem throughout the world. Recently, NIGMS-funded researcher Dr. Barry G. Hall of the University of Rochester developed a computer simulation of microbial evolution. Dr. Hall determined through experiment which bacterial genes are most susceptible to changes that cause resistance to commonly used antibiotics. Using this approach, pharmaceutical companies could create drugs for which bacteria have no evolutionary escape route.

NIGMS is also leading the way in supporting structural studies of infectious diseases. For example, the final piece of the anthrax puzzle—the structure of the third toxic protein responsible for the deadly effects of the anthrax bacterium—was discovered last year by Dr. Wei-Jen Tang of the University of Chicago. The toxin, edema factor, causes potentially lethal swelling and fluid buildup in the body. By completing the detailed, three-dimensional structure of edema factor, Dr. Tang also found that the protein appears to be an ideal drug target, opening the door to a possible new compound to combat anthrax infection, as well as other bacterial diseases.

BASIC RESEARCH: A VITAL RETURN ON INVESTMENT

In closing, it is worth noting that our leading efforts in structural genomics, computational biology, complex biological systems, and multidisciplinary collaboration give NIGMS a pivotal role to play in the trans-NIH "Roadmap" initiatives. Through its partnerships with other NIH institutes and centers, NIGMS will help forge new pathways to discovery and research teams of the future.

It is also important to emphasize that all of the scientific advances I have shared with you today resulted from investing in basic research on fundamental biological processes—the central mission of NIGMS. As administrators of federal research dollars, we are asked to show what we have done to ensure the best possible return on that investment, and to show how we plan to continue doing so in the future. I hope that the examples I have mentioned—from our Nobel Prize-winning achievements to our cutting-edge initiatives—illustrate the tremendous value of basic biomedical research to the strength of our scientific workforce, the security of our nation, and the health of our people.

Thank you, Mr. Chairman. I would be pleased to answer any questions that you may have.

PREPARED STATEMENT OF DR. GLEN R. HANSON

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute on Drug Abuse. The fiscal year 2004 budget includes \$995,614 million, an increase of \$34,496 million over fiscal year 2003 enacted level of \$961,118 million comparable for transfers proposed in the President's request.

NIDA LEADERSHIP

I have been very fortunate and privileged to serve as the Acting Director of the National Institute on Drug Abuse for the past year and a half during a time of burgeoning scientific advances that have dramatically increased our understanding of brain, behavior and addiction. I am extremely confident that the incoming Director for NIDA, Dr. Nora Volkow, will be a strong leader and advocate for drug abuse research. I am pleased to have this final opportunity to showcase some of NIDA's most exciting advances and discuss how these and other research findings are resulting in tangible benefits that will improve the Nation's health.

PUBLIC/PRIVATE VENTURE YIELDS NEW MEDICATION FOR ADDICTION

An important example of how NIDA-supported research is decreasing the tremendous economic and human costs associated with drug abuse and addiction, while meeting the national need for quality treatment, is by bringing a new medication to the clinical toolbox of health care professionals. Buprenorphine, approved by the Food and Drug Administration in October 2002, is the first medication ever available for the treatment of opiate dependence that can be prescribed and dispensed by qualified physicians in an office setting, rather than at a specialized addiction treatment clinic. The nearly 1 million people who suffer from heroin addiction will benefit from the historic collaborations that took place between legislators who passed the Drug Addiction Treatment Act of 2000, Federal agencies, and the private sector (Reckitt Benckiser Pharmaceuticals) to bring this new medication to market. Buprenorphine marks the second medication to come directly out of NIDA's relatively short investment in its Medications Development Program. Developing medications for other drugs of abuse, particularly stimulants like cocaine and methamphetamine, is a top priority for the Institute, as is our commitment to develop practical and more effective science-based behavioral therapies.

NEW TARGETS FOR MEDICATIONS DEVELOPMENT

Building on a series of discoveries regarding the effects of marijuana on the brain, researchers discovered a new neuromodulatory called the cannabinoid system, which is involved in pain regulation, memory, appetite, and addiction. This system was named after the active ingredient in marijuana, tetrahydrocannabinol. Researchers from NIDA's own intramural program have used a compound that blocks cannabinoid receptors to demonstrate that the mood altering and cardiac effects of marijuana in humans can be suppressed. Additionally, they discovered that the cannabinoid system may also be involved in relapse to other drug addictions. In animal models, this same blocking compound prevented drug-seeking for cocaine following exposure to two of the three conditions that typically trigger relapse in human addicts. The discovery of this new brain system has opened the door for the development of new treatments for addiction to a variety of drugs, including cocaine and alcohol, and may also prove useful for treating obesity and pain. As we continue to unravel the complexity of the brain and identify new systems, molecules, proteins, and genes that can be exploited for therapeutic development, the need for a repository or molecular library where this information can be stored and shared with other scientists increases. This is the goal of the proposed Molecular Libraries project in the trans-institute NIH Road Map Initiative. We hope to work with the pharmaceutical companies to more rapidly develop novel and even more effective therapeutic strategies for addiction and other brain diseases that have historically been extremely difficult to treat and control, and are often overlooked by pharmaceutical companies.

STRESS AND THE BRAIN

We also are becoming increasingly knowledgeable about the impact of stress on brain function. Stress can be a major factor in both the initiation of drug abuse and is known to be one of the most powerful triggers to relapse to drug abuse in former addicts. Nowhere was this more apparent than in a study published last year following the September 11th attacks in Manhattan. Twenty-nine percent of the 1,000 respondents interviewed 1-2 months following the event reported an increase in

substance use, with the highest rates in those reporting symptoms of Post-Traumatic Stress Disorder and/or depression. A study released just last month in the journal, *Neuron*, elucidated one of the ways in which stress and drugs of abuse produce a similar adaptation in the brain through an effect on dopamine neurons. As we progress in our understanding of the ways in which stress and drugs of abuse affect common mechanisms, we can develop prevention and treatment strategies that more effectively satisfy the needs of patients, particularly those who suffer from comorbid substance abuse and mental disorders.

THE ROLE OF GENETICS AND THE ENVIRONMENT IN ADDICTION

Powerful new technologies, such as microarrays, 3-dimensional brain mapping, and animal knockouts are accelerating the pace of science and helping us to identify the roles that genes play in addiction. One gene in particular (FAAH) produces an enzyme involved in the breakdown of the brain's natural cannabinoid compound. A recent study showed that a genetic variation in this gene was found more frequently in people who abused drugs compared to those who did not. As other genes that increase the risk of addiction are identified through NIDA's Vulnerability to Addiction Research Initiative, it becomes even more imperative that we understand how the environment can modify this risk. Basic research is giving us important insight into this complex domain of gene-environment interactions. A recent study conducted in monkeys using brain imaging techniques found that the animal's social environment can modify its neurobiology and ultimately its likelihood to self administer drugs of abuse like cocaine. When monkeys were housed together, the ones displaying dominant behavior were shown to have altered expression of D2 receptors, which are important components in the brain's reward pathway. They also were less prone to self administer cocaine (a model of cocaine abuse). This illustrates that the natural state of the dopamine system is altered by the environment, which in turn influences the likelihood of using drugs of abuse. Future studies which determine the interplay between genetic and environmental factors will be important in gaining further insight into the prevention and treatment of drug abuse and addiction.

REDUCING TOBACCO USE BY FIGHTING THE ADDICTION

Tobacco use is responsible for more than 430,000 deaths per year among adults in the United States, making it one of the Nation's top preventable causes of death. It is addiction to nicotine that continues to drive the use of tobacco, and why NIDA's expertise concerning the neurobiology of nicotine and the mechanisms of the addiction process, is so integral to the national effort to reduce this public health burden. NIDA supported research has already paved the way for a number of treatments, including behavioral therapies, nicotine-replacement approaches such as the patch and gum, and Zyban®, that help people conquer their addiction. But we must accelerate our efforts to help the estimated 48 million people according to a 2000 Surgeon General Report who remain addicted to this drug. Capitalizing on new knowledge about the biological substrates and behavioral mechanisms of nicotine and tobacco addiction, NIDA has joined with other NIH institutes to launch a number of new activities to more rapidly translate tobacco addiction research into new treatments. NIDA is also supporting research that focuses on preventing adolescents from starting to smoke.

GOOD NEWS IN PREVENTION RESEARCH

There is good news in the epidemiology and prevention arena. NIDA's long-standing annual Monitoring the Future Survey, which measures drug use among 8th, 10th, and 12th graders, showed substantial decreases in the overall use of all illicit drugs, as well as a reduction in the use of cigarettes, marijuana, club drugs, and alcohol in the past year. One of the most encouraging findings is the significant drop in the use of MDMA (Ecstasy), the abuse of which had been rising at alarming rates in recent years. We attribute these downward trends, in part, to our prevention and education efforts. As a by product of our dissemination of science-based information about all drugs of abuse, America's youth are able to weigh the facts about drugs and are making better health decisions. Understanding adolescent decision-making is an important research area being addressed in NIDA's prevention portfolio. By elucidating the cognitive expectancies of how an adolescent makes the initial and subsequent decisions to try or not to try drugs, we will gain new insight into how to develop interventions aimed at changing the actual decision to use drugs. Preventing the initial use of drugs and stopping the progression of drug use before it escalates to addiction are two targeted objectives of NIDA's National Prevention Research Initiative. The multi-disciplinary teams of basic researchers, community leaders, prevention specialists, clinicians, and health service providers who have

been brought together as part of this Initiative will use the power of science to reduce drug use in the country.

COMBATING HIV/AIDS, HEPATITIS DOMESTICALLY AND INTERNATIONALLY

Our efforts to reduce the burden of drug abuse goes beyond our borders. Given the growing number of countries that report HIV and hepatitis C infection associated with drug injection behaviors, NIDA supports a strong research program that is yielding findings that are beneficial both domestically and internationally. In the absence of a vaccine or cure for AIDS, comprehensive HIV prevention strategies are the most cost effective and reliable approaches for preventing new HIV infections, and other bloodborne infections, such as hepatitis C. NIDA-supported researchers are making progress in curtailing the spread of these diseases. NIDA researchers, using molecular biology techniques, have recently shown that new outbreaks of HIV infection among injection drug users are spreading along drug trafficking routes and spreading from drug users to non-drug using individuals through sexual transmission. Some of the victims of such transmission are homeless U.S. adolescents and AIDS orphans. Understanding how drug use related HIV transmission occurs is critical to the development of culturally specific behavior change strategies. NIDA remains committed to work with other Institutes and federal agencies to discover more effective ways to stop drug abuse-related spread of these infectious diseases and work towards transferring these evidence-based strategies to slow the spread of HIV and other related infections.

CLINICAL TRIALS NETWORK DOES MORE THAN JUST TREAT PATIENTS

HIV prevention interventions are some of the new protocols being developed for testing in NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN). The CTN, which was established in 1999, provides a national infrastructure to bring science-based behavioral and pharmacological treatments for addiction into diverse patient and treatment settings across the country. NIDA added three new sites in the past year, which now allows our 17 centers or nodes to better serve patients across a wider geographic area, in fact through the 115 community treatment programs involved in this endeavor we are serving patients in 27 states. Over 8,000 patients are expected to be enrolled in treatment protocols that are addressing the unmet needs of diverse populations, including adolescents, pregnant women, and women who suffer from Post-Traumatic Stress Disorder. Clinical trial networks for cancer and diabetes have been active for decades, but NIDA's efforts are the first ever to establish this model for addiction. Another first for the field, is the unprecedented efforts being taken to reduce the lag time between translating research discovery into practice. NIDA is working with the Substance Abuse and Mental Health Services Administration to disseminate science-based treatments into SAMHSA-supported Centers and activities. Blending the expertise of researchers, practitioners, and service-oriented professionals is the hallmark of the CTN, and why the CTN has become more than just a way to get quality treatment. It is the conduit through which research meets practice.

CONCLUSION

Reducing the adverse health, economic, and social consequences of drug abuse to individuals, families, and communities is the ultimate goal of our Nation's investment in drug abuse research. That goal is being met by NIDA.

PREPARED STATEMENT OF DR. RICHARD J. HODES

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute on Aging (NIA) for fiscal year 2004. The fiscal year 2004 budget includes \$994,411,000, an increase of \$1,342,000 over the fiscal year 2003 enacted level of \$993,069,000 comparable for transfers proposed in the President's Request. The NIH budget request includes performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's third annual performance report, which compared our fiscal year 2001 results to the goals in our fiscal year 2001 performance plan.

There are today approximately 35 million Americans ages 65 and over, according to the U.S. Bureau of the Census. Thanks to improvements in health care, nutrition, and the overall standard of living, these men and women are more likely than ever before to be healthy, vigorous, and productive: A recent meta-analysis of demographic studies confirms that disability among America's elders has declined stead-

ily over the past decade. More older Americans are able to participate in “instrumental activities of daily living,” such as performing household chores and managing their own medications, while fewer are experiencing limitations in basic physical tasks such as walking or climbing stairs. The prevalence of severe cognitive impairment also appears to be declining, although this finding needs verification.

At the same time, diseases of aging continue to affect many older men and women, seriously compromising the quality of their lives. For example, more than half of all Americans over age 65 show evidence of osteoarthritis in at least one joint.¹ Over half of Americans over age 50 have osteoporosis or low bone mass.² Cardiovascular disease, cancer, and diabetes remain common among older Americans. And, according to the Alzheimer’s Association, as many as 4 million Americans suffer from Alzheimer’s disease (AD), the most common cause of dementia among older persons.

CONQUERING ALZHEIMER’S DISEASE

We have made progress in several important areas of AD research. For example:

We are improving our ability to diagnose AD early.—Scientists are developing and refining powerful imaging techniques that target anatomical, molecular, and functional processes in the brain. These new techniques hold promise of earlier and more accurate diagnosis of AD, as well as improved identification of people who are at risk of developing the disease. For example, researchers have developed a new method of functional magnetic resonance imaging (fMRI) based on oxygen use by the brain during rest. This technique permits visualization of signals from minute subregions of the hippocampus, a brain region important for learning and memory that shows degenerative changes in AD, and the researchers are using it to distinguish between hippocampal changes that are related to normal aging and those that may indicate the presence of neurodegenerative disease. Other researchers are working to improve our ability to image AD’s characteristic amyloid plaques and neurofibrillary tangles in vivo, which will allow us to diagnose the disease with greater accuracy and more closely follow its progression. These and other NIA-funded neuroimaging studies support the broader goals of the molecular imaging component of the NIH Roadmap Initiative.

We are developing new, more effective treatments and preventive interventions for AD.—Research into the underlying biology of AD is suggesting new ways to treat the disease or even prevent it altogether. For example, human stem cells, with their unique capacity to regenerate and give rise to many tissue types, are of particular interest in AD research because of their potential ability to generate new cells that could renew damaged brain tissue, replace dying neurons, or enhance the ability of the brain to respond to age-related impairments. Recent findings suggest that both human embryonic stem cells (hES), which can give rise to many cell types, and “adult” stem cells, which develop into a specific cell type, show promise for the eventual treatment of AD and other neurodegenerative conditions. Researchers have recently developed a method for inducing hES cells to differentiate into neurons. These newly-derived cells exhibit the properties of cells ordinarily found in the brain and central nervous system, suggesting that hES cells could provide a source for neural progenitor cells and mature neurons for therapeutic use. Investigators have also found that in the adult hippocampus, neural stem cells can give rise to functional neurons that can integrate effectively into existing neural circuits.

NIA is currently supporting 18 AD clinical trials, seven of which are large-scale prevention trials. These trials are testing agents such as estrogen, anti-inflammatory drugs, and anti-oxidants for their effects on slowing progress of the disease, delaying AD’s onset, or preventing the disease altogether. Other intervention trials are assessing the effects of various compounds on the behavioral symptoms (agitation, aggression, and sleep disorders) of people with AD. The design and implementation of all of these clinical trials will be carried out in the context of the NIH Roadmap initiative to enhance clinical research infrastructure and methodology.

We are working to reduce the burden on caregivers of persons with AD.—Most Americans with AD are cared for at home by an adult child or in-law, a spouse, another relative, or a friend. For this reason, the AD “patient” is, in a sense, not only the person with the disease, but the entire family unit. The NIA’s REACH Project (Resources for Enhancing Alzheimer’s Caregiver Health), a large, multi-site intervention study aimed at family caregivers of AD patients, was designed to charac-

¹See “Handout on Health: Osteoarthritis,” National Institute of Arthritis and Musculoskeletal and Skin Diseases, July 2002.

²See *America’s Bone Health: The State of Osteoporosis and Low Bone Mass in Our Nation*. National Osteoporosis Foundation, February 2002.

terize and test promising interventions for enhancing family caregiving. Nine different social and behavioral interventions were tested, and investigators found that the combined effect of interventions alleviated caregiver burden, and that interventions that enhanced caregiver behavioral skills reduced depression. The second phase of the study, REACH II, combines elements of the diverse interventions tested in REACH into a single multi-component psychosocial behavioral intervention and is ongoing.

UNDERSTANDING THE BIOLOGY OF AGING

We are continuing to advance our understanding of the molecular and cellular changes that underlie aging processes, with the goals of identifying the factors that affect the life span of an organism and using this information to develop interventions to extend life and delay the onset of disease and/or disability.

Experiments in a number of animal models are providing valuable insights into mechanisms of longevity. Investigators recently created a transgenic mouse carrying a mutation in the *Xpd* gene, which codes for an enzyme involved in both repair of DNA damage and transcription of DNA into RNA (an important first step in gene activation). These mice appear normal at birth but age rapidly and live only about half as long as normal mice. This new mouse model will be useful for studying a number of aspects of aging, including the roles of DNA damage and cell death, as well as mechanisms by which the genome maintains itself and how such maintenance contributes to longevity.

Researchers are also using animal models to identify interventions that might be useful in delaying aging. For example, in one recent study, fruit flies fed the chemical 4-phenylbutyrate throughout adulthood lived significantly longer than expected, with no negative effects on physical activity, stress resistance, or fertility. In addition, last year the NIA issued a Request for Applications (RFA) for the Aging Intervention Testing Program, a large-scale initiative to test intervention strategies that may slow the rate of aging in animal models. A number of unproven strategies are already in substantial and growing use by older Americans; positive results using such strategies in animals could lead to clinical trials to establish safety and efficacy in humans. An important secondary goal is to identify interventions that are not safe or are ineffective.

Work in animal models is also leading to the identification of genes involved in regulation of the life span. In the tiny worm *C. elegans*, researchers used a sophisticated genetic screen to identify about 200 genes that cause an increase in longevity; many of these genes were related to the worm's mitochondria (cellular energy centers), while the exact function of many others remains unknown.

Such findings in model systems, as well as our increasing understanding of genetic disorders such as Hutchinson-Gilford progeria syndrome that exhibit features of premature aging, suggest important roles for genes in human aging. Evidence for a genetic basis of human longevity was strengthened by the recent finding that siblings of centenarians have about half the risk of dying at every age compared with people who do not have a centenarian sibling. In the same study, the investigators found that brothers of centenarians were at least 17 times more likely to reach the age of 100 themselves; sisters were at least 8 times more likely to reach 100 years of age.

REDUCING DISEASE AND DISABILITY

Evidence of the beneficial effects of exercise on older people continues to increase. In a study last year, researchers assessed the results of a resistive strength training program on men and women in two age groups, 20–30 and 65–75. They found that the effects of the program did not differ between the two groups: Participants in both age groups increased strength and showed similar increases in muscle mass and in resting metabolic rates, which generally decrease with age.

NIA is working to translate research findings in action through its highly successful campaign to encourage older people to exercise. Since the campaign was launched in 1998, NIA has distributed nearly one half-million copies of its exercise guide and almost 60,000 copies of its companion video to the public. A Spanish-language version of the guide was published in January 2002, and over 50,000 copies were distributed last year.

We are also working to reduce the troubling health disparities that still exist among different racial and ethnic groups. In one study of elderly heart attack patients, researchers found that black patients did not live as long after discharge from the hospital as white patients. Much of this disparity could be explained by the lower rate of use of certain cardiac procedures among black patients, suggesting

that expanded use of effective procedures could substantially reduce racial differences in long-term survival.

To address disability and disease in special populations, NIA implemented a major new study of health disparities among different racial, ethnic, and socioeconomic groups. The study, Healthy Aging in Nationally Diverse Longitudinal Samples (HANDLS), focuses primarily on cerebrovascular health, cardiovascular health, age-associated changes in cognition, and strength and physical functioning. Through this study, we hope to address hypotheses about aging and health disparities in minority and poor populations to understand the significance of environmental and genetic risk factors for disease. The pilot phase of HANDLS, in which investigators assessed the logistics and feasibility of this community-based study, was completed at the end of 2001, and the larger population-based phase of this study is scheduled to begin in late fall of 2003.

Other areas of research interest include:

Diabetes.—Last year, investigators in the multi-institutional Diabetes Prevention Program (DPP) reported that people who are at high risk for diabetes can sharply reduce their risk through a low-fat diet, and a moderate exercise regimen. This effect was most pronounced among study participants age 60 and over. Treatment with the drug metformin (Glucophage®) also reduced diabetes risk among study participants, but for unknown reasons was less effective among older participants. With other participating NIH Institutes, we are continuing to follow up the DPP participants to determine long-term effectiveness of these interventions.

Menopause.—Women approaching menopause may experience a variety of uncomfortable symptoms, but uncertainty remains over the safety of hormonal therapy due to reports of serious health risks related to some combinations of hormones. NIA-supported researchers are working to find effective treatments for the symptoms of menopause that do not increase risk of adverse effects.

CONCLUSION

It is becoming increasingly obvious that old age need not be associated with illness, frailty, or disability. In fact, we have made tremendous progress against all of the major diseases and conditions of aging. However, much work remains to be done. NIA is committed to supporting high-quality research to address all aspects of aging, from conditions and diseases that primarily affect older people to physical, behavioral, and cellular characteristics of the aging process. As more Americans live longer, NIA will meet the challenges of our rapidly aging society by continuing and intensifying research that improves the health and well-being of older people.

PREPARED STATEMENT OF DR. THOMAS R. INSEL

Mr. Chairman, and members of the Committee, I am pleased to present the President's budget request for the National Institute of Mental Health (NIMH) for fiscal year 2004, a sum of \$1,382 million, which reflects an increase of \$42 million over the fiscal year 2003 enacted level of \$1,340 million comparable for transfers proposed in the President's budget.

In my statement, I will call to your attention the immense burden on our Nation of mental and behavioral disorders. In addition, in the context of a brief review of our research activities and accomplishments, I will suggest how NIMH's expertise in behavioral science and behavioral neuroscience are contributing to the Nation's capacity to prepare for and respond effectively to the psychological impact of bioterrorist attack.

THE BURDEN OF MENTAL ILLNESS

Mental disorders are real illnesses that are mediated by the brain and can be diagnosed reliably and accurately. Thanks to the Nation's willingness to invest generously in research, highly effective treatments exist for most mental disorders; and recovery is a realistic and attainable goal for many people who have a mental disorder. Despite our research progress, our society faces a pressing need to strengthen the quality and accessibility of clinical services for mental disorders for all those who require such services. In keeping with our public health mission, NIMH assigns high priority to the task of moving information gained through research into the hands of providers, systems, patients, and families.

The Surgeon General's Report on Mental Health noted that an estimated 5.4 percent of Americans adults have a serious mental disorder such as schizophrenia, major depression, and bipolar in a given year, and about 5- to 9 percent of children and adolescents suffer from mental and behavioral disorders that are sufficiently se-

vere to cause academic, social, or family impairment. Research supported and conducted by NIMH has significantly strengthened the ability of the Nation's health care providers to treat and manage these disorders; still, the public health challenge posed by mental illness remains formidable, in large part because many serious mental disorders tend to strike in childhood, adolescence and young adulthood, and to persist across much of a person's lifetime.

THE PRESIDENT'S NEW FREEDOM COMMISSION ON MENTAL HEALTH

With the release of the final report of The President's New Freedom Commission on Mental Health scheduled for this Spring, efforts to translate our science into clinical service programs will assume added importance and urgency. The Commission was charged to identify specific examples of community-based care models that are demonstrably successful in achieving desired outcomes. In its interim report, the Commission noted that much can and is being done to improve the delivery of high quality mental health care. The Commission found, however, that the national mental health care system is hampered by fragmentation of services and limited access to effective treatments. We have worked closely with the Commission over the course of its study, and look forward to helping to implement the its recommendations.

An ongoing collaboration between NIH and the Substance Abuse and Mental Health Services Administration (SAMHSA) anticipates the Commission's interest in ensuring that individuals in every region of the country have access to the best available treatments. NIMH, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism have identified specific treatment and preventative interventions that have a strong scientific evidence base and we are working with SAMHSA officials as they develop plans to assist State agencies implement these interventions. Built into this initiative are processes designed to establish a systematic feedback loop that will enable researchers to draw on real world experiences with evidence-based practices in order to inform and guide future intervention research.

Need clearly exists for NIMH to advise SAMHSA of completed research that will improve the quality of care available immediately. Still, opportunities have never been greater for fundamentally revamping our approaches to developing new clinical treatments and preventive interventions. New scientific knowledge about the brain and behavior, as well as the emerging science of genomics, promise to yield new treatments for mental disorders that ultimately will alter the delivery of mental health care in far-reaching ways.

SEARCHING FOR SCHIZOPHRENIA VULNERABILITY GENES

After many years of searching, the recent discoveries of several putative vulnerability genes for schizophrenia have been among the most noteworthy achievements of the past year. Schizophrenia is a genetically complex disorder, in which multiple genes are involved, but no single one of them is sufficient or necessary to cause the disease. Rather, multiple genes, interacting with environmental influences, lead to illness. One newly discovered gene, called G72, plays a role in regulating the activity of glutamate, an important excitatory neurotransmitter in the brain. This is intriguing because decreased glutamate activity appears to play a key role in negative, or deficit, symptoms of schizophrenia such as social withdrawal, a lack of motivation and expressiveness, and an inability to experience pleasure. It is interesting that several of the recently discovered genes believed to be associated with susceptibility for schizophrenia may function by interfering with neurotransmitters in the prefrontal cortex (PFC) and related brain regions. For example, another newly identified gene encodes an enzyme that terminates the activity of dopamine in the PFC. In work led by an NIMH scientist, this research has identified two alleles, or variants, of this gene; one of these has been shown in clinical studies to be associated with deficits in information processing and memory, again symptoms central to schizophrenia. These discoveries highlight the biological basis for schizophrenia and may ultimately yield both diagnostic and therapeutic breakthroughs.

SCREENING FOR DRUG DISCOVERY TARGETS

One initial application of genetic discoveries will be to identify the various molecules they encode and then design medications that act on those molecules when they are implicated in various disorders. Molecular processes gone awry can serve as targets for medications designed to prevent, treat, or halt progression of a given condition. As part of an initiative included in the NIH Roadmap, NIMH is supporting research to generate a library of small molecules with novel actions that will interact with particular biological targets. Subsequent research will test these sub-

stances as candidates for the treatment of mental disorders as well as for their utility as diagnostic agents or research tools.

AUTISM

Autism represents an urgent and significant scientific and public health challenge that, given scientific opportunity and public concern, is the appropriate focus of multiple NIH Institutes. The reported incidence and prevalence of autism appears to be rising. Over the past two decades, estimates of prevalence have escalated from $\frac{1}{10000}$ to as many as $\frac{1}{250}$ (for autism spectrum) to $\frac{1}{400}$ (classic autism). A recent investigation by CDC in Brick Township, New Jersey, found a prevalence rate for autism of 4.0 per 1,000 children and a rate of 6.7 per 1,000 children for the more broadly defined category of autistic spectrum disorders.

A biologically based developmental disorder, autism is characterized by qualitative impairments in social interaction and both verbal and nonverbal communication and behaviors, resulting in a markedly restricted repertoire of activities. High quality clinical care and management of children with autism can exert a draining financial toll on families.

Last year, NIMH accepted leadership of the internal NIH Autism Coordinating Committee (ACC), which operates in close communication with the larger Inter-agency Autism Coordinating Committee (IACC). Other NIH Institutes retain control over their own activities, such as the long-standing Collaborative Programs for Excellence in Autism (CPEAs), a network of sites funded by NICHD and NIDCD. In 2002, NIMH committed to be the primary funding source for the Studies to Advance Autism Research and Treatment (STAART) Centers program mandated by the Children's Health Act of 2000. The Institute awarded grants to develop STAART Centers, with co-funding provided by NINDS, NICHD, NIDCD, and NIEHS. Two Centers were awarded in fiscal year 2002, and six additional Centers are slated for funding in fiscal year 2003. This will complete establishment of the network, exceeding the mandate of at least five centers required by the Act.

Our research is yielding significant dividends. A recent study found risperidone, one of a newer class of anti-psychotic medications, to be successful and well tolerated for the treatment of serious behavioral disturbance associated with autistic disorder in children aged 5 to 17. Also near completion is a study evaluating the safety and efficacy of methylphenidate (Ritalin®) in treating overactivity, impulsivity, and distractibility in children with autism spectrum disorders.

PSYCHOLOGICAL IMPACT OF BIOTERRORISM

In light of the maxim that "the purpose of terror is to terrorize," prudence dictates that we use research not only to treat the consequences of terrorism, but also to help refine our ability to triage those individuals likely to be most susceptible to serious adverse neurobiological responses to a bioterrorist attack and, to the extent possible, to "innoculate" the population against destabilizing or unwarranted anxiety or panic. Over many decades, NIMH has supported a robust behavioral science research portfolio that has informed us about many basic behavioral mechanisms, including those influencing group processes. More recently, we have supported studies that have examined the psychological impact of natural disasters such as floods and tornados, and the terrorist attacks in Oklahoma City in 1995 and on September 11, 2001. Behavioral science and clinical research not only provide a "top-down" systems-level context to help us understand what is happening at molecular and cellular levels in the brain in the face of overwhelming fear and anxiety, but also can help us to prepare for and treat the psychological and social consequences of such events.

A key finding of this research to date is that people are very resilient—the vast majority of victims of mass disaster and terrorist attack do not develop a psychiatric disorder. For those individuals who do, the most frequent adverse outcome is post-traumatic stress disorder, or PTSD. This is a form of anxiety disorder that occurs after exposure to an extreme stressor in which an individual experiences, witnesses, or is confronted with actual or threatened death or serious injury to self or others. Given its prevalence, disabling impact, chronicity, and treatment resistance, PTSD represents a major public health concern. Through the research we have conducted, however, we are gaining an increasingly clear understanding of what variety of psychological and behavioral problems to expect in the event of an attack and the types of services that will be needed. We know that we should expect to see increases in requests for therapy and medications for common and troubling symptoms of fear, anxiety, hyperarousal, and sleep problems. We know that survivors—particularly those with PTSD and others who may have a comorbid, or co-occurring mental disorder—actively use mental health services. In the event of a future attack, as we

move beyond needs for first aid, housing, and food, the majority of those people who were directly affected will have need for supportive counseling and assistance with resuming normal activities such as household routines, school, and work. Research that has examined the use of mental health interventions speaks to the clinical significance of subjective distress even in subjects without recognized psychiatric disorders. We also have information about who is most likely to be at risk for developing longer-term problems and, thus, as people present to health, educational and social service programs for a variety of physical and mental health problems, it will be important to apply what we know with the aim of preventing such problems. I would also note that we also are drawing on behavioral science research involving coping in response to threat to advise individuals and communities how to anticipate and lessen the emotional burden caused by trauma. It is clear that the availability of accurate information, including information about health risk, for example, blunts the anxiety- and panic-provoking nature of unjustified speculation about risk and permits people to decide on action that they can take. Research on basic behavioral processes involved in decision-making, judgment, and health risk assessment—all involved in shaping attitudes, affect, and behavior—is very useful in shaping the messages we convey to our citizens.

I will be pleased to answer any questions.

PREPARED STATEMENT OF DR. STEPHEN I. KATZ

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The fiscal year 2004 budget includes \$502.778 million, an increase of \$17.005 million over the fiscal year 2003 enacted level of \$485.773 million comparable for transfers proposed in the President's request.

The budget increases over the last few years have made a tremendous difference in the studies we have been able to launch, particularly in clinical research including clinical trials in a wide variety of diseases as well as the expansion of vital scientific infrastructure in a creative way. As stewards of these funds, we have worked with a wide range of advisers, both from the scientific community and from the lay public, to ensure that we target areas of greatest scientific opportunity. In addition, we worked to undertake studies that could either be done solely or better by the Federal government. I am pleased to be able to share highlights of some of the stories of progress and promise that have resulted from our investments in medical research.

PUBLIC/PRIVATE PARTNERSHIPS

One of the priority areas in the new NIH Roadmap Initiative is the development of public/private partnerships. The NIAMS has had a number of positive experiences in this area, and I will mention two ongoing examples. The first is the Osteoarthritis Initiative. Our Institute partnered with the National Institute on Aging and several other NIH components as well as with three pharmaceutical companies in launching this public/private partnership aimed at developing clinical research resources that support the discovery and evaluation of biomarkers and surrogate endpoints for osteoarthritis clinical trials. This seven-year project is being undertaken by four clinical sites and one data coordinating center, and this consortium will likely serve as a model for future endeavors that link the public and private sectors.

The second partnership involves the NIH and the Muscular Dystrophy Association (MDA). The NIH has been actively engaged in implementing the mandates of the MD-CARE Act, and has worked closely with representatives of the muscular dystrophy (MD) research and patient communities in this effort. Specifically, the NIAMS, NINDS, and NICHD have partnered to issue new research solicitations for MD cooperative research centers, and for developmental planning grants for future centers. In addition, we are developing an initiative to support the training of basic and clinical researchers to study muscular dystrophy. To underscore the importance of stimulating and supporting further work in this area, the NIH has established an MD Research Task Force, which includes NIH scientific staff, as well as researchers, clinicians, and patient representatives. This group will help ensure that we pursue all promising opportunities to boost MD research and training, and it will also complement the work of the newly established inter-agency Muscular Dystrophy Coordinating Committee, which was called for in the MD-CARE Act.

MUSCLE DISEASES

One of the most active and productive areas within the Institute's research portfolio is in the muscular dystrophies—a group of genetic diseases characterized by progressive weakness and degeneration of the skeletal or voluntary muscles which control movement. Research advances from NIAMS investments in this area include: (1) the finding that people with facioscapulohumeral muscular dystrophy (FSHD) have an exclusive association with one of the two different forms of the chromosomal region linked to the disease. This work may lead to a better understanding of the instability of the genetic locus associated with FSHD. (2) the discovery of how to reverse muscle degeneration in a mouse model of Duchenne muscular dystrophy, a genetic disorder in which muscle cells become progressively more damaged and die. Scientists have devised a way to revitalize wasting muscle by using a special viral carrier to introduce the missing dystrophin gene into the diseased muscle tissue—a finding that could eventually lead to gene therapies for patients with Duchenne muscular dystrophy. (3) the report that a faulty gene is key to understanding myotonic dystrophy. The genetic defect affects the conductance of electrical signals, resulting in delayed muscle control. (4) the isolation of muscle-generating stem cells that can improve muscle regeneration and deliver the missing protein dystrophin to damaged muscles in a mouse muscular dystrophy model. These results signal that some of the major obstacles to stem cell transplantation may be overcome, resulting in more effective treatments for muscular dystrophy and other muscle-related diseases. and (5) the creation of a new animal model that has been labeled a “marathon mouse,” which expresses an energy-metabolizing protein that increases the proportion of particular muscle fibers that give distance runners their muscular stamina. Further work in this area could benefit research efforts against muscle-wasting diseases like the muscular dystrophies.

SYSTEMIC LUPUS ERYTHEMATOSUS

Some of the most promising research results in our mission areas have come from the ability of researchers to apply the explosion of information in genetics and genomics. One example of this is the very recent research report that a particular genetic “signature” has been linked to the blood of patients with severe systemic lupus erythematosus (SLE or lupus). A team of scientists supported by the NIAMS, other parts of the NIH, and the private sector (the Minnesota Lupus Foundation and the Alliance for Lupus Research) has discovered a genetic “signature” present in some patients with lupus who develop such life-threatening complications as blood disorders, central nervous system damage, and kidney failure. These researchers analyzed thousands of genes in the blood of patients with lupus, and, surprisingly, 14 of the thousands of genes studied were linked to a subset of lupus patients with severe disease. These 14 genes are associated with a complex family of proteins involved in the regulation of immune responses, and these findings provide strong support for developing new therapies to block the affected pathways in patients with severe lupus, as well as for identifying patients most likely to benefit from these new therapies.

I want to also mention an important new clinical trial that we launched in children with lupus. The trial is designed to test the efficacy of statins (cholesterol-lowering agents) in preventing or delaying progression of cardiovascular disease in children with lupus. This research study involves 20 centers from the Pediatric Rheumatology Research Network in establishing the largest cohort of pediatric lupus patients ever prospectively studied.

BONE AND OTHER MUSCULOSKELETAL DISEASES

One dimension of the NIH Roadmap Initiative is translational research, and we know that translating the results of basic bone biology research into therapies that prevent or treat musculoskeletal diseases can have a very significant impact on public health. Development and maintenance of a healthy skeleton depends on interactions between bone and bone marrow, blood vessels, and even the central nervous system. Understanding these complex interactions will depend on studies employing genetic and genomic tools, including NIAMS-supported efforts in animal models that are expected to translate into insights guiding the development of new preventive and therapeutic approaches to conditions such as osteoporosis. In recent advances, a variety of pharmacological agents and biochemical factors, some already familiar in other contexts, has been found to have unexpected effects on bone mass. For example, the actions of the cholesterol-lowering drugs called statins, the hormone leptin (originally identified as important for controlling obesity), and nitric oxide (best known for its effects on the heart and blood vessels) all provide clues to ways

that new therapies might improve bone health. In addition, studies of the genetics of bone mass are increasingly productive, including reports of a gene that was previously unsuspected of playing any role in bone emerging as a possible key to restoring bone in cases of osteoporosis.

Research that has direct applicability to daily life of affected individuals has determined that limb reconstruction and amputation after trauma to the lower leg result in similar outcomes in terms of function. We anticipate that the findings of this study will help surgeons and patients make better informed decisions when choosing between reconstruction (limb salvage) or amputation of a limb that has been severely damaged. With a look to the future, a large United States/Canada cooperative project is now underway to resolve differences of opinion on the best way to repair the fracture of the tibia—the most common long bone fracture in the human body. Factors that will be considered in determining which of the groups being studied has a more successful outcome include how soon patients return to work and their general health status and quality of life. Finally, plans are underway for an NIH Consensus Development Conference on Primary Knee Replacement in December 2003 to address the issues that exist in this area, to review the current state of the science, and to identify directions for future research.

SKIN DISEASES

NIAMS-supported researchers recently reported exciting and promising results from their gene therapy studies in the recessive form of the devastating blistering skin disease dystrophic epidermolysis bullosa. This disease is caused by the absence of a specific gene, and researchers used a particular enzyme as the base for gene transfer. The researchers were successful in stably integrating the DNA from the missing gene into genomes of cultured skin cells from four patients with this inherited skin disease. The skin that was developed using these cells displayed stable correction of the hallmark features of this disease. These results establish a potential practical approach to nonviral genetic correction of severe human genetic disorders that require stable genomic integration of large DNA sequences.

The Institute has recently called on scientific experts and lay representatives to help us in three particular areas of skin diseases research: (1) In response to fiscal year 2002 Congressional language, the NIAMS sponsored the “Workshop on the Burden of Skin Disease” in September 2002, to discuss the elements that comprise the burden of skin diseases and their impact on public health and daily living; current knowledge and data-collection instruments, and how to access the data more effectively; and future data needs and instruments for facilitating the collection of the data. The recommendations from this workshop are being reviewed by the Institute to determine the need and path for future initiatives in this area. The lessons learned from this workshop can serve as a paradigm for other areas—all of which share the challenge of defining the burden of a disease on an individual, the family, the workplace, and society as a whole. (2) The NIAMS teamed with the National Alopecia Areata Foundation in sponsoring the Fourth International Research Workshop on Alopecia Areata in November 2002, bringing together investigators from around the country for an exchange of recent findings in alopecia areata and related fields of hair biology. Results of this workshop will guide future research in this field. (3) The Institute is planning a workshop on immune modulation in the treatment of skin diseases, which will include new treatments for psoriasis, atopic dermatitis, autoimmune bullous diseases, and other skin diseases. The workshop will focus on trying to understand how some new treatments are actually working so that we may better understand the mechanisms underlying these diseases.

HEALTH DISPARITIES

In research related to health disparities, there are four efforts that I want to highlight: (1) The NIAMS continues to support the diversity initiative it has created and developed over the last few years—the Health Partnership Program, a collaborative community-based effort in Washington, D.C., that is directed at developing research programs to understand and address health disparities in rheumatic diseases in African American and Hispanic/Latino communities. (2) Differences have been documented in the damage caused by lupus in studies of Hispanic, African American, and Caucasian individuals with this disease. The proportion of patients who had any organ damage was higher among Hispanics than among the other two groups, confirming the greater negative impact of lupus among members of this ethnic group. The association of organ damage with poor coping skills was reported for the first time, and it suggests that approaches designed to modify patients’ behaviors and attitudes to their illness could reduce the damage to the body caused by lupus. (3) Research suggests that women with lupus are at increased risk for both clinical

osteoporosis and cardiovascular complications at a much younger age, and more aggressive control of the risk factors for these complications is needed to prevent these conditions in women with lupus. (4) Social experience has been shown to influence joint replacement decisions; that is, when people think about having a hip or knee replaced, knowing someone who has had the surgery may influence their decision. A recent study funded by the NIAMS and the Robert Wood Johnson Foundation suggested that one reason African Americans may be less likely than Caucasians to seek joint replacement surgery, a procedure that makes a significant difference in alleviating pain and improving function of severely affected individuals, is because they know fewer people who have had this procedure.

CONCLUSION

We are proud of the advances that scientists supported by the NIAMS have achieved and we are excited about initiatives that we have launched. Patients and their families are looking to us with hope and anticipation for answers to what causes their diseases, as well as how their diseases can be better treated and even prevented. We are confident that public health in general as well as daily life for affected individuals in particular will benefit from NIAMS research in the extensive and diverse array of chronic diseases within our mission areas of bones, joints, muscles, and skin.

I would be happy to answer any questions.

PREPARED STATEMENT OF DR. GERALD T. KEUSCH

The fiscal year 2004 budget includes \$64,266,000, an increase of \$2,073,000 over the fiscal year 2003 enacted level of \$62,193,000 comparable for transfers proposed in the President's request.

SCIENCE FOR GLOBAL HEALTH

Thirty five years ago, the Fogarty International Center was established to honor the memory of Congressman John E. Fogarty of Rhode Island. The authorizing legislation, introduced by Representative Melvin Laird of Wisconsin, stated “. . . the committee has provided funds to plan a lasting memorial to a man who for more than a quarter of a century worked tirelessly for a healthier America in a healthier world.” (Congressional Record, House, May 25, 19867, p. 14062). It is my privilege to report to you, that for the past 35 years, the Fogarty International Center (FIC) has fulfilled this promise—Mr. Fogarty and Mr. Laird would be proud of their legacy. Today the FIC is an essential component of the DHHS and NIH response to global challenges in health, representing the nexus between science and diplomacy and promoting both at the same time. FIC is known and respected around the world for its critical role in promoting research and capacity building for global health.

The research and training supported by FIC is a window to a brighter future for the low- and middle-income countries with heavy burdens of disease. While people in these countries typically suffer from high infant, child and maternal mortality rates, amplified manifold by the threats represented by AIDS, TB, malaria and other seemingly intractable infectious diseases, increasingly these populations are now subject to the ravages of chronic disease and premature mortality represented by cardiovascular disease, diabetes, and cancer. All of these conditions limit societal productivity, economic growth, and stability. To this end FIC supports research to better understand the impact of improving health on economic development, political and social stability, and active participation in the global marketplace of the 21st century. Because economic growth invariably impacts on the environment, usually in an adverse manner, FIC has also developed a research agenda to improve our understanding of the impacts on population's health and individual's well-being related to sustainable economic development. These programs are crucial as we identify health care interventions that improve both health and development.

The programs of the FIC directly address five of the eight goals outlined in the United Nations Millennium Declaration, including eradication of extreme poverty (Goal 1), reducing child mortality and improving maternal health (Goals 4 and 5), combating HIV/AIDS, TB and malaria (Goal 6), and ensuring environmental sustainability (Goal 7). These goals are daunting, but not incapacitating. As U.N. Secretary General Kofi Annan has said, “They are achievable, not by holding more world conferences, but by people in every country, coming together and taking action.” This is precisely what FIC does every day. To maximize and leverage the impacts of FIC programs, the Center has collaborated extensively within the NIH, across the Department of Health and Human Services, and beyond, including other

components of the Federal government, bilateral and multilateral agencies here and abroad, foundations, and international organizations such as the World Health Organization, The World Bank and the Regional Development Banks.

STRENGTHENING THE GLOBAL CULTURE OF RESEARCH

For scientists to come together and take action requires them to share a common culture of scientific ethos and values. This can only be accomplished in an environment in which rapid communication is possible, wherein scientific knowledge is readily available to all, and where research is conducted based on partnership and equity. When American scientists work across geographic boundaries in this manner, the beneficiaries are the collaborating scientists, science in general, the United States and foreign partner countries.

FIC strengthens this "global culture of research" through a range of programs. The FIC International Bioethics Education and Career Development Award provides trainees with a strong background in ethics and an understanding of research. The cadre of thoughtful and knowledgeable people trained through this program will insure that internationally and United States-accepted ethical principles are upheld in studies around the world, including in poor nations. An additional component to strengthening a global culture of science is to ensure that technological advances made in one country are accessible to the greatest extent in all countries.

FIC addresses the growing divide in the development and use of genetic technologies through the International Collaborative Genetics Research Training Program. FIC-supported training in the technology of modern genetics research is accompanied by a strong component of ethical, social, and legal considerations and focuses on the implications of performing genetics research in low- and middle-income countries.

The third pillar in support of the global culture of science is access to information, which is addressed by the International Training Program in Medical Informatics. This program enables U.S. institutions to support training in order to build the capacity of scientists in developing countries to access, utilize and construct computer-based tools to access and exchange information to advance biomedical research and public health. This program will re compete in fiscal year 2004. As a companion to this initiative, FIC in collaboration with the National Library of Medicine is embarking on additional programs to support and improve the editorial content of key biomedical research and health journals in developing countries, and to improve the quality and accuracy of reporting on medical research and health by developing country journalists, whether they are working in print, radio or television.

As FIC works to strengthen the global culture of science through all its programs, to maximize the benefits of individual initiatives in fiscal year 2004 FIC proposes to pilot innovative International Glue Grants. These grants will provide resources to link together regional and national institutions in developing countries with their several U.S. partner institutions, taking advantage of the perspective of biomedical, clinical and behavioral and social scientists in creating new ways to explore old and emerging health problems. We expect the "glue" will bring investigators together in a common framework for addressing critical issues, enabling these collaborators to work more cost-effectively and with greater productivity on critical challenges such as AIDS, maternal health, and impacts on health from environmental pollution.

Support for the movement of junior researchers across borders is the fourth pillar of the broader effort to strengthen the global culture of research and science. FIC will continue to invest in the Global Health Research Initiative Program (GRIP), which provides resources for developing country scientists who trained in the United States to obtain, on a peer-reviewed merit-based system, funding to conduct research upon their return home and remain linked in collaborative research with their U.S. mentors. As a corollary to this program, FIC is also investing in career pathways in international research for young American investigators through the FIC International Research Scientist Development Award (IRSDA). The IRSDA supports junior U.S. scientists as they conduct research in the developing world on issues of global import, then provides additional opportunities and a "safety net" on their return home. In addition, in fiscal year 2004, will bring the first crop of students of medicine, public health and allied medical sciences into a new program to provide a year of mentored clinical research training in a developing country collaborative research program. The rationale for this new program is to expose students as early as possible in their professional careers to research needs and prospects in the developing world as a means to encourage them to select global health challenges as long-term career pursuits. A partnership with the Ellison Medical Foundation, the Association of American Medical Colleges, the Association of Schools of Public Health and the FIC, the program will pair a U.S. student with

one from the host country to train and participate in clinical research under the guidance of expert mentors from the United States and the foreign country who already work together on clinical research studies.

A previously neglected area is that of gender and global health research. Not only may risk factors, disease progression, and response to treatment vary by gender, but societal responses based on gender may exclude women from accessing health care or may imbue them with stigma that adds significantly to the burden of disease. FIC is initiating two new programs to address these issues. First, the Stigma and Global Health research program, expected to be funded in fiscal year 2003, will support studies to better understand the exclusion of stigmatized populations from the benefits of medical care and participation in medical research. Importantly, it will identify interventions to address the major needs. Second, FIC, the NIH Office of Research on Women's Health, the Canadian Institutes of Health Research, and Harvard and Yale Universities are working with experts around the world to develop a framework for the inclusion of gender issues across the range of global research and training programs the Center and other science funding agencies support. Included in this initiative is an effort to enhance career development for women scientists from the developing world.

CONTINUING TO INVEST IN COMMUNICABLE DISEASE RESEARCH

FIC currently supports a broad program of research and training in AIDS, tuberculosis, malaria and other emerging infectious diseases. In fiscal year 2004 the Center will pursue these major global health problems in three ways, first through its continuing focus on AIDS, the greatest epidemic threat of our time, and second, through support of a comprehensive program, the Global Infectious Disease Training and Research Program (GLIDTR), to focus on infectious diseases that are predominantly endemic in or impact primarily upon people living in tropical countries. Under the AIDS programs, a major new initiative will be fully launched with the awarding of the first set of comprehensive grants under the International Clinical, Operational and Health Services Research and Training Award for AIDS and TB (ICOHRTA-AIDS/TB). This program has as its major goal the promotion of excellent clinical research in support of care of AIDS patients, along with the necessary operational and health services research to move new knowledge into practice as soon as possible. The GLIDTR is augmented by FIC/NIH enlarging investments in the Ecology and Infectious Diseases research program, a major collaboration between FIC and the National Science Foundation. This innovative program is oriented towards identifying predictive models for emergence of infectious diseases so that preventive strategies can be implemented before a new global calamity is unleashed on the world. Finally, FIC's Division of International Epidemiology and Populations Studies is conducting and coordinating research involving mathematical modeling of epidemic disease, whether due to events in nature or caused by humans, in an effort to better identify key questions and intervention points. Working closely with NIAID, NIGMS, and the Office of Public Health Emergency Preparedness at DHHS, FIC is coordinating work with leading academic mathematical modeling groups in the United States and abroad.

EXPANDING INVESTMENTS IN NON-COMMUNICABLE DISEASES

With the aging of populations worldwide, including in poor nations, along with changing lifestyle patterns and migration into cities, there is a growing recognition that the global burden of disease will increasingly include non-communicable diseases. FIC's current programs in this broad field address the burden of mental illness, the broad range of brain disorders across the life cycle, and the major epidemic of tobacco use and the inevitable epidemic of chronic pulmonary, cardiovascular disease and cancer that will follow. To complement this set of critical issues, FIC intends to explore ways to address the huge and growing burden of morbidity and mortality due to trauma and injury, whether intentional or un-intentional, such as road-traffic accidents. Areas of interest include training and research activities designed to better understand the body's systemic responses to major injury, fostering more rapid application of this knowledge to wound healing following trauma and burns, development of innovative low-cost and low-maintenance prosthetic devices, integration of mental and physical rehabilitation into primary care for victims of trauma, and to develop and test effective cost-effective interventions.

A complete description of the FIC Strategic Plan is available on the World Wide Web at <http://www.nih.fic.gov/about/plan.html>.

CONCLUSION

Today, FIC, together with the Institutes and Centers at the NIH, is exerting leadership in global health research in important new ways, addressing critical global health problems while investing in the training of United States and foreign researchers who can, together, identify the solutions for tomorrow. As expressed by John E. Fogarty before his death in 1967, "The alternative is that the United States will reduce its leadership role in furthering humanitarian programs, and may become more of a responder than a leader."

PREPARED STATEMENT OF DR. RAYNARD KINGTON

Mr. Chairman, Members of the Committee: I am pleased to present the President's budget request for the Office of the Director (OD) for fiscal year 2004, a sum of \$317,983,000, which reflects an increase of \$44,031,000 over the comparable fiscal year 2003 appropriation. The OD provides leadership, coordination, and guidance in the formulation of policy and procedures related to biomedical research and research training programs. The OD also is responsible for a number of special programs and for management of centralized support services to the operations of the entire NIH.

The OD guides and supports research by setting priorities; allocating funding among these priorities; developing policies based on scientific opportunities and ethical and legal considerations; maintaining peer review processes; providing oversight of grant and contract award functions and of intramural research; communicating health information to the public; facilitating the transfer of technology to the private sector; and providing fundamental management and administrative services such as budget and financial accounting, and personnel, property, and procurement management, administration of equal employment practices, and plant management services, including environmental and public safety regulations of facilities. The principal OD offices providing these activities include the Office of Extramural Research (OER), the Office of Intramural Research (OIR), and the Offices of: Science Policy; Communications and Public Liaison; Legislative Policy and Analysis; Equal Opportunity; Budget; and Management. This request contains funds to support the functions of these offices.

In addition, the OD also maintains several trans-NIH offices and programs to foster and encourage research on specific, important health needs; I will now discuss the budget request for each of these trans-NIH offices in greater detail.

THE OFFICE OF AIDS RESEARCH

The Office of AIDS Research (OAR) coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. Our response to the epidemic requires a unique and complex multi-institute, multi-disciplinary, global research program. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of the NIH Institutes and Centers. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently, allowing NIH to pursue a united research front against the global AIDS epidemic.

Each year, OAR oversees the development of the comprehensive NIH AIDS-related research plan and budget, based on scientific consensus about the most compelling scientific priorities and opportunities that will lead to better therapies and prevention strategies for HIV disease. The Plan serves as the framework for developing the annual AIDS research budget for each Institute and Center; for determining the use of AIDS-designated dollars; and for tracking and monitoring those expenditures. OAR identifies scientific areas that require focused attention and facilitates multi-institute activities to address those needs. OAR coordinates, monitors and fosters plans for NIH involvement in international AIDS research and training activities. OAR supports a number of initiatives to enhance dissemination of research findings to researchers, physicians, patients and communities. The fiscal year 2004 budget request for OAR is \$60,942,000.

THE OFFICE OF RESEARCH ON WOMEN'S HEALTH

The Office of Research on Women's Health (ORWH) serves as the focal point for women's health research for the Office of the Director, to ensure that women are appropriately represented in biomedical and biobehavioral research studies supported by the NIH, and to develop and support biomedical careers. The report: *An*

Agenda for Research on Women's Health for the 21st Century, provides the basis for the ORWH to collaborate with the scientific and advocacy communities to address scientific initiatives about women's health and sex and gender factors in health and disease. In fiscal year 2004, the OD budget request of \$41,231,000 includes an increase of \$808,000 over the fiscal year 2003 enacted budget of \$40,423,000 for the ORWH to continue stimulating new research and to implement innovative career development programs.

Research priorities for women's health emphasize the importance of interdisciplinary collaboration, especially for chronic, multi-systemic conditions; prevention and elimination of high risk behaviors, such as overeating and physical inactivity, which contribute to morbidity and premature mortality of women; and reproductive health, including such gynecologic conditions as uterine fibroid tumors, and further exploring issues related to the menopausal transition, such as hormone therapy. The ORWH continues to partner with Institutes and Centers to monitor compliance with NIH policies for the inclusion of women and minorities in clinical research, and to ensure that analyses by sex/gender are addressed. The ORWH is witnessing exciting expansion of new research in its specialized centers of interdisciplinary research in women's health and sex and gender factors. The ORWH has also expanded its unique interdisciplinary career development program in women's health research that fosters the mentored development of junior faculty and assists them in bridging advanced training for junior investigators with research independence. In addition, the ORWH has now implemented a new Intramural Program on Research on Women's Health to focus on NIH intramural women's health and sex and gender comparison research.

THE OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

The NIH has a long history of funding health-related behavioral and social sciences research, and the results of this work have contributed significantly to our understanding, treatment, and prevention of disease. The Office of Behavioral and Social Sciences Research (OBSSR) furthers NIH's ability to capitalize on the scientific opportunities that exist in behavioral and social sciences research by providing leadership in identifying and implementing research programs in behavioral and social sciences that are likely to improve our understanding of the processes underlying health and disease and provide directions for intervention. OBSSR works to integrate a behavioral and social science approach across the programs of the NIH. The fiscal year 2004 OD budget includes \$26,179,000 for OBSSR, an increase of \$513,000 over the fiscal year 2003 appropriation.

Many exciting scientific developments are occurring at the intersection of behavioral and social science research and biomedical research. OBSSR and several ICs are in the process of developing new approaches to train individuals to undertake a program of research that extends well beyond traditional disciplinary boundaries. One such initiative is a new postdoctoral program that would provide individuals trained in one discipline with formal course work and hands-on training in a second field. Collaboration between social and behavioral scientists and biomedical investigators is still relatively uncommon, in part, because traditionally trained social and behavioral researchers lack sufficient expertise in the biomedical fields and vice versa. The initiative will provide a mechanism for training investigators to work in interdisciplinary teams to tackle some of our most pressing health problems.

OBSSR is also developing an initiative that will encourage investigators to expand on the current theoretical base of change processes and intervention models, to expand our understanding of how change, once achieved, is maintained over the long term. Maintaining behavior change over the long term appears as challenging, if not more so, than the initiation of behavior change. Past research efforts have typically focused on short-term behavioral change. However, other research indicates that relapse rates for addictive behaviors such as substance abuse and tobacco use are very high. Additionally, while the positive association between education and health has been well documented, there is a paucity of scientific information on the biological mechanisms and the causal pathways that underpin this association. OBSSR in collaboration with other ICs issued a Request for Applications to increase extramural research activity on this important scientific question.

THE OFFICE OF DISEASE PREVENTION

The primary mission of the Office of Disease Prevention (ODP) is to stimulate disease prevention research across the NIH and to coordinate and collaborate on related activities with other federal agencies as well as the private sector. There are several other offices within the ODP organizational structure.

The Office of Medical Applications of Research (OMAR) has as its mission to work with NIH Institutes, Centers, and Offices to assess, translate and disseminate the results of biomedical research that can be used in the delivery of important health services to the public. The Office of Disease Prevention (ODP) has several specific programs/offices that strive to place new emphasis on the prevention and treatment of disease.

In fiscal year 2004, the Office of Dietary Supplements (ODS) within ODP requests a budget of \$18,778,000. It will continue to promote the scientific study of the use of dietary supplements by supporting investigator-initiated research in conjunction with other ICs at NIH and stimulating research through conduct of conferences and through presentations at national and international meetings. In its continuing efforts to inform the public about the benefits and risks of dietary supplements, the ODS expanded the International Bibliographic Information on Dietary Supplements (IBIDS) database to include a consumer-oriented search strategy. It has also disseminated a database devoted to federal funding of dietary supplement research, called CARDS, which is currently populated with data about the NIH investment from fiscal year 1999–2001. ODS publishes Fact Sheets about vitamin and mineral dietary supplements in collaboration with the NIH Clinical Center, as well as Fact Sheets about botanical supplements in conjunction with the National Center for Complementary and Alternative Medicine. ODS, in collaboration with the National Heart Lung and Blood Institute and other NIH ICs, has sponsored a systematic review of the relationship between omega-3 fatty acids and a series of clinical indications, particularly coronary heart disease. Several reports will be published in fiscal year 2003 and fiscal year 2004 based upon this review, which will serve as the basis for planning further NIH research on omega-3 fatty acids. To determine the future research studies of efficacy and safety of dietary supplements containing ephedra, ODS sponsored a systematic review of ephedra efficacy and safety, which has recently been completed. ODS has initiated work on a pre-clinical study of ephedra by the National Toxicology Program. Congressional language in the fiscal year 2002 and fiscal year 2003 appropriation reports directed ODS to enhance an ongoing collaboration for the development, validation, and dissemination of analytical methods and reference materials for botanical dietary supplements. ODS works with other partners in the public and private sectors to meet this objective. ODS supports the National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention, in order to provide more information about dietary supplement use in the US population. This will inform future research about potentially important target populations, such as children, women, and the elderly. Funding is used to create and populate a database of dietary supplements, as well as to support the measurement of blood levels of key metabolites associated with dietary supplement use. In fiscal year 2003, ODS and USDA published the proceedings of a workshop that examined the emerging needs for dietary assessment, including supplement use, in national surveys such as NHANES. A key outcome has been to develop an analytically-based database of dietary supplement ingredients.

Another component of ODP, the Office of Rare Diseases (ORD), develops and disseminates information to patients and their families, health care providers, patient support groups, and others and forges links among investigators with ongoing research activities in this area. The ORD supports workshops and symposia to stimulate research on rare diseases.

To provide better and faster information, ORD, together with the National Human Genome Research Institute (NHGRI), established the Genetic and Rare Diseases Information Center to respond to requests for information about genetic and rare disorders. The fiscal year 2004 budget request for ORD is \$11,423,000.

The ORD, supports together with NIH Institutes and Centers research on rare diseases. Approximately 25 million people in the United States are affected by an estimated 6,000 rare diseases. A “rare disease” is defined as a condition affecting fewer than 200,000 Americans. On November 6, 2002, the President signed the Rare Diseases Act of 2002 (Public Law 107–280). The purposes of this Act are to establish the Office of Rare Diseases in statute at the National Institutes of Health and to increase the national investment in the development of diagnostics and treatments for patients with rare diseases and disorders.

THE OFFICE OF SCIENCE EDUCATION

The Office of Science Education (OSE) plans, develops, and coordinates science education programs to strengthen and enhance efforts of the NIH to attract young people to biomedical and behavioral science careers and to improve science literacy in both adults and children. The office’s mission is to help people understand and

use new knowledge uncovered by the NIH in pursuit of better health for everyone. The OSE works toward this mission by: creating programs to improve science education in schools (the NIH Curriculum Supplement Series); creating programs that stimulate interest in health and medical science careers (the new LifeWorks Web site); creating programs to advance public understanding of medical science, research, and careers; promoting NIH educational resources and programs; and advising NIH leadership about science education issues. All office programs target diverse populations including under-served communities, women, and minorities, with a special emphasis on the teachers of students from Kindergarten through grade 12. The OSE works closely with NIH institutes, centers, and offices on science education issues, and maintains the OSE Web site as a source of information about available resources and programs. <http://science.education.nih.gov>.

The NIH Curriculum Supplements series are National Science Education Standards-based lesson plans that are distributed free to K-12 teachers across the country. They incorporate the best of both science and education communities, and are intended to update science content and allow the teacher to incorporate the latest NIH research into classroom instructions. *Life Works* is a new OSE Web site created as a source of career information for students, teachers, counselors, and parents. The site will allow exploration of the educational requirements, knowledge, skills, and abilities required for over 100 health and medical science careers. The fiscal year 2004 Budget request for OSE is \$3,866,000.

LOAN REPAYMENT AND SCHOLARSHIP PROGRAM

The NIH, through the Office of Loan Repayment and Scholarship (OLRS), administers the Loan Repayment and Undergraduate Scholarship Programs. The NIH Loan Repayment Programs (LRPs) seek to recruit and retain highly qualified physicians, dentists, and other health professionals with doctoral-level degrees to biomedical and behavioral research careers by countering the growing economic disincentives to embark on such careers, using as an incentive the repayment of educational loans. There are loan repayment programs designed to attract individuals to clinical research, pediatric research, health disparities research, and contraception and infertility research, and to attract individuals from disadvantaged backgrounds into clinical research. The AIDS, Clinical, and General Research Loan Repayment Programs are designed to attract investigators and physicians to the NIH's intramural research and research training programs. The NIH Undergraduate Scholarship Program (UGSP) is a scholarship program designed to support the training of undergraduate students from disadvantaged backgrounds in biomedical research careers and employment at the NIH. The fiscal year 2004 Budget request for OLRS is \$6,843,000.

NIH ROADMAP

The NIH Director is taking an innovative approach to accelerate fundamental discovery and translation of that knowledge into effective prevention strategies and new treatments—an effort referred to as the NIH Roadmap. The fiscal year 2004 budget request for the Office of the Director includes an increase of \$35,000,000 for strategic “roadmap” initiatives. These funds will be allocated by the NIH Director to the Institutes and Centers to address critical roadblocks and knowledge gaps that currently constrain rapid progress in biomedical research. Three broad initiatives will be stimulated with these funds: (1) new pathways to discovery, which includes a comprehensive understanding of building blocks of the body's cells and tissues and how complex biological systems operate, regenerative medicine, structural biology, molecular libraries, nanotechnology, bioinformatics and computational biology, and molecular imaging; (2) research teams of the future, including multidisciplinary research and public-private sector partnerships; and (3) re-engineering the clinical research enterprise. These efforts will allow the NIH to rethink the infrastructure that is required to translate findings from the genomic era into front-line treatments and prevention strategies that benefit people in this country and abroad.

Thank you for giving me the opportunity to present this statement; I will be pleased to answer questions.

PREPARED STATEMENT OF DR. CLAUDE LENFANT

I am pleased to appear before this Committee once again on behalf of the National Heart, Lung, and Blood Institute (NHLBI). We are extremely grateful for the generous budget increases of recent years that have enabled us to capitalize on extraordinary research opportunities.

PROGRESS AND CHALLENGES

A recent report in *The New York Times* (“Gains on Heart Disease Leave More Survivors, and Questions”) highlighted how far we have come in the battle against heart disease—and how far we have yet to go. The well-known good news is that heart disease death rates have been plummeting for decades, and serious disease manifests itself much later in life. The bad news is that an acute problem has become a chronic problem that affects millions of Americans—this is “the endgame of the cardiovascular disease epidemic” that we now confront.

CLINICAL RESEARCH AND THE NIH ROADMAP

Our vigorous research effort is rapidly uncovering new knowledge and technologies that will undoubtedly lead to treatments undreamed of even 10 or 20 years ago. While they are being developed and tested, however, we must do our best to ensure that rigorous science guides appropriate use of more conventional treatments. Indeed, clinical research that has direct application to public health issues is a major focus of the NIH Roadmap that is currently being drawn and refined. The NIH investment in clinical research and, particularly, in clinical trials is absolutely critical if we are to provide health-care givers and their patients with science-based information to guide their decision-making. This is a role that the NIH is uniquely able to fill; indeed, it is a job that would never be undertaken without support from public funds. In this light, I am very pleased to mention some findings from recent clinical trials that have enormous practical significance for disease prevention and treatment.

BLOOD PRESSURE MEDICATIONS

The benefits of treating hypertension are widely appreciated. However, the choice of a means to achieve blood-pressure lowering has been complicated in recent years by the arrival on the market of new drugs (e.g., calcium-channel blockers, angiotensin-converting-enzyme inhibitors, alpha blockers) that, while expensive, were thought to have advantages over older drugs. The ALLHAT (Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial) compared these new drugs with a diuretic—one of a class of blood pressure-lowering drugs that has been used for many years and can be had for mere pennies a day. It found that the diuretic did at least as good a job as newer agents in preventing complications of hypertension—and a better job, according to some measures. The study was conducted in a variety of practice settings and its participants, all aged 55 and over, included high proportions of women, minorities, and persons with type 2 diabetes. Thus, the results are widely applicable to Americans with hypertension, who number about 50 million, according to the National Health and Nutrition Examination Survey.

POSTMENOPAUSAL HORMONE THERAPY

The merit of conducting rigorous research to challenge widely held, but unproven, assumptions about treatment and prevention is illustrated even more starkly by recent studies of hormone therapy in postmenopausal women. When the NIH Women’s Health Initiative was started more than a decade ago, belief in the manifold benefits of estrogen—and particularly its benefits with respect to heart disease prevention—was so widespread that some thought such a trial was neither feasible nor ethical. Thus, it was major news when the trial reported last summer that a widely used form of postmenopausal hormone therapy (estrogen plus progestin) is ineffective in reducing cardiovascular disease risk and appears, in fact, to be harmful. Estimates from U.S. Census data indicate that more than 40 million American women are postmenopausal, so the implications of this trial, in terms of both health and costs, are potentially very great.

TREATING ATRIAL FIBRILLATION

Yet another example of a study that contradicted popular wisdom is the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial. It compared a well-regarded rhythm-management approach to treating atrial fibrillation (an abnormal heart rhythm) with a rate-control strategy. The trial found that the purported benefits of the rhythm-management approach were nonexistent and, moreover, that the approach carried an increased risk of adverse drug effects. These findings are expected to alter fundamentally our method for preventing complications, most notably stroke, of this arrhythmia, which affects an estimated 2.3 million people in this country, according to data from the American Heart Association.

PREVENTING RECURRENT BLOOD CLOTS

Finally, the PREVENT (Prevention of Recurrent Venous Thromboembolism) trial was recently halted ahead of schedule because of persuasive intermediate results. It found that long-term use of low-dose warfarin (a blood thinner) to prevent the recurrence of two blood-clotting disorders, deep vein thrombosis and pulmonary embolism, provided major benefits without significant side effects. As was the case with the ALLHAT study, this trial addressed a research question that would never have been pursued by industry, and identified an important use for an old, very inexpensive therapeutic agent.

NEW RESEARCH TO ADDRESS CRITICAL PUBLIC HEALTH ISSUES

Two of the most pressing public health priorities of today are obesity and diabetes, conditions that have become epidemic in modern America. Both are the object of NIH-wide multifaceted efforts; they are, moreover, the special focus of concerted NHLBI attention because their victims are inordinately susceptible to cardiovascular disease complications. The NHLBI is undertaking new programs in both areas, with the ultimate goal of reducing the toll of such complications.

OBESITY

Innovative worksite interventions for preventing and controlling obesity in adults will be designed and tested. Although traditional obesity-control strategies have focused on the individual, the workplace constitutes a promising location for making positive, long-lasting behavioral and environmental changes that may affect a broad range of adults. It is envisioned that researchers will consider a variety of approaches to make healthful foods available, affordable, and desirable; promote physical activity; and establish support systems that enable achievement and long-term maintenance of appropriate weight.

A comprehensive research initiative on asthma and obesity will also be undertaken. Studies have found that body mass index is strongly and independently associated with risk of adult-onset asthma, and that excessive weight gain in elementary school greatly increases risk of developing asthma among young girls. Overweight also appears to contribute to asthma exacerbations and diminished pulmonary function. Experts from a variety of relevant disciplines believe that research conducted collaboratively by scientists with expertise in asthma and in body weight issues may yield important clues about hormonal, genetic, and mechanical factors that influence the relationship between these conditions. Stimulation of such collaboration is the goal of this new program.

DIABETES

A major new clinical trial will test approaches to lowering risk of cardiovascular disease in adults with type 2 diabetes. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study will evaluate the effects of intense blood sugar control along with very aggressive control of blood pressure and lipids. Type 2 diabetes presents an enormous public health challenge; its many victims are highly susceptible to developing such serious consequences as heart attack, stroke, and limb amputation due to impaired circulation and an estimated 70 percent of them ultimately die of cardiovascular disease. More than 15 million Americans have diagnosed type 2 diabetes, and the number is expected to climb to 27 million by 2050; thus, if this new program uncovers a better treatment approach, its impact will be significant.

The Institute is also working to develop a program to study the causes, prevention, and treatment of cardiovascular disease in the generally younger population of patients with type 1 diabetes. Such patients who have advanced microvascular complications suffer cardiovascular disease rates 10–20 times those of the general population, and there is an urgent need to identify effective approaches to prevent or postpone this complication. Undoubtedly, some common factors contribute to the risk of cardiovascular disease in both type 1 and type 2 diabetic patients, but the differences in pathophysiology between the two diseases suggest there may also be different factors. It is hoped that a closer look at existing data regarding such factors will form the basis for development of innovative preventive interventions.

SPARK II CONFERENCE

Although this testimony has focused attention on programs and activities of immediate and obvious clinical relevance, I want to assure the Committee that the Institute is moving forward briskly on all fronts. This past October, we began revisiting a process (called SPARK, a reference to the expectation that it would ignite a new world of ideas) which had been first undertaken in 1998 to assist us in deter-

mining the best use of the funds that came our way as part of the doubling of the NIH budget. First, a working group of select scientists was assembled to assist in identifying important opportunities that the Institute should address over the next 3 to 5 years. Subsequently, a conference was held to obtain the views of representatives of three major professional societies associated with the mission of the NHLBI (i.e., the American Heart Association, the American Thoracic Society, and the American Society of Hematology). A research schema was developed that focused on five areas of opportunity: regenerative biology and replacement therapy, development and embryogenesis, immunology and inflammation, health promotion and disease prevention, and public health applications of genomics and proteomics. I expect that we will have much good news to report to the Committee in the upcoming years as the recommendations of SPARK II are implemented.

BUDGET STATEMENT

The fiscal year 2004 budget includes \$2,868 million, an increase of \$76 million over the fiscal year 2003 enacted level of \$2,792 million comparable for transfers proposed in the President's request.

I would be pleased to answer any questions that the Committee may have.

PREPARED STATEMENT OF DR. TING-KAI LI

I am pleased to present the President's budget request for the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for fiscal year 2004. The fiscal year 2004 budget includes \$430 million, an increase of \$14 million over the fiscal year 2003 enacted level of \$416 million comparable for transfers proposed in the President's request. Alcohol is the third leading preventable risk factor for premature death in developed countries, according to the 2002 World Health Organization report. In the United States, alcohol misuse costs society about \$185 billion each year.¹

The reason alcohol takes such a heavy toll is that its potential to cause harm extends beyond alcoholism and behaviors that lead to fatal injuries, major problems in themselves. Alcohol is not only a psychoactive substance, but also a toxin that can damage any tissue or organ in the body, unlike illegal drugs. Alcohol's toxic actions cause or contribute to certain cancers, liver and pancreatic disease, brain damage, and disturbances of the immune and endocrine systems, among other conditions. But alcohol also presents a paradox. While heavy drinking substantially raises the risk of heart disease and stroke, studies suggest that moderate drinking appears to reduce them. Thus a major contributor to disease appears to have the potential to improve certain aspects of health.

VARIATION HOLDS THE ANSWER

The explanation for the paradox lies not only in degree of drinking in terms of the quantity and the frequency of drinking, but also in differences in our biological make-up. When we can answer the question of why alcohol is harmful in some circumstances, but appears to be beneficial in others, we'll also be likely to find answers to other questions fundamental to our research: Why do only some of the people who drink, but not others, develop alcoholism or tissue damage? Why does the same medication result in sustained recovery from alcoholism in some people, but fail completely in others?

The answers lie largely in variations in our genes and the hundreds of biochemical activities they influence in our cells and, ultimately, our organs and behaviors. Different individuals and different ethnic populations can have different gene variants to yield a four-fold difference in their metabolic and behavioral responses to alcohol.

Much of our research is aimed at identifying and understanding: (1) the genes that influence how our organs and behaviors respond to alcohol, (2) the association of specific variants of these genes with specific alcohol-related outcomes, such as tissue damage or alcoholism; (3) patterns of variation in gene activity, protein activity, and metabolic activity with specific alcohol-related outcomes, and (4) how environmental factors interact with these biological factors to increase or decrease risk of alcoholism and alcohol-related problems.

¹National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism. *The Economic Costs of Alcohol and Drug Abuse in the United States, 1992*. Analysis by the Lewin Group, Harwood, H.; Fountain, D.; and Livermore, G. Bethesda, MD: DHHS, NIH, NIH Publication No. 98-4327 (September 1998).

Findings from this research form the basis on which we develop and test pharmacological and behavioral strategies for prevention and treatment. Through studies in humans as well as animals, a high-risk, high-technology project currently underway is developing a biosensor that will help us understand vulnerability to alcoholism and organ pathology. This unobtrusive sensor will enable us to continuously measure and integrate over time levels of alcohol and, simultaneously, measure products resulting from alcohol metabolism in a number of bodily processes.

One approach is an external skin sensor that periodically and imperceptibly inserts a probe smaller than a human hair into an individual subject's tissue or the fluid around it.

Another is to implant a microchip sensor subcutaneously. The continuous data it generates will provide valuable information about metabolic patterns of vulnerability. Clinically, alcohol levels also will reveal whether patients are complying with treatment regimens, providing clues about which treatment strategies are most effective.

CLINICAL IMPLICATIONS

Data from our basic research will enable us to do several crucial things. We will be able to provide clinicians with reliable biomarkers—laboratory tests—that will tell them which of their patients are biologically and/or genetically at risk of becoming alcoholic or of developing alcohol-induced tissue injury. Clinicians also will have the potential to predict which patients are biologically and/or genetically predisposed to respond to a specific medication for treatment of alcoholism, and which patients will respond to another.

At the same time, this research is helping us to identify molecular targets for new medications to treat both alcoholism and alcohol-induced organ damage, a pressing need in the clinical setting. As we follow the pathways from genes to physical and behavioral outcomes, we're asking where, within the many biochemical reactions that occur along the way, we can find the best molecular points at which to aim pharmaceuticals that block alcohol's actions. We also are asking if these points for intervention vary depending on variations in a person's constellation of genes, necessitating different medications or molecular targets for subtypes of the disorders.

One such point for intervention is about to be tested in human clinical trials. Our scientists used several approaches to test a hypothesis that blocking a specific receptor on brain cells—the CB1 receptor, a docking site for the brain's own version of marijuana-like substances called endocannabinoids—reduces desire for alcohol. In each approach, the CB1-receptor blocker (Rimonabant) reduced drinking. Pending results of the clinical trials, Rimonabant could become an important addition to our currently limited arsenal of effective treatments for alcoholism. We have identified another 16 compounds that are potential candidates for further development.

Our research also can help us isolate the biological mechanisms that underlie alcohol's apparent beneficial effects. Since we don't yet have clinically useful biomarkers that tell us who can benefit from moderate alcohol use and who is at risk of alcohol-related problems, and because alcohol carries with it so many well-documented risks, a recommendation to drink moderately for those who do not drink would be irresponsible at this point. If we can isolate the mechanisms that underlie whatever benefits alcohol might have, we have a chance of designing pharmaceuticals that mimic the actions of these mechanisms, but don't have alcohol's many deleterious effects.

BRAIN RESEARCH

Alcohol exerts its principal actions in the brain. It is here that heavy alcohol use results in brain-cell adaptations that lead to alcohol addiction. We're approaching this crucial area of brain research with our Integrative Neuroscience Initiative on Alcoholism (INIA). This initiative is extending beyond traditional models of collaboration to capture the potential of input from the many fields that necessarily contribute to alcohol research, including genetics, imaging, molecular biology, and behavior—each of which may use different methods and attach different significance to findings.

At the scientific level, INIA has provided its investigators with technologies and standardized animal models which ensure that the significance of findings from each field are placed in the context of alcohol research. INIA collaborations are occurring not only across fields of research, but also across universities and organizations, nationally and internationally.

More than that, INIA has created an operational structure that enables us to pursue the most productive research, relatively unencumbered by inflexible funding mechanisms. INIA's funding strategy allows us to pursue productive investigations

as they emerge, to continue them, and to discontinue those that prove to be less promising or have reached their potential. In short, INIA has removed roadblocks to progress. This is enabling us to identify the structure and function of neural circuits, networks of brain cells that work in concert as intermediaries of alcohol's behavioral outcomes.

Molecular imaging techniques are permitting INIA investigators to link alcohol-induced molecular responses with behaviors, in real time. Through computational biology, INIA researchers are creating models that predict how different brain structures and functions will respond to alcohol under different scenarios. This kind of research can help us determine optimal points for therapeutic intervention. A recent expansion of INIA will enable us to conduct translational research, to test whether neurobiological changes that occur in our animal models of alcohol-related behavior also occur in humans.

UNDER-AGE DRINKING

Drinking by children and adolescents is a concern reflected not only in our research, but also in parents and the media. Young brains are still forming nerve-cell connections, and they appear to be more sensitive to the deleterious effects of alcohol. Researchers are investigating how alcohol affects this and other processes in the developing brain, and for how long. Early indications are that adolescents who have gone through alcohol addiction and withdrawal risk long-term deficits in learning ability and memory. Research also shows that people who begin drinking at young ages are much more likely than those who begin later to become alcoholic at a later point in life.

Children and adolescents also are still developing decision-making capabilities, so important in formulating responses to environmental influences, such as peer pressure, that are powerful contributors to their choices about drinking. Almost 30 percent of 9th–12th graders surveyed report that they have had five drinks in a row at least once in the previous month.²

An important question in alcohol research is how different drinking patterns affect risk of developing alcohol-related problems. Heavy, episodic drinking (sometimes referred to as “binge drinking”) appears to be popular among some youth—notably college students, as newspaper headlines frequently attest. A study widely publicized in the media last year estimated that 1,400 college students die each year from alcohol-related causes and that 500,000 are injured.³

In addition to our investigator-initiated research in this area, we have formed the Task Force on College Drinking, a collaboration between college presidents and scientists. The Task Force has released recommendations on prevention strategies, literature for various audiences, and a website, and has organized regional workshops. The Institute recently issued a research announcement calling for scientists with expertise in underage drinking to form rapid-response partnerships with colleges that request help. Episodic heavy drinking of alcohol has been ritualized and is an accepted part of life at certain celebratory events in our society, not only among youth, but also among adults. Among the questions we're asking are: How does this kind of drinking practice become ritualized in our society in spite of its deleterious consequences? How can we change the culture that leads to it?

Meanwhile, our initiative on the biological mechanisms of adolescent alcohol abuse is using imaging techniques that correlate brain structure with function and behaviors, in addition to other techniques, to reveal how alcohol affects specific brain areas, in human and nonhuman primate and rodent animal model studies. We're also asking how developmental and environmental factors and the interplay between genes and environment affect youths' choices to drink and their physical and behavioral responses to alcohol.

PREVENTION AND RISK REDUCTION

Alcohol prevention research is aimed at reducing the causes and consequences of alcohol abuse and alcoholism. For example, whether the relationship between early onset of drinking and subsequent alcoholism is one of cause and effect or the result of factors that predispose people to both those behaviors, and others, is unclear. Our investigators are studying this issue, and their findings will help us understand why people become alcoholic. Meanwhile, preventing youth from drinking and reducing

²Centers for Disease Control and Prevention, *Youth Risk Behavior Survey*. <http://www.cdc.gov/nccdphp/dash/yrbbs/2001/youth01online.htm>

³Hingson, R.W.; Heeren, T.; Zakocs, R.C.; Kopstein, A.; Wechsler, H. *Magnitude of alcohol-related mortality and morbidity among U.S. college students ages 18–24*. *Journal of Studies on Alcohol*, 63(2):136–144, 2002. (164269)

the harm it causes are essential, not only because early onset drinking predicts subsequent alcoholism, but also because of the immediate harm that alcohol misuse can cause injury, violence, early introduction into the criminal justice system, legal repercussions, derailed scholastic careers, and death, to name a few.

We are conducting studies that develop and test strategies to prevent drinking by youth of different ages and backgrounds. Particularly important among these are longitudinal studies that can tell us whether strategies that show promise among a given subgroup of youth, such as rural adolescents, are successful or can be adapted for others, such as urban youth. These studies examine the impact of a number of factors, such as school programs, parental and family influence, peer influence, alcohol advertisements, and community policies and practices.

Prevention research at NIAAA also focuses on the general population and segments with unique needs. Among them are pregnant women (and their unborn children, who are at risk of fetal alcohol syndrome) and the elderly, who may be prone to depression and dangerous interactions between alcohol and prescription drugs. One of our initiatives is determining if community-based approaches successful in preventing alcohol-use disorders in the short-term can result in long-term prevention at different life stages.

OUTREACH

Public and private partnerships are helping us send our prevention messages to the community. The Leadership to Keep Children Alcohol-Free, a prevention campaign in which the Robert Wood Johnson Foundation has joined us, has recruited 33 governors' spouses to act as spokespersons.

Other partners in our efforts to prevent under-age drinking include the National Highway Traffic Safety Administration, the Department of Justice, the Department of Education, and the Substance Abuse and Mental Health Services Administration. Our outreach efforts also target clinicians, including physician groups such as the National Hispanic Medical Association, and the National Medical Association, that serve special populations. A science-to-service program provides clinicians with information about current research, and links them with scientists who advise them on specific areas of practice, at the clinician's request. We work with States to engage their treatment providers and administrators. After exchanging information about our current research findings and the practitioners' obstacles to providing treatment, we place experts in temporary residencies in treatment programs that have identified specific areas of need. Medical schools generally aren't thorough in their coverage of alcohol-related problems, and we have produced a physician's guide to help fill the gap. Through these efforts, we promote the practical application of our research where it's most needed.

PREPARED STATEMENT OF DR. DONALD A. B. LINDBERG

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Library of Medicine (NLM) for fiscal year 2004, a sum of \$316,040,000, which reflects an increase of \$9,334,000 over the fiscal year 2003 enacted level of \$306,706,000 comparable for transfers proposed in the President's request.

For more than 150 years one institution has been the nation's primary source of published medical information—your National Library of Medicine (NLM). Originally part of the Army, the Library became a civilian organization in the 1950s and a part of the NIH in the 1960s. Innovation in disseminating medical information has been a hallmark of the Library since the 19th century, including the first successful application of computers (40 years ago) to a large-scale bibliographic system. Today NLM not only maintains the world's largest collection of biomedical books and journals, but it has become, via the Web, a ubiquitous source of authoritative information for scientists, health professionals, and consumers around the world. Some half a billion searches of the various NLM databases are done each year.

The NLM in the 21st century is distinguished especially by two features unknown to it just two decades ago: the institution has become the leading source of human genome information and at the same time an important source of nontechnical health information for the public. The proximate source of the information that makes both these features possible is the National Institutes of Health. The NLM, through the Web operations of its National Center for Biotechnology Information, receives more than a quarter million visitors a day seeking molecular biology information ranging from DNA sequences and protein structures to the related research literature. On the other hand, the extensive health information issued by the var-

ious NIH institutes and centers forms the backbone of the MEDLINEplus information service offered to the general public.

An unusual aspect of the NLM's contemporary role is that there is a direct connection between the Library's research and information programs and the defense against bioterrorism and medical and public health preparedness for disaster management and terrorist attack. To cite a few examples: genomics research databases for targeted development of drugs, vaccines, and other forms of treatment for such diseases as smallpox, anthrax, plague, Ebola, and cholera; informatics R & D related to terrorism and disaster management; training for health professionals in the use of pertinent information resources; developing experimental information resources targeted at first responders; and improving the information infrastructure so that vital data can be shared during a crisis. As to post-9/11 information services, NLM quickly placed pages on its Web site about post-traumatic stress disorder, biological and chemical warfare agents, anthrax, and other information related to bioterrorism.

TOOLS FOR SCIENTISTS AND HEALTH PROFESSIONALS

In its role as the world's largest medical library, the National Library of Medicine continues to provide access to the enormous literature of the health sciences, including even priceless historical treasures dating to the 11th century. Most medical researchers and health professionals have, directly or indirectly, availed themselves of the Library's services some time in their career; there are those who access MEDLINE/PubMed (to take one popular example) almost daily. Another heavily used information resource is GenBank (with DNA sequence data).

MEDLINE is a database of 12 million references and abstracts to the world's medical literature published since the 1960s; PubMed is the Web-based retrieval system that makes this wealth of information freely and easily searchable to health professionals and others. MEDLINE/PubMed is an evolving system. The database expands at the rate of about half a million records a year. Several years ago NLM introduced links between MEDLINE references and publisher websites so users could retrieve the full text of articles. Today, more than 3,000 of the 4,600 publications indexed for MEDLINE have such links. Another element in the evolution of MEDLINE is converting information from the 1950s, MEDLINE form, so that valuable research data, on smallpox and tuberculosis to take just two pertinent examples, will be available to today's scientists. A recent improvement is a text version of PubMed for users who require special adaptive equipment to access the web. This has had the additional benefit of making the system much more friendly for those using hand-held devices.

GenBank, on the other hand, is accessed primarily by scientists—some 50,000 of them each day. It is a collection of all publicly available DNA sequences and is thus a key element in ensuring that the flood of data resulting from research around the world, including the Human Genome Project here at home, is available for further research and for further analysis and for gene discovery. GenBank is maintained by NLM's National Center for Biotechnology Information (NCBI) and now contains more than 15 million sequences and 29 billion base pairs from over 130,000 species. These are limited to chromosome maps, gene protein products, and other relevant genetic information for human and many smaller species.

An increasingly popular NCBI service for the scientist and health professional is PubMedCentral. This is a digital archive of life sciences journal literature under which publishers electronically submit peer-reviewed research articles, essays, and editorials to be included. NLM undertakes to guarantee free access to the material; copyright remains with the publisher or the author. Creating "digital archives" is an important NLM responsibility in this electronic age.

Electronic health data standards are also part of the information infrastructure of the 21st century. Such standards are needed for safe and effective health care, efficient clinical and health services research, and timely public health and bioterrorism surveillance. NLM plays an important role in HHS initiatives to promote standardization of electronic patient data by supporting the maintenance, distribution, and linking of key clinical terminologies within the Unified Medical Language System (UMLS) Metathesaurus. As a result, these clinical terminologies are available for use throughout the United States in clinical research databases, patient care, and public health surveillance. NLM is providing funding for the development, enhancement, and distribution of several clinically specific vocabularies. The UMLS Metathesaurus provides a common distribution vehicle for such vocabularies and a mechanism for linking them to HIPAA-mandated administrative code sets, basic research vocabularies, and thesauri designed to index the scientific literature. In addition, pilot projects for testing the use of the vocabulary in different settings will be

critical for maximizing the benefit of electronic health data standards for improving patient safety, reducing costs, and enhancing effective information exchange to combat bioterrorism.

INFORMATION SERVICES FOR THE PUBLIC

Since 1998, NLM has expanded its mission beyond serving health professionals and researchers to encompass providing high quality electronic health information services for the public. To serve this audience, the Library developed a new information resource, MEDLINEplus, a Web-based service that provides integrated access to the high quality consumer health information produced by NIH and HHS components and other reputable organizations. About 1.8 million unique visitors obtained health information from MEDLINEplus in January 2003. The main features of MEDLINEplus: 600 "health topics," from Abdominal Pain to Yeast Infections, consumer-friendly information about thousands of prescription and over-the-counter drugs, an illustrated medical encyclopedia and medical dictionaries, directories of hospitals and health professionals, a daily health news feed from the major print media, 150 interactive and simply presented tutorials (with audio and video) about diseases and medical procedures, and connections from the health topics to current clinical trials.

Like MEDLINE, MEDLINEplus is a constantly evolving system. Links are checked daily and new health topics added weekly. A completely Spanish-language version of MEDLINEplus was introduced in 2002 and is receiving heavy use. Early in 2003 a prototype "MEDLINEplus Go Local" system was introduced in North Carolina, a joint effort of the University of North Carolina and the NLM. This system allows MEDLINEplus users access to "NC Health Info," which contains links to local, county, and state health services in North Carolina and, conversely, users of NC Health Info can link into the detailed, authoritative health information about particular diseases and conditions in MEDLINEplus.

The NLM casts a wide net in creating and promoting MEDLINEplus, working closely with the Public Library Association and other organizations not associated with NLM's mission, as well as with the 4,700 member institutions of the National Network of Libraries of Medicine. Network librarians not only assist in identifying and evaluating information to be included in MEDLINEplus, but are of tremendous help in demonstrating MEDLINEplus locally and publicizing it.

Another major consumer information resource, ClinicalTrials.gov, was developed by the NLM on behalf of the entire NIH in response to a mandate from Congress. The database provides patients and families access to information about clinical trials and opportunities to participate in the evaluation of new treatments. The site was launched in February 2000 and currently contains approximately 7,200 clinical studies sponsored by NIH, other Federal agencies, and the pharmaceutical industry.

NLM RESEARCH AND DEVELOPMENT PROGRAMS

The Library is at the cutting edge of research and development in medical informatics—the intersection of computer technology and the health sciences. NLM has a program of grants and contracts to university-based researchers and also a cadre of in-house scientists in the Lister Hill National Center for Biomedical Communications and the National Center for Biotechnology Information. The Lister Hill Center sponsors many exciting communications research projects, such as those in telemedicine and the Visible Human Project. The NLM-supported "A Clinic in Every Home" is an especially promising telemedicine project for medically underserved rural Iowa residents to provide them with access to high quality health care. The expectation is that this system will both raise the quality of health care and lower costs. Another Lister Hill Center program is the initiative to fund projects that demonstrate the medical community's technical needs in using high-speed communications networks for critical healthcare applications, including computing in support of disaster management.

The Visible Human Project comprises two enormous data sets, male and female, of anatomical MRI, CT, and photographic cryosection images. These data sets, licensed to more than 1,700 individuals and institutions in 43 countries, are being used in a wide range of educational, diagnostic, treatment planning, virtual reality, artistic, mathematical, and industrial applications. Projects run the gamut from teaching anatomy to practicing endoscopic procedures to rehearsing surgery. NLM's AnatLine is a web-based image delivery system that provides retrieval access (even from a home computer) to large anatomical image files of various parts of the Visible Human male thoracic region, such as the heart and stomach, including 3D images.

The other major NLM component involved in R & D is the National Center for Biotechnology Information, noted above as the source of the GenBank database of DNA sequence information. NCBI is more than just assembler of genomic data, however. NCBI investigators have developed sophisticated computational tools such as the BLAST suite of programs that makes it dramatically easier for researchers to scan huge sequence databases for similarities, and to evaluate the resulting matches. Another NCBI product, Entrez, is an integrated database that allows users to easily and quickly search enormous amounts of sequence and literature information. The newest tool is the "Reference Sequence Collection" that is serving as a foundation for genomic research by providing a centralized, integrated, non-redundant set of sequences, including genomic DNA, transcript (RNA), and proteome (protein product) sequences, integrated with other vital information for all major research organisms. As genomic sequence data continues to accumulate and be made available in ingenious ways through the web, we can expect discoveries that promise future medical breakthroughs.

NLM extramural programs have an important role in supporting R & D in bio-communications. One timely example is the early warning public health surveillance system developed at the University of Pittsburgh and recently demonstrated to the President. NLM's grant program also is a key supporter of NIH's "Biomedical Information Science and Technology Initiative." The Library has expanded its support from 12 to 18 training programs at universities across the nation to train experts to carry out research in general informatics and in bioinformatics. The NLM has recently augmented each of the training programs with a "BISTI supplement" and has also funded two planning grants that will eventually lead to the development of what are called National Programs of Excellence in Biomedical Computing.

SERVING SPECIAL COMMUNITIES

The NLM has been working with the National Institute on Aging to create NIHSeniorHealth.gov. Accessible from MEDLINEplus, the new site contains information in a format that is especially usable by senior citizens. At present NIHSeniorHealth.gov contains information on topics like Alzheimer's and exercise for older adults, but it will soon be expanded to include more topics of special interest to seniors as other NIH institutes contribute to it. NLM is working on adapting special software that would allow the visually impaired to exercise control and hear Web pages read to them. This would also be a boon to some senior citizens.

The National Network of Libraries of Medicine, noted above in connection with MEDLINEplus, places a special emphasis on outreach to underserved populations in an effort to reduce health disparities. For example, there are programs to assist in remedying the disparity in health opportunities experienced by such segments of the American population as African Americans, Latinos, Native Americans, senior citizens, and rural populations. One of the NN/LM outreach efforts involves a tele-medicine "connections" program for Native Americans in the Pacific Northwest conducted through the Regional Medical Library at the University of Washington.

Another highly successful NLM outreach program has been strengthening Historically Black Colleges and Universities so that they can train people to use information resources in dealing with environmental and chemical hazards. Under this program, faculty and students in more than 80 minority institutions have received such training. Through these schools, NLM is working to promote high-quality Internet connectivity and using technology for research and education.

There are other NLM programs targeting groups of citizens with special health information needs. In the past several years, the Library has made more than 50 awards to continue its HIV/AIDS-related outreach efforts to community-based organizations, patient advocacy groups, faith-based organizations, departments of health, and libraries. This program supports local programs to improve information access for AIDS patients, the affected community, and caregivers. Emphasis is on providing information in a way meaningful to the target community, and may include training in information retrieval, sending interlibrary loans, and providing Internet access.

NLM's efforts to reach special populations in need are not limited to the United States. An international partnership in which the NLM is a key player is the Multilateral Initiative on Malaria. NLM's mandate as leader of the Communications Working Group has been to leverage partnerships (at 13 installations) to create a malaria research network in Africa, enabling scientists there to have full access to the Internet and the Web as well as access to medical literature. The aim is to allow researchers, any time of the day or night, to have instantaneous Internet access that will enable them to send and receive e-mails, search for literature, interrogate data-

bases, share files and images with colleagues, and generally move to a new and more efficient way of doing collaborative research.

FUTURE PROSPECTS

NLM is responsible for acquiring, indexing, cataloging, and preserving the world's biomedical literature—in all languages and media—and for providing reference and research assistance and document delivery from this comprehensive collection. NLM also collects, processes and distributes genome sequence data through NCBI. Both of these core areas are experiencing unprecedented growth. The cost of purchasing the biomedical literature typically increases about 10 percent per year, irrespective of general inflation, and the move to electronic publishing has not diminished this rate of increase. NLM uses advanced technology to improve the efficiency of its basic operations, and contractors currently perform the majority of activities required to provide NLM's basic services.

PREPARED STATEMENT OF DR. KENNETH OLDEN

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget for the National Institute of Environmental Health Sciences (NIEHS). The fiscal year 2004 budget includes \$630,774,000, an increase of \$17,358,000 over the fiscal year 2003 enacted level of \$613,416,000 comparable for transfers proposed in the President's request.

INTRODUCTION

Voluminous literature derived from epidemiological studies as well as human and animal experiments has shown that environmental factors play an important role in human health and disease. That is, most complex diseases arise from the interplay between genetics, environment and behavior. However, understanding of these interactions has remained grossly descriptive and the molecular mechanisms elusive. But, thanks to the rare confluence of technology breakthroughs in genomics and proteomics and the rethinking and redirection of the environmental health sciences over the past decade, the link between the environment and human health and disease can now be investigated with more rigor and specificity. For example, the sequencing of the human genome and the development of high throughput technologies to monitor the expression of genes and proteins in response to specific environmental exposures has created an unparalleled opportunity to study gene-environment interactions.

NEW INITIATIVES

Breast Cancer and Environment Research Centers.—There is surprisingly little information on the development of the normal breast. The lack of knowledge about the biological and molecular mechanisms involved in normal breast development hinders our ability to identify environmental triggers of breast cancer. How can we identify early adverse changes in breast tissue if it is not known how the tissue normally develops? To fill this research gap, NIEHS is funding a consortium centers program that will provide new information on the normal growth and development of the breast and reproductive systems, evaluate the impact of environmental exposures on the breast, and explore potential times of increased sensitivity and vulnerability of breast tissue to environmental effects. These centers represent a collaborative effort with the National Cancer Institute.

NIEHS is also continuing the effort to establish a cohort of unaffected sisters of breast cancer cases to clarify the gene-environment interactions in this disease. This cohort can be used to examine breast cancer risk in relation to factors such as endogenous hormones, growth factors and environmental contaminants, and to study these factors jointly with genes to elucidate genetic modifiers of response.

Toxicogenomics.—NIEHS developed the National Center for Toxicogenomics (NCT) to coordinate a nationwide research effort for the development of a toxicogenomics knowledge base. Toxicogenomics is a new discipline that studies how genes respond to environmental stressors or toxicants. It combines genetics (genomic-scale mRNA expression), proteomics (cell and tissue-wide protein expression), metabolomics (metabolite production) and bioinformatics with conventional toxicology to investigate the role of gene-environment interactions in health and disease. New molecular technologies, such as DNA microarray analysis and protein chips, can be used to measure the expression of thousands of genes and proteins, providing the potential to accelerate discovery of toxicant pathways and specific chemical and drug targets.

When a person is exposed to a chemical, cells in the body may respond by switching on some genes and switching off others. The on/off pattern of various genes is different for different chemicals, creating a characteristic pattern or "signature," which scientists hope will be useful in classifying chemicals and other stressors by their biological activity. This signature pattern would provide a means of predicting effects on human health from chemicals we currently know little about. Toxicogenomics seeks to use these signature gene expression patterns to go beyond the traditional toxicological tools of testing animals for adverse outcomes that might indicate toxicity.

One aim of the NCT is to create a Chemical Effects in Biological Systems (CEBS) Database. The CEBS database will contain data on global gene expression, protein expression, metabolite profiles, and associated chemical/stressor-induced effects in multiple species. With such information, it will be possible to derive functional pathways and network information based on cross-species homology. Once sufficient high quality data have been accumulated and assimilated, it will become possible to predict the toxicity of an unknown chemical by comparing its gene and/or protein expression profile to compendia of expression profiles in the database. As the field of toxicogenomics evolves, toxicogenomics databases will begin to support predictive toxicology and hazard assessment. This will help scientists predict the toxicologic impact of suspected toxicants and calculate how much of a hazard these toxicants actually represent to human and environmental health.

The pharmaceutical industry is making huge investments in this technology because of their interest in finding ways to speed up the process of toxicological assessment of new research and development products. Identifying molecular events that serve as precursors of adverse health outcomes early in the development process would eliminate much of the expense (estimated in the billions of dollars annually) associated with the development of new pharmaceutical products.

Susceptibility to Environmental Exposures.—Although reference is made to the human genome, the concept of a single genome is misleading. Each individual's genetic makeup, with the exception of identical twins, is unique. While the genomes of individuals are 99.9 percent identical, the 0.1 percent variation leaves considerable room for individual differences among the approximately three billion nucleotide base pairs that make up the human genome. However, it should be emphasized that genes are not the only factors that contribute to differences in susceptibility to environmental exposures; age or stage of development, behavior, and general health or nutritional status can have a spectacular influence. Both the genetic and age/stage of development-related aspects of susceptibility are being addressed by NIEHS.

Differences in susceptibility to environmental exposures had received little attention until NIEHS launched the Environmental Genome Project (EGP) and the Children's Environmental Health Research and Prevention Centers in 1998. There is now considerable evidence that hundreds of genes exist in the human genome that make some individuals more or less susceptible to the effects of pollutants or other environmental chemicals, contributing to everything from cancer to birth defects and Parkinson's Disease. The key objective of the EGP is to discover the alleles or genetic variants (called polymorphisms) that confer susceptibility or resistance.

The Children's Environmental Health Research and Prevention Centers were developed, in collaboration with the EPA, to explore the relationship between the timing of exposure, the stage of development and susceptibility. Because of the rapid rate of growth and development of major organ systems (e.g., the lung, brain, and heart), children are thought to be particularly vulnerable to environmental toxicants. They can be more vulnerable than adults to adverse health outcomes, and the consequences of these adverse effects are sustained throughout life, making the reduction of childhood exposures a critical component of environmental public policy.

We are also exploring the possibility of susceptibility studies in seniors. For a variety of reasons, older Americans are also more susceptible to environmental stress (e.g., the combination of poor air quality and extreme heat during the summer months). This important public health issue has received almost no attention, but dialogue is ongoing with the EPA and the National Institute on Aging about ways to include older Americans in more environmental health studies.

Parkinson's Disease Research Consortium.—NIEHS created a Parkinson's Disease Consortium Centers Research Program in 2002 because we believe that a collaborative, multidisciplinary, multi-institutional approach is required to elucidate the complex interactions between genes and environmental factors likely to be involved in the development of this devastating disease. Collectively, the three centers that make up the consortium have expertise in basic neurosciences, human genetics, clinical research, and epidemiology, and long-standing collaborative interactions with the various non-profit organizations that represent patient advocates. These sci-

entific disciplines were included in the consortium because a major impediment in Parkinson's Disease research has been that significant findings in one field were not readily disseminated among investigators in the other related fields. It is our intent to expand the Consortium Centers concept in 2004 to capture some of the outstanding activities not funded earlier.

The knowledge and technologies developed in the Institute's EGP, the Mouse Genome Centers, and the National Center for Toxicogenomics will also be made available to this cohort of investigators as they become available. For example, new Parkinson's Disease susceptibility genes and new environmental risk factors are likely to be discovered, and new mouse models of the disease are likely to be created using gene "knockout" and "knockin" technologies. These new resources will be invaluable to the Parkinson's Disease research community.

The Development of Multidisciplinary Research Teams and Novel Technologies.—The solution to complex problems often requires the collective knowledge and experience of multiple investigators and novel approaches developed at the boundary of several disciplines. While the individual investigator approach remains the cornerstone of innovation of science and technology development, translation often requires a team approach. In fact, lack of infrastructure to support the development of multidisciplinary research teams is hampering our ability to realize the benefits of the nation's expenditures for biomedical research. While the NIH has invested in infrastructure to build maps of the human genome and develop technologies for genotyping and monitoring gene and protein expression, it is the deployment of these data bases and technologies to prevent human illness that has proven to be the most challenging.

Also, the inadequacy of current analytical methods to investigate complex interactions involving genes, proteins and environmental factors has been a bottleneck in understanding the development of complex diseases resulting from such interactions. While high resolution structural analysis of proteins is critical for understanding molecular interactions between genes, or proteins and toxic chemicals, new technologies will be needed to determine how the latter disrupts structure and function of highly coordinated biological pathways or networks at the level of the cell and tissue. NIEHS has developed the Center Programs described here to catalyze the formation of multidisciplinary research teams to investigate gene-environment interactions using emerging expertise and technologies.

SUMMARY

The data generated by the studies I have described will allow for a more rational approach of gauging environmental threats, and will reduce the need to rely on default assumptions in extrapolating results from animal models to humans and in setting exposure limits. These studies will also lead to the development of high throughput technologies that could both accelerate and reduce the costs of toxicity testing of pharmaceuticals and environmental xenobiotics. This approach to understand how genes and the environment interact shifts the focus of disease management from symptom-based classification to biological causation and prevention. The objective is to provide a database that will allow for the use of precursors or molecular markers in assessment of disease states.

PREPARED STATEMENT OF DR. AUDREY S. PENN

Mr. Chairman and Members of the Committee, I am Audrey Penn, Acting Director of the National Institute of Neurological Disorders and Stroke (NINDS). I am pleased to present the President's budget request for NINDS for fiscal year 2004. The fiscal year 2004 budget includes \$1,469 million, an increase of \$13 million over the fiscal year 2003 enacted level of \$1,456 million comparable for transfers proposed in the President's request.

The mission of NINDS is to reduce the burden of neurological disorders, that is, the many diseases that affect the brain, spinal cord, muscles, and nerves of the body. Neurological disorders cause enormous suffering and loss of life, often defying the best efforts of modern medicine. However, we are making progress in prevention and in treatment, derived from continuing advances in fundamental scientific understanding of the nervous system, which enhance the prospects for the future. Today I will touch on these points and concentrate on what NINDS is doing to expedite progress.

THE BURDEN OF NEUROLOGICAL DISORDERS

Neurological disorders can compromise the complex thinking and emotions that make us human, the routine perception and movement that we take for granted, and even the control of bodily systems that are normally beneath our awareness. Diseases of the nervous system strike at every age. Some, such as stroke, chronic pain, epilepsy, and traumatic brain injury, are among the most common of all causes of death and disability. Hundreds of less common neurological disorders take an incalculable toll on patients and families too. Also demanding attention are substantial disparities in impact by ethnic group, gender, socioeconomic status, and geography.

PROGRESS AND PROSPECTS FOR THE FUTURE

Progress in preventing and treating neurological disorders has been notable. As Dr. Zerhouni has testified previously, this year alone almost a quarter of a million fewer deaths from stroke will occur in the United States than would have been expected without advances in prevention—progress that represents the cooperative efforts of many groups, public and private. Prevention of nervous system birth defects, such as spina bifida, and genetic counseling for inherited disorders, such as Tay-Sachs disease, are also having a major impact on public health. The first acute treatments for ischemic stroke and spinal cord injury—though still far from adequate—have proven effective for reducing neurological damage. Immune therapies now reduce relapses and slow the progression of disability in multiple sclerosis. Surgical options employ implantable devices to compensate for brain circuits unbalanced by disease in Parkinson's disease and epilepsy. Enzyme therapies have brought the first successes in treating lipid storage disorders. Advances in molecular genetics and brain imaging are further augmenting clinicians' insights to diagnose and to guide therapy.

Progress is gaining momentum, with an unprecedented variety of new treatment and prevention strategies under development: drugs to home in on the molecules that cause disease, stem cell therapies to replace lost nerve cells, neural prostheses to read control signals directly from the brain, immune tolerance approaches to prevent stroke, therapies to repair or replace defective genes, and behavioral interventions to encourage the latent "plasticity" of the brain and spinal cord toward self-repair. Each of these strategies relies upon remarkable advances in understanding how the normal nervous system works and what goes wrong in disease.

A few findings from the past year illustrate this progress: Scientists studying genes discovered a mutation that causes a form of Charcot-Marie-Tooth disorder, a common disabling disease of peripheral nerves; pinpointed the site of a gene contributing to autism; and found clues about how a chromosome defect causes facioscapulohumeral dystrophy, a common form of muscular dystrophy. In animal models of human disease, themselves often the product of gene research, gene therapies have yielded encouraging results for neurofibromatosis, Fabry disease and Parkinson's. Scientists on the trail of cell therapies discovered that primitive precursor cells in the adult rat brain can respond to experimental damage by multiplying, migrating to the site of damage, and making new nerve cells, and that transplanted embryonic stem cells show promise in animal models of Parkinson's disease, stroke, and other disorders. Scientists focusing on the immune system found that a strategy, which suppresses immune reactions, prevents strokes in hypertensive rats; that an anti-cholesterol drug, the statin Lipitor, reduces symptoms in an animal model of multiple sclerosis; and that the gene defect in Batten disease may result in unexpected immune reactions, which could contribute to the devastating consequences in the brain. In research on drug treatments, the antibiotic minocycline slowed progression of amyotrophic lateral sclerosis in mice; the natural brain chemical inosine stimulated rewiring of the brain following stroke in rats; and coenzyme Q10 may slow progression of Parkinson's disease. Scientists studying new technologies developed a device that enabled rats to control a robot arm just by thinking about it; devised better ways to deliver therapeutic agents to the brain; used microarrays to monitor the activity of thousands of genes, yielding insights about brain tumors and multiple sclerosis; and for the first time, recorded activity of the human fetal brain in response to light, which may lead to better prenatal diagnostics.

EXPEDITING PROGRESS

NINDS continues to rely on the insight and ingenuity of scientists and physicians throughout the nation to seek out scientific opportunities, propose research studies, and advise on promising ideas. Since Congress began the NIH budget doubling effort, the Institute has taken a more active role in directing research. Efforts are mo-

tivated by scientific opportunity, enabled by resources, guided by extensive and inclusive planning efforts, and quality-assured through peer review. Programs target specific diseases and cross-cutting opportunities to enhance the effectiveness of research. A few examples illustrate the wide range of activities:

The NIH Parkinson's Disease Research Agenda is the pacesetter for disease-focused NINDS activities. The Agenda began in January 2000 with a working group that included Parkinson's disease researchers, patient advocates, industry representatives, and NIH scientific staff. Follow-up meetings, most recently a July 2002 "summit" called by the NIH Director, have updated priorities to reflect the changing scientific landscape and to address roadblocks to progress. Since March 2000, the Parkinson's effort has included more than 20 solicitations, more than a dozen workshops, establishment of a network of Morris K. Udall Centers, major clinical trials, and funding of the Deep Brain Stimulation Consortium. The NINDS Office of Minority and Health Research is also leading a major effort to implement the NINDS Five Year Strategic Plan on Minority Health Disparities, and developing goals specific to neuroAIDS, stroke and epilepsy. Implementation of planning efforts in brain tumor, stroke, and epilepsy are also under way. Other initiatives are focusing on diseases such as autism, muscular dystrophy, and spinal muscular atrophy, and NINDS continues to support a variety of disease-focused scientific workshops to assess current understanding, stimulate research interest, and foster collaborations.

Re-engineering the research enterprise.—NINDS has designed and conducted pioneering clinical trials to test the safety and effectiveness of interventions to prevent and treat neurological disorders. In recent years, the Institute augmented clinical trials activities with new grant mechanisms for planning trials and for pilot trials; developed procedures and increased professional staff to optimize trial design and monitoring; and created a subcommittee of the NINDS Council to provide broad advice on priorities for clinical research, including trials. This year, NINDS is beginning to supplement ongoing clinical trials to capture genetic samples for a newly established DNA and cell line repository. For the future, the Institute is exploring options to create a network of physician-investigators to carry out clinical trials. Such a program might speed trials, minimize costs, enhance accessibility for patients, facilitate the recruitment of a diverse spectrum of participants, improve feasibility of trials for rare diseases, and accelerate the transfer of results to practice in community settings.

A highlight of the clinical trials program is an innovative trial of neuroprotective drugs for Parkinson's disease, that is, drugs which slow disease progression rather than just temporarily improving symptoms. The Institute reached out widely to academia and industry, here and abroad, for suggestions of possible drugs, and developed a rigorous evaluation process, which has selected the most promising drug candidates. A network of more than 40 clinical sites, with central statistical and data coordination, has been established to carry out the trial. NINDS is working closely with voluntary groups to recruit patients. The first pilot studies may begin this spring.

Translational research is another major focus of cross-cutting efforts. NINDS has a long history of translational research, which moves fundamental discoveries about the brain and disease toward therapies and clinical trials. Advances in neuroscience are yielding increasing opportunities for translation, and NINDS responded in July 2002 by launching a comprehensive program to foster translational research. Essential to this program are peer review criteria tailored to the needs of translational research, milestone driven funding, and training a cadre of investigators to carry out translational research. The goal is to provide an environment where coalitions of basic scientists and clinicians can design and carry out preclinical studies required to bring therapeutic candidates to the point where clinical studies can begin.

New pathways to discovery.—Several NINDS programs are exploring new avenues for discovery. NINDS has established a goal of identifying small molecules that are active in the nervous system and show promise as therapeutic candidates, diagnostic agents, or research tools. In 2002, the Institute established a consortium to test more than 1000 drugs, most previously approved by the U.S. Food and Drug Administration (FDA) for other conditions, against 29 rapid laboratory assays (tests) related to neurodegenerative diseases. The best candidate chemicals are moving to further testing in animal models through an NINDS supplement program. NINDS has also awarded a contract for a high throughput screening (HTS) center, and is soliciting proposals for the development of assays for HTS. HTS rapidly tests thousands of chemicals to find lead compounds for drug development. In another effort, a contract-based approach to therapeutics development for spinal muscular atrophy will test a new model that might apply to other diseases. The NIH Molecular Library Roadmap Project will speed the discovery process for drugs and chemical research tools by providing access to information databases and to potentially useful

compounds. The Institute has also established a facility to provide researchers access to microarray technology, which allows simultaneous monitoring of the activity of thousands of genes in health and disease. Stem cell research remains a high priority for the Institute. NINDS has provided supplements for grantees to pursue stem cell research, and joined with other components of NIH in stimulating this research and targeting aspects critical for the nervous system. An NINDS intramural investigator will lead a new NIH facility to characterize the available approved lines of human embryonic stem cells.

Research teams of the future.—Increasingly, progress against neurological disorders requires cooperation among multi-disciplinary teams of investigators. NINDS is enhancing the opportunities for team approaches with general programs to support common resources and specific initiatives tailored to areas such as Parkinson's disease, stroke, autism, muscular dystrophy, spinal cord injury and health disparities. The Institute is also addressing critical training needs in areas such as translational and clinical research. In the NIH Intramural program, the John Edward Porter Neuroscience Center will bring together scientists from ten NIH components that focus on the brain.

CONCLUSION

Neurological disorders have always challenged the best efforts of medicine. The intricacy of the brain is awesome, its workings are elusive, and an extraordinary variety of disorders affect the nervous system. Furthermore, the brain and spinal cord are difficult to access, sensitive to intervention, and reluctant to regenerate following damage. However, building on advances in basic science, progress is improving peoples' lives, and prospects for the future are even more encouraging. We are working to engage the best minds in the nation and provide them with the resources they need to devise ways to prevent, treat, or, ultimately, cure neurological disorders. Thank you.

PREPARED STATEMENT OF DR. RODERIC I. PETTIGREW

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Biomedical Imaging and Bioengineering (NIBIB). The fiscal year 2004 budget includes \$282,109,000, an increase of \$3,838,000 over the fiscal year 2003 enacted level of \$278,271,000 comparable for transfers proposed in the President's request.

The NIBIB's mission is to lead the development and application of breakthrough technologies in the physical and engineering sciences to facilitate an improved fundamental understanding of complex biological processes. This research agenda will dramatically advance the Nation's health care by improving the detection, management, understanding and, ultimately, the prevention of disease. Health care and technology have long been linked in the United States. Today, cardiac pacemakers, mammograms, sustained release medications, and artificial hips are but a few examples of how biomedical imaging and bioengineering are transforming health care.

In September 2002, I began my tenure as the first Director of the NIBIB. I assumed my role during a time when the landscape of conducting biomedical research is changing. It is this altered landscape, wherein the most efficacious medical advances depend on multidisciplinary findings obtained from researchers working together at the interface between the biological and quantitative sciences, that led to the creation of the NIBIB. This new environment, combined with recent budgetary increases, visionary predecessors, the rapid pace in technology development, and high-quality investigator-initiated research, has allowed the NIBIB—just in its second year of operation—to establish a strong research foundation on which to capitalize. To illustrate these points, my testimony will highlight recently achieved milestones, outline research plans and directions, and describe areas of progress and opportunity.

MILESTONES TO SUCCESS

The NIBIB, the newest Institute at the National Institutes of Health (NIH), was established by law December 29, 2000, and received its first appropriation and grant funding authority in fiscal year 2002, just 15 months ago. Since its establishment, NIBIB staff have achieved significant milestones. In fiscal year 2002 the NIBIB funded approximately 300 research applications, participated in approximately 170 extramural symposia, planned 16 NIH-based symposia and workshops, served as lead on 5 trans-NIH initiatives, and collaborated on 4 trans-NIH programs.

Additional milestones have been achieved in fiscal year 2003. In January, the NIBIB held the first meeting of its National Advisory Council. The Institute has also built a solid research infrastructure through the release of numerous basic and applied research solicitations in promising areas of scientific investigation, including tissue engineering, advanced biomaterials, image-guided interventions, low-cost medical imaging modalities, biosensor technology, and cellular and molecular imaging.

The NIBIB has successfully fostered extensive linkages and collaborations with other NIH Institutes and Centers, Federal agencies, academic institutions, private industry, and scientific societies. As examples, the NIBIB administers and participates in the Bioengineering Consortium (BECON), an NIH-wide consortium dedicated to promoting and coordinating bioengineering research across the NIH. The NIBIB and the National Science Foundation are collaborating with the National Academy of Engineering—a private, independent, nonprofit institution—on a project entitled “Engineering and the Health Care System.” This study focuses on ways to harness advances in engineering applications to improve health care delivery. The NIBIB will collaborate with the National Institute of Diabetes and Digestive and Kidney Diseases to develop a program for monitoring pancreatic insulin cell failure in diabetes. This would constitute a significant advance in diabetes research.

THE NIBIB RESEARCH PORTFOLIO

In December 2002, the NIBIB officially launched its strategic planning process with an interactive workshop entitled “Future Research Directions.” This workshop helped identify high-priority research focus areas and associated high-impact projects and technologies that could contribute significantly to biomedical research and global healthcare needs. Areas identified as highly relevant to NIBIB’s mission include image-guided interventions, cellular and molecular imaging, computational biology, biosensor technologies, optical imaging technologies, and regenerative medicine. The Institute is now poised to realize the promise within these areas of opportunity.

ADVANCED TECHNOLOGIES

Biomedical imaging and bioengineering are interdisciplinary fields that require collaborations not only among imagers and engineers, but also with biologists, chemists, mathematicians, computer scientists, and clinicians of all specialties. Today, the imaging and engineering sciences are essential for improved understanding of biological systems, detecting and controlling disease, and enhancing human health. Recent advances in these fields have enabled the diagnosis and treatment of various diseases using increasingly less invasive procedures. Benefits associated with minimally invasive imaging applications include quicker and more accurate diagnoses leading to improved patient outcomes at reduced costs. Minimally invasive image-guided interventions now serve as powerful tools in the operating room and can be applied to surgical procedures in urology, oncology, neurosurgery, ophthalmology, cardiology, and orthopedics. However, these techniques are in relatively early stages of development. A goal of the NIBIB is to further establish and validate minimally invasive image-guided therapies as standards for patient care and to support additional research in therapeutic areas where minimally invasive technologies do not yet exist. The NIBIB also has initiatives underway to encourage investigator-initiated research for tracking anatomical targets and instruments and for developing steerable devices, including catheters, endoscopes, and needles. A goal is to develop these techniques so that they may be used to routinely identify disease at its earliest stages, even before symptoms arise. At that point, treatments can be instituted to cure the disease or preempt any serious consequences.

The combination of image-guided therapies with genomics and proteomics, has given researchers the capacity to develop new molecular probes and targets for disease detection, and to immediately direct treatment to the diseased site. By studying how a person’s genetic blueprint is expressed through proteins, and how these proteins differ in healthy and diseased cells, researchers will be able to develop therapies tailor-made for an individual. As a first step towards “personalized medicine,” NIBIB researchers are investigating tiny “barcoded” metal particles as a method for analyzing proteomes—the complete set of an organism’s proteins. Advances in miniaturized devices not only have the potential to identify and characterize new proteins, but to advance the rapid screening of multiple compounds in the drug development process.

Molecular imaging provides a way to monitor cellular activities in normal and diseased states. The development of novel imaging technologies, combined with new or enhanced probes that bind to defined cellular targets, will allow this technique to

be more broadly applied to biomolecules that are known indicators of a diseased state, such as an enzyme that may be overexpressed in a specific tumor. For example, NIBIB researchers have developed artificial fluorescent agents, called quantum dots, that glow and act as cell markers when bound to certain cancer cells. Further testing of these agents in animal models of cancer will determine their utility as effective imaging agents for the early detection of cancer in humans.

BIOINFORMATICS AND COMPUTATIONAL BIOLOGY

Advances in bioinformatics and computational biology have been identified as one of the areas of greatest need, and one of the areas having the greatest potential for positive impact on the universe of medical science and health care. In recognition of the critical role these disciplines play in biomedical imaging and bioengineering, NIBIB supports fundamental research in computing technology, the targeted development and application of new biocomputing tools, and technologies that provide structural and functional data at the cellular level. Areas of NIBIB interest include the development of high performance computing and visualization methods applicable to the modeling of biological systems, the utilization of medical imaging data in computational modeling of biological systems and human physiology, the development of algorithms and software for the manipulation and analysis of imaging data, and computer modeling of tissue mechanics. Our goal is to advance an understanding of the integrated function of biological systems through the development and application of computational models, and to apply these models to the design of novel treatments and therapeutics. In support of this goal, a NIBIB researcher is developing a brain-computer interface (BCI) system that acquires and analyzes brain signals to create a communications channel directly between a person's brain and a computer. BCI technologies can allow people who are completely paralyzed to express wishes to caregivers and to use computer programs.

NANOTECHNOLOGY: SENSORS FOR MEDICINE

The term nanotechnology is used to describe many types of research at the atomic, molecular, or macromolecular level-research where the characteristic dimensions are less than one-thousandth of the diameter of a human hair. Biosensors are nanoscale devices that detect, monitor, and transmit information about a physiological change, or about the presence of various chemicals, gases, or biological materials (bacteria and viruses). Laboratory diagnostics used in hematology, clinical chemistry, pathology, and microbiology already employ sensor technologies to perform simultaneous measurements for hundreds, maybe thousands, of substances in urine, blood, saliva, sweat, and interstitial fluids. The NIBIB has an active research program in sensor technologies and is expanding this area of research.

Knowledge gained through NIBIB-supported advances in nanotechnology, particularly in the areas of biosensors and molecular imaging, will be further leveraged for the development of sensors that can be applied to other critical research areas. For example, NIBIB researchers are adapting highly sensitive and selective biosensor arrays to provide a fingerprint for the identification of harmful bacteria and environmental health hazards. Future NIBIB efforts being planned in nanotechnology and sensors focus on the development of low-cost, miniaturized, integrated sampling detector systems for field use, including the development of systems that provide "detect-to-warn" capabilities, and that enable the rapid and accurate verification of exposure to harmful environmental agents.

MULTIDISCIPLINARY RESEARCH TEAMS OF THE FUTURE

The era of the solo independent investigator is passing. Our research culture must be redirected to the formation of teams that span academic departments and scientific disciplines. Their formation is critical to the development and validation of new technologies to aid in disease detection, treatment, and prevention. Therefore, a major goal of the NIBIB is to catalyze team science through initiatives that encourage multi-organizational and multidisciplinary teams. Programs differ from traditional NIH opportunities as they require collaborative efforts between quantitative and biomedical researchers. These will support institutional needs, infrastructure development, and the costs associated with making team science viable and attractive to academic institutions. Within a given area, specific clinical problems-such as our current effort to image pancreatic beta cell function in diabetes-will be identified to serve as a catalyst to drive the formation of the research team. The value in catalyzing team science lies not only in strengthening research capacity, but in fostering the formation of research teams among disciplines where they previously have not naturally formed.

In conclusion, the NIBIB is dedicated to promoting the development of emerging technologies and establishing opportunities that will encourage the necessary interdisciplinary collaborations to advance biomedical and global health care priorities. I would be pleased to respond to any questions that the Committee may have.

PREPARED STATEMENT OF DR. JOHN RUFFIN

Mr. Chairman and members of the Committee: I am pleased to present the President's budget request for the National Center on Minority Health and Health Disparities (NCMHD) for fiscal year 2004, a sum of \$192,724,000, which represents an increase of \$7,010,000 over the comparable fiscal year 2003 appropriation.

Despite improvements in the overall health of the general population, over the past decade, African Americans, Hispanics, American Indians, Alaska Natives, and Asians and Pacific Islanders the fastest growing communities in this country and the urban and rural poor, continue to suffer an unequal burden of death, disability, and disease.

With the goal of addressing health disparities through science, the Congress enacted Public Law 106-525, the Minority Health and Health Disparities Research and Education Act of 2000, to establish the NCMHD. The mission of the Center is to promote minority health and to lead, coordinate, support, and assess the National Institutes of Health's (NIH) effort to ultimately eliminate health disparities. I am grateful to the Congress for its wisdom in creating the NCMHD so that America can be more responsive to its increasingly diverse and complex health and human services needs. And, I thank you for your ongoing support of the Center. I also want to thank Dr. Elias Zerhouni, Director of the NIH, and the Directors of the NIH Institutes and Centers (ICs) and Offices for all of their cooperation and continued commitment to making the elimination of health disparities a top priority for the NIH.

In January 2003, the NCMHD celebrated its second anniversary. The staff at the NCMHD has been diligent, working hard to make the priorities envisioned for the Center by the Congress a reality. Today, I am happy to report to you the highlights of our accomplishments.

TRANS-NIH STRATEGIC PLAN AND BUDGET

The NCMHD has worked together with the Director of the NIH and the Directors of the other ICs at the NIH, to develop the first comprehensive *NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities*. This Plan, which was developed with substantial stakeholder input from the health disparities populations, has three main goals—research, research infrastructure, and community outreach through information dissemination and public health education. This is an evolving document, that will be updated each year, and it includes current NIH activities and future plans to: address the health disparities; build a culturally competent cadre of biomedical and behavioral investigators; and increase the number of minority clinical and basic medical scientists who are essential to the success of our efforts. The Plan will be posted for public comment on the NCMHD website at www.ncmhd.nih.gov.

NIH FISCAL YEAR 2001 ANNUAL REPORT ON HEALTH DISPARITIES RESEARCH

The NCMHD also collaborated with the other ICs to develop the *NIH fiscal year 2001 Annual Report on Health Disparities Research*, which highlights the NIH's activities, and describes the progress emanating from the NIH's research strategies, structures, processes, and programs to ultimately reduce and ultimately eliminate health disparities.

NCMHD PROGRAMS

As authorized by the Congress, the NCMHD has established its three core programs, which have been successfully launched with substantial assistance from the other NIH ICs. The Centers of Excellence in Partnership for Community Outreach, Research on Health Disparities, and Training (Project EXPORT) Program supports the conduct of research, research training, and community outreach activities in the field of health disparities at Centers of Excellence. The Research Endowment Program is designed to build minority health and other health disparities research capacity at Health Resources and Services Administration (HRSA) Section 736 Centers of Excellence. The NCMHD has established two distinct extramural Loan Repayment Programs to increase the participation of health professionals in health disparities research and to increase the participation of individuals from disadvantaged backgrounds in clinical research. The Center also administers the Research

Infrastructure in Minority Institutions (RIMI) Program to provide support for institutions that enroll a number of students from minority health disparity populations to develop and enhance their capacity and competitiveness to conduct biomedical or behavioral research. By expanding the infrastructure of institutions committed to health disparities research and supporting the education and training of racial and ethnic minorities, as well as the medically underserved, these programs will provide sustained effort aimed at eradicating health disparities.

NCMHD CO-FUNDED RESEARCH

The NCMHD also supports research through collaborative agreements with other NIH ICs and HHS agencies, for example the: *Racial and Ethnic Approaches to Community Health Program (REACH 2010)* at the Centers for Disease Prevention and Control (CDC); *Excellence Centers to Eliminate Ethnic/Racial Disparities Program (EXCEED)* at the Agency for Healthcare Research and Quality; *Jackson Heart Study* at the National Heart, Lung and Blood Institute (NHLBI); *Appalachia Cancer Network and Native Hawaiian Cancer Awareness Research & Training Network* at the National Cancer Institute (NCI); *National Latino and Asian American Study* at the National Institute of Mental Health, and *Tribal Epidemiology Centers Program* at the Indian Health Service.

Through these and many other co-funded projects the NCMHD works to: pilot new health disparities programs; improve recruitment and retention of racial and ethnic minorities in clinical trials; and provide competitive supplements to expand the focus of existing research programs.

NIH HEALTH DISPARITIES RESEARCH

Along with the NCMHD, all of the ICs at the NIH actively support health disparities research within their categorical missions. Let me provide a few illustrative examples:

The NHLBI supports the Jackson Heart Study, co-sponsored with the NCMHD, to address the cardiovascular health of African Americans; the Strong Heart Study, directed at cardiovascular disease risk factors and development in American Indians; the Multi-Ethnic Study of Atherosclerosis, which is examining the development and progression of subclinical disease in a multi-ethnic and predominately minority population; the Family Blood Pressure Program, which is identifying major genes associated with high blood pressure in a predominately African American population; studies aimed at identifying genetic and other biological factors that increase susceptibility to hypertension-related injury and damage; and programs examining genetic factors associated with asthma in minority populations.

To lead the NCI's efforts to examine the causes of cancer health disparities, develop effective and sustainable interventions to eliminate them, and actively facilitate their implementation across the cancer continuum, the NCI established the Center to Reduce Cancer Health Disparities. Among the NCI's other major initiatives are the expansion of public, private, academic, and community-based partners to increase enrollment of minorities in clinical treatment and prevention trials and to investigate the socioeconomic, cultural, health system related, and other causes of disparities in cervical cancer mortality. The NCI also has established interdisciplinary research Centers for Population Health and Health Disparities to better understand the interaction of determinants of cancer and the behavioral and biologic factors that contribute to them, and the Institute has expanded and improved the efficiency and utility of the Surveillance Epidemiology End Results Program on several fronts.

The National Institute of Allergy and Infectious Diseases (NIAID) continues to focus on those research areas that have a major impact on health disparities by supporting: the Innovation Grant Program, which fosters exploratory investigator-initiated HIV vaccine research at the early stages of concept development; the Legacy Donor Registry Project, which supports efforts to increase organ donation in minority populations; Genetic studies in African-American kidney transplant recipients regarding tissue (organ) rejection; Autoimmunity Centers of Excellence, which evaluate immunotherapies for Systemic Lupus Erythematosus (SLE) and Scleroderma; the Inner City Asthma Consortium, which evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in minority children in inner city dwellings; and Hepatitis C Cooperative Research Centers, which study factors that contribute to resistance to treatment in African Americans and disease outcome in Alaska Natives and Hispanics.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has established its Office of Minority Health Research Coordination to help implement its strategic plan for health disparities. The Institute places high priority on

supporting studies of many diseases, including type 2 diabetes, hepatitis C, and kidney disease, which disproportionately impact the health of minority populations. Recently the Diabetes Prevention Program showed that modest improvements in diet and exercise could dramatically decrease the incidence of type 2 diabetes in those at risk, the benefits of which extend to all racial and ethnic groups. American Indian and Alaska Native communities have the highest rates of diabetes in the world. Using the network of Tribal Colleges and Universities, the NIDDK Diabetes-Based Science Education in Tribal Schools Program is developing supplemental curricula for Tribal elementary, middle and high schools to instruct students about lifestyle changes that can dramatically reduce the risk of diabetes. The NIDDK also has initiated the National Kidney Disease Education Program, initially targeting cities with African-American populations showing high incidence of chronic kidney disease.

Since the National Institute of Child Health and Human Development (NICHD) launched its national "Back to Sleep" campaign in 1994, the Sudden Infant Death Syndrome (SIDS) rate has fallen by more than 50 percent. Even though the death rates from SIDS have declined at about the same rate for White and African-American infants, a disproportionate number of African-American infants are still lost to SIDS. To begin closing this gap, the NICHD enlisted the help of the Alpha Kappa Alpha sorority, the National Coalition of 100 Black Women, and the Women in the NAACP to conduct a series of "summit" meetings in three U.S. cities with high rates of African-American SIDS deaths. These summits will help develop strategies and create an infrastructure for establishing community-based programs to further reduce SIDS among African-American infants. The NICHD also is developing outreach activities and products that encourage American Indian/Native American communities to place babies on their back to sleep.

CONCLUSION

The NCMHD is working together with the other ICs at the NIH to ensure that all Americans have an opportunity to lead long, healthy, and productive lives. I am grateful to the Congress for giving the Center a unique opportunity to bring together the expertise of health professionals, researchers, businesses, communities, academia, public health agencies, and government to eliminate health disparities. It's going to take all of us working together to build a healthy America.

PREPARED STATEMENT OF DR. PAUL A. SIEVING

Mr. Chairman and members of the Committee: I am pleased to present the President's budget request for the National Eye Institute (NEI) for fiscal year 2004. This budget includes \$648 million, an increase of \$16 million over the fiscal year 2003 enacted level of \$632 million comparable for transfers proposed in the President's request.

It is my privilege to be here as the Director of the NEI and tell you about progress laboratory and clinical scientists are making in combating blindness and visual impairment and about the unique opportunities that exist in the field of vision research.

GLAUCOMA RESEARCH

Glaucoma leads to blindness from damage to the optic nerve of the eye. Glaucoma is often, but not always, associated with increased pressure within the eye caused by inadequate drainage of aqueous humor, the fluid within the eye that nourishes the cornea and lens. Results from two important clinical trials were reported during this past year. Investigators conducting the Ocular Hypertension Treatment Study found that eye drops used to treat elevated pressure inside the eye can be effective in delaying the onset of glaucoma. The study identified several significant risk factors that were associated with the development of glaucoma in study participants. These included personal risk factors, such as older age and African descent, as well as ocular risk factors, such as higher eye pressure and certain characteristics of the optic nerve and cornea. These results mean that treating people at higher risk for developing glaucoma may delay or possibly prevent the disease.

In a separate study researchers conducting the Early Manifest Glaucoma Trial, which was designed to compare the effect of immediate therapy to reduce pressure inside the eye with late or no treatment on the progression of newly detected open-angle glaucoma, found that progression was less frequent in the treated group (45 percent) than in the control group (62 percent), and occurred significantly later in

treated patients. This finding demonstrates definitively that treatment to lower pressure inside the eye can slow glaucoma damage and subsequent vision loss.

Continuing the progress in the genetics of glaucoma reported last year by the finding of a new gene mutation that caused a form of adult-onset glaucoma, scientists recently reported identification of a human gene that is linked to a disease known as "low-tension" glaucoma. This form of glaucoma has the characteristic pattern of optic nerve degeneration but the elevation in pressure within the eye normally associated with this pattern of damage is not evident on clinical examination. The gene that was identified produces a protein that is expressed in a number of tissues including the brain and retina and is believed to have a significant neurological function. The identification of genes associated with glaucoma provides a tool to study the biochemical pathways leading to optic nerve degeneration, as well as giving insight into designing neuroprotective strategies. Additionally, NEI sponsored a meeting on ganglion cell and optic nerve degeneration that brought together laboratory and clinical scientists studying glaucoma and those studying other neurodegenerative diseases to explore common mechanisms of nerve cell damage and potential methods of protection.

RETINAL DISEASE RESEARCH

The retina is the transparent, light-sensitive tissue that lines the back of the eye. Diseases and disorders of the retina and its blood vessels account for much of the blindness and visual disability in this country. An important barrier to therapeutic intervention in human retinal disease is the identification of the gene or genes that cause vision loss. Visual loss and the degenerative and other changes in the retina are largely linked to rod and cone photoreceptors, the light-sensing nerve cells in the retina.

Scientists have recently undertaken a comprehensive genetic analysis of rod photoreceptors, the most abundant sensory neuron in the retina, in order to identify all the possible genes expressed in these cells. Rod cells play an essential role in the visual pathway and may be especially vulnerable to any genetic defect involving the retina or other visual centers. For many identified retinal disease genes, a photoreceptor gene is mutated and its product is altered due to the mutation. Work is progressing on completing a database that will simplify the identification of candidate retinal disease genes, and many new genes in rod photoreceptors have already been identified.

Scientists have identified a mutation in a gene on the X chromosome that normally is associated with a form of retinitis pigmentosa (RP) that causes a progressive loss of rod photoreceptors in the peripheral retina and results in blindness in adulthood. This mutation was also reported to cause a unique type of degeneration in the macula, in a particular family. Further study may help us understand how this mutation specifically targets the macula and causes this unique loss of cones. This may lead to an understanding of the mechanisms of damage in other forms of macular degeneration and perhaps to the development of the means to prevent this type of damage to the macula.

The NEI is also funding studies on ocular albinism, a set of hypomelanotic diseases and conditions that are characterized by deficient cellular production of the pigment melanin. Deficiency in this pigment causes a cosmetic loss of ocular and skin pigmentation, but more importantly, it limits the development of vision in infants and children by fundamentally altering the connections between the eye and the brain. Recently the OA1 gene, which is associated with most cases of the disease, was identified. The form of the disease associated with OA1 is an X-linked or hereditary blinding eye disease that primarily affects boys at an early age. Although the cause or causes are unknown, misrouting of the neurons that go from the retina to the brain is involved. Understanding the causes of the abnormal neural cell axon guidance in ocular albinism may help us understand the fundamental neurobiology that underlies this disease and represents an important research initiative for the NEI.

CORNEAL DISEASE RESEARCH

NEI-supported scientists have also made progress against blinding diseases of the cornea. The cornea is the transparent tissue at the front of the eye that plays an important role in refracting or bending light to focus visual images sharply on the retina. Because the cornea is the most exposed surface of the eye, it is especially vulnerable to damage from injury or infection. One such infection is ocular onchocerciasis, commonly known as river blindness. Although river blindness is rare in developed countries, it is the second leading infectious cause of blindness in the world. This infection occurs when a nematode worm infects the cornea. Researchers

have found that development and growth of the worm depends on a bacterium that lives within it. They found that the blindness associated with the infection was due to the reaction of the patient's immune system to the bacterium and not to the worm. The scientists discovered that an antibiotic that killed the bacterium also caused the death of the worm but without causing blindness. Further development of this treatment could revolutionize treatment of river blindness throughout the developing world.

CATARACT RESEARCH

Although cataract treatment in this country is one of the most successful of all surgical procedures, development of non-surgical approaches to preventing or treating cataracts remains an important area of research, because of the potential that it holds for reducing costs to the Medicare system and improving the quality of life of our senior citizens. A cataract is an opacity of the eye's normally clear lens that interferes with vision. Age-related cataract formation is believed to result from the complex effects of aging on normal physiological processes. Because the end-result, cataract formation, is in most cases far removed in time from the initial insult, exacting a cause and effect relationship has been difficult. Lens transparency results from the very high concentration of soluble proteins, the crystallins, within a specialized lens fiber cell. During aging and cataract formation, soluble lens crystallins tend to combine or aggregate into large complexes that cause light to scatter. NEI-sponsored researchers have found that alpha-crystallin, which normally protects the lens by binding to other proteins, may itself become the vehicle for the aggregate formation that accelerates cataract formation. Additional research in this area may provide the means for clinicians to intervene prior to the formation of a clinically evident cataract.

Other scientists are attempting to determine the genes that control one of the earliest events in the development of the eye, the development of the lens. Scientists studying lens development have identified a master gene that controls the expression of a number of other critical genes. Two of these critical genes that have recently been discovered. Without these two genes, the development of the lens is stopped and crystallin-synthesizing cells fail to form. These findings add to our understanding of the overall control of lens and eye development and may ultimately enhance our knowledge of the molecular basis of congenital diseases of the eye, thereby opening the possibility of future interventions.

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING RESEARCH

The most frequent causes of vision loss in our children are strabismus, a misalignment of the eyes, and the development of amblyopia, or lazy eye. Strabismus results in diseases in which visual processing is abnormal. Amblyopia can result from this misalignment or from unequal refraction between the eyes. NEI-supported scientists have found that eye drops used to treat amblyopia work as well as the standard treatment of patching the eye. This research finding may lead to better compliance with treatment and improved quality of life in children with this eye disorder. Patients continue to be followed in this study to better assess the long term effects these treatments have on visual acuity.

Recent work by NEI-sponsored researchers has helped our understanding of nerve cell regeneration. Following injury or disease, neurons in the central nervous system (CNS) have a limited regenerative capacity, unlike nerve cells in the peripheral nervous system.

Nerve cells typically have two types of extensions that arise from their cell bodies. Axons are normally quite long and extend over considerable distances. Dendrites are much shorter and extend short distances from the cell body. The inability of CNS neurons to regenerate is due to the failure of their axons to re-grow. These scientists found that axon growth may be due to a factor within the nerve cell itself rather than in the surrounding environment and may be regulated by signals from other nerve cells. Further research may allow discovery of the signals that switch neurons back to the axonal growth mode to repair damage to nerve tissue from injury or disease.

HEALTH DISPARITIES

Scientists recently reported the prevalence of glaucoma in a population-based study conducted among 4,774 Mexican American adults residing in two communities in Arizona. Glaucoma prevalence rates have been reported previously for white and African American adults, but no similar studies have been conducted among the U.S. Hispanic population. The prevalence of open-angle glaucoma in this Mexican American population was intermediate between the high rates reported for African

Americans and the lower rates reported for whites. Of those diagnosed with glaucoma, only 38 percent were aware they had the disease. The prevalence of glaucoma increased rapidly with age and was the leading cause of bilateral blindness in this population. This information will allow health educators to create additional glaucoma awareness campaigns to increase awareness of the importance of glaucoma treatment in the Mexican American population, thereby allowing eye care providers to identify and treat those at greatest risk so that blindness can be prevented.

PROGRAM INITIATIVES

Diabetic retinopathy is a potentially blinding complication of diabetes characterized by the uncontrolled growth of fragile new blood vessels in the retina that may leak fluid and blood threatening vision. It is the leading cause of new cases of blindness in working age adults in the United States. Macular edema secondary to diabetic retinopathy is also a major cause of visual loss in patients with diabetes. The NEI is developing a clinical research network of core centers and participating clinics that will help satisfy the need to evaluate promising new approaches to treat diabetes induced retinal disorders and to investigate other approaches as they become available. This network approach will provide a framework for rapid initiation of important studies, efficient use of pooled clinical expertise in idea generation and protocol development, and efficient use of central resources for data management, quality control, and endpoint evaluation.

The NEI is also planning to increase the pace of research in age-related macular degeneration (AMD) prevention and treatment by supporting a wide array of laboratory and clinical studies. AMD is the leading cause of severe vision loss in older persons in the United States, and it will have an increasingly important social and economic impact as the population ages. These studies may range from pilot work to the establishment and implementation of clinical research networks. It is anticipated that a network approach to AMD clinical research will hasten development of the more successful therapies for the treatment or prevention of AMD.

The NEI is also undertaking a major effort to reinvigorate the intramural research program and enhance resources to neurodegenerative and genetic forms of vision loss. Ocular genetics research has demonstrated that many common eye diseases have complex genetic and environmental etiologies that must be understood before innovative biological treatments can be designed. NEI is working on a new laboratory program devoted to complex human eye disease to hasten progress in this area.

Mr. Chairman that concludes my prepared statement. I would be pleased to respond to any questions you or other members of the committee may have.

PREPARED STATEMENT OF DR. ALLEN M. SPIEGEL

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for fiscal year 2004, a sum of \$1,670,007,000, which reflects an increase of \$66,846,000 over the comparable fiscal year 2003 appropriation. The fiscal year 2004 budget comprises \$1,820 million which includes \$150 million (\$100 million in fiscal year 2003) for the Special Appropriation for Research on Type 1 Diabetes through Public Law 107-360. The NIDDK transfers some of these to other institutes of the NIH and to the CDC. Adjusted for these mandatory funds, this is an increase of \$48 million over the fiscal year 2003 enacted level of \$1,622 million comparable for transfers proposed in the President's request. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report, which compared our fiscal year 2002 results to the goals in our fiscal year 2002 performance plan.

OBESITY RESEARCH

I appreciate the opportunity to testify on behalf of the NIDDK, which supports research on a wide range of chronic, debilitating diseases. Many of these diseases, including type 2 diabetes, nonalcoholic fatty liver disease, gallstones, end-stage kidney disease, and urinary incontinence, are caused, directly or indirectly, by obesity. Data from the Centers for Disease Control and Prevention documents that obesity is growing at an alarming rate in both adults and children, and that it disproportionately affects minorities. Recent results from the Framingham Heart Study indicate that obesity cuts six to seven years off of life, comparable to the effects of smoking. The 2001 *Surgeon General's Call to Action to Prevent and Decrease Overweight*

and *Obesity* reports that each year, it costs this country an estimated \$117 billion in health care related expenditures.

We must approach obesity, not as a cosmetic or moral problem, but rather as a health problem. To address this problem, research is vital, and the NIDDK and the National Institutes of Health are formulating a bold and coordinated research plan. Obesity and its associated diseases result from complex interactions of biologic and environmental factors. The environmental factors include social, demographic, and economic changes that encourage people to eat more food than necessary to meet their energy requirements, and discourage physical activity that would increase their energy expenditure. These environmental factors disproportionately affect individuals who are biologically more susceptible to becoming obese and to develop obesity-associated diseases.

Tremendous progress has been made recently in understanding the biologic basis of obesity, and I will cite just a few examples. We now understand better how appetite is controlled through newly discovered hormones such as ghrelin and PYY. They are produced by the stomach and small intestine, and signal the brain, respectively, to increase and decrease appetite. Blood levels of ghrelin peak just before meals, and peaks are significantly higher in obese individuals who have lost weight by dieting, perhaps explaining why sustaining weight loss is so difficult. Bariatric, or gastric bypass, surgery is being increasingly performed in the United States, and part of its effectiveness in achieving sustained weight loss may be explained by the recent finding that ghrelin levels are suppressed by some forms of the surgery. Blocking the action of ghrelin is thus a potentially attractive target for drug development.

Similar advances are being made in understanding how the body decides whether and where to metabolize or store fat. Discovery of hormones such as leptin and adiponectin secreted by fat have shown that fat signals to brain, liver, and muscle to regulate fuel metabolism and response to insulin. Such discoveries help explain how obesity leads to insulin resistance and type 2 diabetes, and offer new ways of treating or preventing obesity-associated disorders. Epidemiologic results and clinical studies show that differences in distribution of body fat may also be important in determining which individuals develop obesity-associated disorders.

Progress in behavioral research provided the basis for the lifestyle intervention of our Diabetes Prevention Program (DPP), which revealed that participants who lost 5 to 7 percent or more of their body weight and who performed at least 150 minutes of physical activity per week reduced their risk of developing type 2 diabetes by 58 percent. We are conducting a follow-up DPP Outcomes Study to assess the durability of the DPP interventions in preventing diabetes, and to determine whether the interventions reduce cardiovascular disease. Our Look AHEAD: Action for Health in Diabetes clinical trial is testing the effect of sustained weight loss on prevention of cardiovascular disease in obese individuals who already have type 2 diabetes.

To further sharpen the NIDDK's obesity research efforts, I recently announced creation of a new Office of Obesity Research within the NIDDK that is bringing together expertise in our Division of Diabetes, Endocrinology, and Metabolic Diseases, and our Division of Digestive Diseases and Nutrition, both of which have important input to obesity research. This new group is framing initiatives across a wide range of obesity research areas to address the epidemic of obesity, from the fundamental biologic aspects to the behavioral and environmental. Examples include a study of the life cycle of the fat cell directed at discovery of novel targets for treatment of obesity and associated metabolic disorders. In order to address obesity-associated diseases such as type 2 diabetes, we will expand our Diabetes Genome Anatomy Project to include genetic analysis of all the major organ systems affected by diabetes and its complications. We are helping re-engineer the clinical research enterprise by creating a new Bariatric Surgery Clinical Research Consortium (BSCRSC). The BSCRSC will develop a common data collection protocol to accelerate clinical research and progress in understanding the development of severe obesity and its complications, as well as understanding the risks and benefits of bariatric surgery as a treatment method.

In behavioral research, we have begun a clinical trial to develop effective strategies to prevent type 2 diabetes in children. This initiative focuses on school-based primary prevention programs to decrease risk factors for type 2 diabetes and lower the incidence of the disorder. We are supporting research to translate the results of the highly successful Diabetes Prevention Program, into clinical practice for prevention of type 2 diabetes in individuals and communities at risk. Of particular interest will be interventions that focus on underserved and minority populations disproportionately affected by the disease. Given the environmental influences fueling the obesity epidemic, we are encouraging research to study promising interventions that would target environmental factors contributing to inappropriate weight gain.

in children, adolescents and adults. We are asking investigators to partner with community organizations or businesses, such as schools, supermarkets, restaurants, churches, community groups, and worksites to develop interventions that could potentially be translated into larger-scale interventions.

These are just some of the ways we are encouraging research to combat obesity and its co-morbid conditions. We believe NIDDK and NIH research is our best hope for stemming the tide of this epidemic. Why? Because we stand poised, given new information about the human genome and the advent of new research tools to determine the biologic and genetic factors that make one person more (or less) susceptible to obesity than another. Why is this important? Because it should allow targeted obesity prevention and allow the development of new kinds of drugs and therapies that should be more successful in preventing weight gain and in helping people lose weight and to sustain weight loss. Tied to this is improved research-based behavioral approaches to weight loss and maintenance. In addition, NIH research ultimately will provide the scientific basis for policy decisions on needed changes in environmental factors that affect diet, nutrition, and physical activity. Obesity is a complex problem requiring a multi-disciplinary research approach if we are to reverse this ominous threat to our nation's health.

DIABETES

Approximately one million Americans suffer from a type of diabetes that is not obesity-related. Rather, type 1 diabetes involves immune destruction of the insulin-producing beta cells of the pancreas. We are vigorously pursuing cutting-edge research opportunities for prevention of type 1 diabetes through our TrialNet, and for treatment and cure of type 1 diabetes through support of the field of regenerative medicine. One example of the latter is our Beta Cell Biology Consortium, which brings together multi-disciplinary teams of investigators with expertise in pancreatic development, beta cell biology, stem cell biology, and bioinformatics. Through such collaborative research programs, we are laying a solid foundation for the future development of innovative, cell and regenerative growth factor therapies for diabetes and other debilitating diseases. Increased understanding of beta cell biology should also improve our ability to develop noninvasive, functional imaging technology that would, for example, help monitor type 1 diabetes prevention trials.

HEPATITIS C

The hepatitis C virus is the cause of the most common form of end-stage liver disease in the United States. We recently held a Consensus Development Conference on the management of hepatitis C that recommended directions for future research, and led to development of initiatives that are encouraging further basic and clinical research on hepatitis C, research on management of hepatitis C in people with chronic kidney disease, and research on new therapies for children with hepatitis C. From such research should emerge more effective forms of treatment and prevention.

GASTROINTESTINAL DISEASES

We are bolstering our research activities across the full spectrum of gastrointestinal (GI) diseases, ranging from celiac disease, in which a known dietary factor triggers intestinal damage in genetically susceptible individuals, to functional GI disorders such as irritable bowel syndrome. Our strong research portfolio in inflammatory bowel disease (IBD) is paying dividends. A recent clinical trial reported that a recombinant monoclonal antibody that blocked the action of certain cell adhesion molecules could be used to reduce the symptoms and improve quality of life of patients with Crohn's disease, an inflammatory bowel disease. The NIDDK supported the basic research underpinning this exciting work, providing another example of the critical role of NIH research in the development of therapies for human disease. Our IBD Genetics Research Consortium aims to identify genes associated with increased risk of developing Crohn's disease and ulcerative colitis. The long-term goal is to increase molecular understanding of IBD so as to facilitate development of novel therapies and new diagnostic methods.

KIDNEY DISEASE

We are addressing the sharp rise in end-stage renal disease (ESRD) by supporting research on the causes, treatment, and prevention of the major forms of kidney disease leading to ESRD. The discovery that the proteins encoded by the polycystic kidney disease (PKD) genes are localized to cilia (hair-like projections) in kidney tubular cells demonstrates the rapid progress in understanding the pathogenesis of the

major cause of inherited ESRD. Results from some of our major kidney disease trials have significant implications for clinical practice. Our African American Study of Kidney Disease and Hypertension (AASK) showed that angiotensin-converting enzyme inhibitors, compared with calcium channel blockers, slowed kidney disease progression by 36 percent, and drastically reduced the risk of ESRD by 48 percent in patients who had at least one gram of protein in the urine, a sign of kidney failure.

The Institute's HEMO clinical trial recently showed that the standard recommended hemodialysis dosage and filters are adequate for reducing morbidity and mortality in ESRD patients, and that increasing dialysis dose using a conventional three times per week regimen does not provide greater benefit to patients. However, the important question now is the duration and frequency of dialysis. We therefore have planned clinical trials to compare conventional dialysis with more frequent dialysis in patients with ESRD. We also have launched a prospective epidemiological study of children with chronic kidney disease to determine the risk factors for decline in kidney function, and associated morbidities such as impaired neurocognitive development, cardiovascular disease, and growth failure.

UROLOGIC DISEASES

Our major clinical trial on Medical Therapy of Prostate Symptoms (MTOPS) recently demonstrated that two drugs commonly used to treat benign prostatic hyperplasia (BPH), finasteride and doxazosin, are significantly more effective at preventing symptomatic BPH incidence and progression when given in combination. Samples collected during the MTOPS trial will be used by our new MTOPS Prostate Samples Analysis Consortium to discover and validate biologic markers for detection and risk assessment of BPH.

Our Bladder Progress Review Group report provides a strategic plan for future bladder research. We are already implementing the report's recommendations on interstitial cystitis (IC), a debilitating, chronic syndrome of urinary urgency, frequency, and pelvic pain, by encouraging basic research pertinent to IC, the ultimate goal being the development of reliable diagnostic tools, and new and effective disease treatments and prevention.

Mr. Chairman and Members of the Committee, these are just a few examples of our many research advances and initiatives. I would be pleased to answer any questions.

PREPARED STATEMENT OF DR. STEPHEN E. STRAUS

I am pleased to present the President's fiscal year 2004 budget request for the National Center for Complementary and Alternative Medicine (NCCAM). The fiscal year 2004 budget includes \$116,202 million, an increase of \$2.9 million over the fiscal year 2003 enacted level of \$113,302 million comparable for transfers proposed in the President's request.

INTRODUCTION

Arthritis, depression, menopause, cancer . . . for millions of Americans, these and other health concerns are not being adequately addressed through conventional medicine. Many are turning outside the medical mainstream to approaches that embrace the whole person—mind, body, and spirit. From acupuncture to dietary supplements, complementary and alternative medicine (CAM) approaches are affordable and accessible, but largely untested. Under NCCAM's leadership, researchers are applying the tools of modern science to discover which CAM practices work, why and how they work, and whether they are truly safe. Exploring CAM through rigorous science will lead to the integration of proven CAM practices with conventional medicine, thus improving the lives of all Americans.

STANDARDIZATION & CHARACTERIZATION OF DIETARY SUPPLEMENTS

Dietary supplements, one of the most popular categories of CAM practices, are used by 10 percent of American adults.¹ Many consumers use dietary supplements with the expectation that they are effective in the self-treatment and prevention of disease and the promotion of wellness and, further, with the assumption that they

¹ Hanyu NI, Catherine Simile and Ann M. Hardy, "Utilization of Complementary and Alternative Medicine by United States Adults: Results From the 1999 National Health Interview Survey," *Medical Care*, Vol. 40, No. 4, pp. 353–358.

are safe. Under the law, supplements are classified as foods and not held to the same rigorous standards as drugs.

Research supported by NCCAM indicates that Americans who take ginseng on a regular basis cannot rely on the label to accurately reflect the product's contents. After examining 25 commercial ginseng products, one NCCAM grantee recently reported that, the concentrations of ginseng differed by as much as ten-fold from the label. The lack of standardized dietary supplements is not only an issue of consumer safety; it is also an issue for researchers who need to protect their patients and work with well-characterized and standardized products to scientifically and accurately examine study their purported benefits.

NCCAM's recent experience with PC SPES, a patented mixture of eight herbs, is an example of the other vexing problem with some dietary supplements contamination. In 2001, thousands of men with advanced prostate cancer in America took were taking PC SPES. Based on encouraging early clinical results, NCCAM was supporting four research studies, including a clinical trial, to determine the safety, efficacy, and mechanism of action (i.e., how it works) of PC SPES. In February 2002, the California Department of Health Services and the Food and Drug Administration reported that PC SPES was contaminated with undeclared prescription drug ingredients. This finding led the manufacturer to recall the product and subsequently cease its operations. NCCAM immediately put its studies on hold and convened meetings with scientists, prostate cancer specialists, patients, and industry representatives to determine how if a "cleaner" an uncontaminated product could be made available to the public reenter the marketplace and the research pipeline, allowing the research to resume. As part of this strategy a result of these meetings, NCCAM resumed its laboratory studies of the cellular and molecular biology of PC-SPES and pronounced declared its interest in resuming clinical trials once an unadulterated, fully characterized, and standardized product is available.

NCCAM is taking several steps is taking several steps to address the critical issue of product standardization and quality. Among the top-selling products in the dietary supplement industry are products like echinacea (*Echinacea purpurea*), taken to prevent and treat colds, milk thistle (*Silybum marianum*), taken to treat chronic hepatitis and cirrhosis, and feverfew (*Tanacetum parthenium*), taken to lower fevers. All of these products have shown promise in small uncontrolled studies; however, each has problems with standardization, precluding their full and objective study. NCCAM is making awards under using the Small Business Innovative Research (SBIR) program to obtain well-characterized and standardized clinical-trial-grade materials of these supplements. This investment in high-quality products essential first step will be followed by studies to define the optimal dose of each product. To implement this second step, in 2004, NCCAM plans to plans to establish a Dietary Supplement Standardization and Characterization Center (DSSCC), which will to serve as a resource for the analysis of dietary supplements, especially botanical products, before they are used in clinical trials.

DETERMINING THE MECHANISMS OF ACTION OF CAM INTERVENTIONS

While pursuing innovative approaches to ensuring the safety of its clinical trial products, NCCAM continues to support basic and clinical studies NCCAM continues to support basic and clinical studies. The central objective of many of these studies is to examine the mechanisms of action underlying various CAM therapies. In 2002, for example, NCCAM-supported researchers conducted an important body of research on alternatives to conventional hormone therapy—an area of obvious interest for millions of menopausal women who are seeking safe and effective alternatives to conventional hormone therapy for relief of menopausal symptoms and related conditions. Specifically, scientists are using *in vitro* systems to examine how some popular dietary supplements act on biochemical pathways responsive to estrogen. Others are examining the estrogenic activity and specific mechanisms of estrogen receptor regulation of a Chinese herbal extract; identifying the active compounds of black cohosh (*Cimifuga racemosa*) and red clover (*Trifolium pratense*); and investigating the range and mechanisms of action of two plant-based estrogens, genistein and diadzein, and extracts of soy on immune function. These studies will clarify what biochemical effects supplements might have on women and indicate which, if any, are worthy of testing in a clinical trial.

Building on the results of a detailed scientific review that NCCAM conducted with the Agency for Healthcare Research and Quality on the popular dietary supplement, S-Adenosyl-L-Methionine (SAME), the Center is also supporting mechanistic projects on the mechanisms of action of SAME that are consistent with the findings of the report associated with key areas identified by the report. One grantee is using cultured cells to better characterize the biochemistry of liver injury and what role

SAME may play in preventing liver damage. Another investigator is using a mouse model of hepatitis and liver cancer to study the role of SAME in regulating liver cell growth and death.

A trio of studies indicate that Ginkgo biloba may provide multiple levels of protection to neural tissues and contribute to the body of evidence explaining how Ginkgo may be beneficial in preventing the onset of dementia. NCCAM-supported investigators reported that a standardized Ginkgo extract protects cells from oxidative stress and apoptosis (programmed cell death). Using model systems to study the factors that regulate cell death, the investigators showed that the Ginkgo extracts increase the lifespan of the worm, *Caenorhabditis aenorhabditis elegans*, protect cultured neural cells from undergoing programmed death, and hinder an early step in the biochemical processes leading to neurodegeneration.

In fiscal year 2003, NCCAM made several awards as part of the initiatives it launched with NIH partners to elucidate the underlying biological pathways of the placebo effect and to reveal factors important for eliciting the placebo effect in clinical practice setting. The Center designated mind-body medicine as a priority research area in fiscal year 2003, recognizing the potential contributions to prevention and treatment of chronic diseases that could be made by interventions based on evidence from innovative psychophysiological research. NCCAM will enhance the support for research into the mechanisms of mind-body medicine. Most recently, NCCAM joined other NIH partners to solicit applications from institutions poised to advance research on mind-body interactions and health. The Center also designated mind-body medicine as a priority research area in fiscal year 2003, recognizing the potential contributions to prevention and treatment of chronic diseases that could be made by interventions based on evidence from innovative psychophysiological research.

EVALUATING CAM THERAPIES IN RIGOROUS CLINICAL TRIALS

A chief goal of the basic and preclinical research NCCAM supports is basic and preclinical research to test therapies for eventual use in clinical trials with the ultimate objective being to translate safe and effective therapies into widespread practice. Another purpose of NCCAM-supported clinical trials is to test CAM products already being widely used by the public. Ultimately, NCCAM wants to answer the central question: "does it work?"

In 2002, NCCAM announced the results of its first large-scale clinical trial. The trial evaluated a one product containing St. John's wort (*Hypericum perforatum*) product, a popular herbal remedy for depression, as a treatment for major depression of moderate severity and found it to be ineffective as compared to placebo. Although the results of this trial were negative showed that St. John's wort is not effective for this type of depression, the outcome provided practitioners and patients alike with valuable data. In addition, the outcome informed researchers who are testing St. John's wort as a treatment for less severe forms of depression. NCCAM is following-up on this finding by co-funding a new trial to test St. John's wort as a treatment for minor depression, a less severe but very common type of depressive illness. The trial begins this year and will enroll 300 patients at three sites nationwide.

Because CAM products and practices are already used by millions of Americans, NCCAM supports relatively more a higher percentage of clinical research than all of the other NIH Institutes and Centers. As part of its clinical research portfolio, the NCCAM extramural research program is already supporting 12 ongoing large-scale clinical trials with other NIH Institutes and Centers. These trials include the largest ever herbal study of Ginkgo biloba for the prevention of dementia a critical study given the aforementioned body of evidence that exists regarding Ginkgo's potential protective effects. The list also includes the largest ever study of dietary supplements (selenium and vitamin E), involving 30,000 men, for the prevention of prostate cancer. In fiscal year 2002, NCCAM cosponsored the first large clinical trial to test chelation therapy as a treatment for coronary artery disease. Also in fiscal year 2002, the NCCAM Intramural Research Program initiated its first clinical trial, which is evaluating electroacupuncture in reducing the severe nausea experienced by many children following intensive cancer chemotherapy. NCCAM is taking action to ensure the quality and safety of NCCAM-supported clinical trials.

In 2002, the Center established the Office of Clinical and Regulatory Affairs to help plan, coordinate, and monitor NCCAM-supported clinical trials. All of these activities reflect NCCAM's rich investment in and commitment to clinical research.

BUILDING RESEARCH INFRASTRUCTURE AND INTELLECTUAL CAPITAL

The success of NCCAM's future research endeavors is contingent upon depends on the availability of skilled investigators in both the conventional and CAM research communities. Toward this end, NCCAM is supporting dozens of mentored and independent trainees, from the pre-doctoral level through mid-career and senior faculty members. In 2002, NCCAM made institutional training and clinical research career awards to CAM institutions and joined the new NIH-wide loan repayment program with awards to two junior practitioner-investigators, marking a series of "firsts" for NCCAM.

In addition to its support of investment in training programs, NCCAM continues to support a robust research centers program, providing a critical CAM research infrastructure. In 2002, NCCAM sought to strengthen its centers program by convening sought to strengthen its centers program by cing an expert panel to evaluate the program's current structure and objectives. The panel recommended a more flexible approach to supporting future centers research. This new approach, which employs a mix of funding and research mechanisms, will ideally expand ideally the participation among investigators with varying degrees of research expertise at both CAM and conventional institutions in a multi-disciplinary fashion. Implementation of this strategy began in fiscal year 2003 and will continue through fiscal year 2005.

CONCLUSION

NCCAM has made remarkable significant progress in its first 4 years. Between fiscal year 2000 and fiscal year 2001, the number of people enrolled in NCCAM-supported clinical research projects doubled. The Center, in a partnership with other NIH Institutes, launched some of the largest clinical studies of CAM therapies ever conducted. NCCAM took pro-active steps to improve the safety and efficacy of its clinical research studies and the quality of the information disseminated to the public about CAM therapies. Finally, the Center increased its level of support to researchers who are applying cutting-edge scientific tools to study the most promising CAM approaches to the most important public health challenges facing our nation. I look forward to keeping you and the American public apprised of NCCAM's future activities and accomplishments.

PREPARED STATEMENT OF DR. LAWRENCE A. TABAK

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Dental and Craniofacial Research (NIDCR) for fiscal year 2004. The fiscal year 2004 budget includes \$382,396,000, an increase of \$11,254,000 over the fiscal year 2003 enacted level of \$371,142,000 comparable for transfers proposed in the President's Request.

MOLECULAR MEDICINE ENTERS THE MOUTH

When molecular biologists discuss the future of medicine and dentistry, many foresee a day when health care professionals will possess the technological tools to dust a patient's cells, like a detective dusts for fingerprints, and pull up a "molecular fingerprint" of the activity inside. This fingerprint will allow them for the first time to examine the patterns within the cells for disease-causing abnormalities in the genes, proteins, and protein networks. Based on these specific biological clues, doctors will have far more detailed information at hand to make a correct diagnosis and perhaps one day tailor a person's care to treat the specific molecular defects that underlie the disorder.

SALIVARY DIAGNOSTICS

Scientists have long recognized that our saliva serves as a "mirror" of the body's health, in that it contains the full repertoire of proteins, hormones, antibodies, and other molecular analytes that are frequently measured in standard blood tests. The Institute recently launched a major research effort that, in keeping with the National Institutes of Health (NIH) Roadmap initiative, seeks to identify and address major cross-cutting biomedical challenges, and will further develop needed technologies and create the first comprehensive baseline catalogue of all proteins found in oral fluids of healthy individuals. The NIDCR envisions that this basic research could one day translate into miniature, hi-tech tests, or so called "labs" on a silicon chip, that rapidly scan oral fluid for the presence or absence of multiple proteins linked to various systemic diseases and conditions. Ultimately, this approach could

be used for real-time health surveillance—rapidly identifying persons most at risk at the earliest moments of detectable change in key diagnostic markers.

THE GENOMICS AND PROTEOMICS OF PERIODONTAL DISEASES

Although “molecular medicine” is still in its infancy, the NIDCR continues to help lay its basic intellectual foundations. The tools of molecular medicine offer promising new strategies for addressing oral infectious diseases such as periodontitis. These conditions begin when bacteria colonize a “biofilm” that forms on the surface of teeth. Many of these microorganisms remain uncultivated and only recently have some of these bacteria been identified by their molecular fingerprints. Some of these bacteria are highly virulent; they elaborate noxious substances that damage hard and soft tissues of the mouth. Furthermore, oral bacteria can trigger an immune response that often proves destructive both within the mouth and elsewhere in the body. Indeed, recent studies with animal models and epidemiologic surveys have linked periodontal diseases with pre-term delivery and low birth weight.

With the advent of more powerful research tools, NIDCR supported scientists will now be able to assemble a molecular “parts list” of all the genes and proteins involved in periodontal diseases. For the first time, a detailed understanding of the microbial and host signaling pathways that are activated or deactivated during periodontal disease progression will be mapped. This represents an important step in defining new therapeutic targets to overcome one of the most prevalent infectious diseases of humankind.

TISSUE ENGINEERING

The NIDCR continues to invest heavily in regenerative medicine, with a strong interest in engineering new bone to repair dental and craniofacial wounds and birth defects. Of particular interest are adult bone marrow stromal stem cells, the natural progenitors that create the body’s bone-forming cells. In recent years, scientists have envisioned healing bone fractures by inserting these cells directly into the wound. The adult stem cells would replicate in the wound, create millions of new bone cells, and heal the fracture rapidly and efficiently. As appealing as this approach is, however, technical challenges have emerged to slow the research. One of the most formidable obstacles is the discovery that adult bone marrow stromal stem cells stop growing soon after they are introduced into cell culture and quickly lose their ability to form new bone. Because hundreds of thousands of stem cells are required to heal even a minor bone fracture, scientists have been hard pressed to generate an adequate supply of these precursors.

For the first time, NIDCR scientists and grantees reported that they have more than doubled the life span of adult bone marrow stromal stem cells, under laboratory conditions, by incorporating the catalytic, or active, component of a much-studied enzyme called telomerase, termed the hTERT gene, into the stem cells. This was particularly interesting because hTERT is the catalytic, or active, component of a much studied enzyme called telomerase. Telomerase has been shown to counter the shortening of telomeres, the tips of chromosomes, by triggering a chemical reaction that adds new base pairs to them and extends the life of the cell. In follow-up animal studies, the scientists found that the newly formed bone, generated from the stem cells, had all of the hallmarks of normal bone—including organized collagen fibers and various mineral components.

SJÖGREN’S SYNDROME

The NIDCR is also applying tissue engineering strategies to Sjögren’s syndrome, a relatively rare condition that affects over one million Americans. The syndrome is caused when the immune system mistakenly attacks various parts of the body, often including cells that produce saliva. When this occurs, people develop chronically dry mouths, which can impair their ability to taste and swallow as well as lead to oral disease. While studies are ongoing to pinpoint the root cause of this condition, NIDCR continues to explore the possibility of developing an artificial salivary gland, an approach that one day could help to restore adequate levels of saliva for Sjögren’s patients.

In studying Sjögren’s syndrome, one of the major barriers always has been logistical. People with the syndrome are scattered throughout the country, and scientists are sometimes uncertain about how to find them. To ensure that researchers have access to sufficient numbers of Sjögren’s patients with well defined clinical histories and relevant biological samples, NIDCR will support the first international registry of Sjögren’s patients. The registry will be crucial in tracking the incidence and natural history of the condition. It also will allow NIDCR to launch more rapidly the necessary clinical trials to evaluate promising diagnostic and therapeutic

leads as they emerge. NIDCR also plans to identify biomarkers—genes, proteins, or even protein networks—which will allow early diagnosis, determination of disease progression, and stratification of high risk individuals. By developing a battery of sensitive and highly specific diagnostic and prognostic biomarkers, critical molecular information will be available to more accurately diagnose and treat Sjögren's syndrome, a long-held hope of many Americans affected by this condition.

PAIN RESEARCH

For the past four decades, the NIDCR has been one of the key players at NIH in the study of the basic biology and treatment of pain. While current analgesic drugs help many ease discomfort, millions of others have pain management needs that remain completely or partially unmet. Nearly all available analgesics were developed based on overly simplified, linear models of pain transmission. Recent advances show that pain transmission is a far more dynamic process that often involves multiple routes, or pathways. Each pathway integrates a convergence of molecular signals, then relays them along their own specific, hard-wired routes to the brain. The research challenge is to define the molecular details of these multiple routes of pain transmission with the aim of increasing the repertoire of pain management strategies.

In keeping with the NIH Roadmap initiative, progress is now being made in defining the biological pathways and networks of pain. For example, a group of NIDCR grantees have discovered several biological factors that influence pain perception. This multidisciplinary team focuses its research on developing novel, real-time imaging techniques that track the mu-opioid system, a specific type of protein receptor in the brain that researchers have long suspected triggers a dampening of the pain. In a seminal study published last year, the team confirmed the role of the mu-opioid system in enhancing a person's tolerance of pain. According to the research team, this marked the first study ever that combined prolonged pain with simultaneous brain scan monitoring of the mu-opioid system and self-reported pain ratings of human volunteers.

The group found that the onset and slow release of jaw muscle pain (that mimics, in part, the symptoms of individuals suffering from Temporomandibular muscle and joint diseases and conditions) over 20 minutes caused a surge in the release of endorphins, naturally produced chemicals that bind to the mu-opioid protein receptors that are displayed on the surface of brain cells. Once the endorphins activated the receptors, the volunteers said they felt a reduction in pain and emotions related to the sensation. Specific brain regions—especially those that play a role in emotional responses or that help to process signals from the body's sensory systems—had the greatest increase in endorphin levels. The research also revealed major variations among volunteers in baseline and pain-induced levels of opioids. The scientists noted that their results establish that people vary both in their capacity to produce mu-opioid receptors and in their ability to release the anti-pain chemicals themselves. This variability appears to determine the emotional and sensory aspects of a painful experience and might explain why some people react to pain differently. It may also help to explain why some people are more prone to chronic pain conditions or do not benefit from certain anti-pain medications.

The group and its collaborators have published two important followup studies. In the first study, the scientists observed that, at matched levels of pain intensity, men and women differ in the degree and direction of the mu-opioid response in distinct areas of the brain. In particular, men had greater activation of mu receptors in specific regions of the brain—the anterior thalamus, ventral basal ganglia, and amygdala. Women, conversely, had reductions in the resting levels of these receptors when they experienced pain in the nucleus accumbens, an area of the brain previously associated with hyperalgesic responses to the blockage of these receptors.

In the second study, the scientists focused on a gene that produces a key enzyme involved in the mu-opioid system. The group found that people who inherit an extremely common variation in the gene have a lower natural threshold of pain than those who were born without the variation. The scientists speculated that the variant gene encodes a slightly altered enzyme that functions somewhat differently than the normal enzyme, leading to lower brain levels of pain-killing endorphins. This finding highlights the growing recognition that pain treatment should be customized to meet the specific needs of individual patients.

Because of the mouth's unique role in the human body, NIDCR is well positioned to make key contributions to the future of molecular-based medicine—not only in alleviating oral conditions but also toward improving systemic health. This Institute's continued contributions represent hope for millions of Americans today, as well as improved health and quality of life for generations to come.

PREPARED STATEMENT OF DR. JUDITH L. VAITUKAITIS

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Center for Research Resources (NCRR) for fiscal year 2004, a sum of \$1,053,926, a decrease of \$84,738,000 from the fiscal year 2003 enacted level of \$1,138,664 comparable for transfers proposed in the President's request.

Infrastructure is at the heart of NCRR. For more than 40 years, it has been NCRR's mission to develop and support essential research resources that strengthen and enhance research environments for health-related studies. NCRR provides the nation's scientific community with access to broad-ranging resources, including animal models, advanced technologies, research facilities, and clinical research centers that explore new approaches for diagnosing, treating, and preventing human disease.

To be responsive to emerging needs, NCRR works in trusted partnership with the biomedical research community, with other NIH institutes and centers, and, in some cases, with other Federal agencies and private sector organizations. In anticipation of emerging needs, NCRR in recent years has funded construction of biocontainment laboratories for the study of dangerous infectious agents; islet cell resources to explore novel therapies for diabetes; and creation of transgenic animals that enhance understanding of human disease.

Scientists today are exploring biomedical problems of enormous complexity. Some of the nation's most pressing health concerns can best be addressed through multidisciplinary research teams, which integrate technologies and expertise from a variety of fields. NCRR, with its cross-cutting mission, is ideally positioned to facilitate this evolving approach. Today I will outline NCRR's plans for meeting the ever-changing infrastructure needs and describe just a few of the research advances enabled through NCRR-supported research infrastructure.

ADVANCED TECHNOLOGIES

NCRR has a long history of developing and enhancing access to new technologies. Magnetic resonance imaging, mass spectrometry, synchrotrons for crystallography and optical imaging are just a few of the now-indispensable tools that NCRR supported in their infancy, primarily through the nationwide network of Biomedical Technology Resource Centers. NCRR must remain positioned to ensure that innovative technologies are developed and accessible before research progress is compromised.

Novel insights into the prevention or treatment of disease will arise from synthesis of massive amounts of molecular, genetic, and biologic data. To take advantage of these rich sources of information, researchers need new bioinformatics tools and approaches to selectively retrieve, analyze, and interpret data stored in many different formats and at different levels of aggregation in locations spread across many sites. Tool development, including new database architecture, is needed to manipulate large data sets with data object entries that vary markedly in size and complexity. Seamless integration of information across these data sources is a major research challenge.

NCRR has begun to address such issues through its Biomedical Informatics Research Network (BIRN). The test bed encompasses diverse locations nationwide. The initial development of BIRN focuses on generating several robust technologies, computational tools, and communications networks. These networks simplify and facilitate the sharing of scientific expertise, technologies, and data. BIRN currently provides links, via Internet2, among several General Clinical Research Centers and Biomedical Technology Resource Centers. NCRR now plans to extend the scope of these networked resources by connecting all NCRR-supported research resource centers to Internet2, which will enhance nationwide access to databases, bioinformatics tools, and enabling resources for clinical and basic research in a second test bed that will concentrate on infrastructure for clinical research.

In another facet of the BIRN development, NCRR will work in concert with other NIH components to expand the advanced technologies used or developed for BIRN and apply them to build a National Electronic Clinical Trials and Research network, called NECTAR. This effort will include designing a web-based approach for entering clinical data, developing advanced tools for integrating datasets, and enabling manipulation of complex datasets from remote sites. Initial development of the NECTAR network will focus on therapeutic development networks, particularly for the treatment of rare diseases. Ultimately, the tools developed for NECTAR may be readily scaled up for larger investigations, including collaborations.

With today's multifaceted studies, biomedical scientists increasingly depend on a systems approach that integrates, for example, advanced technologies for

macromolecular structures, structure-based drug design, novel technologies to discern the gene-gene interactions and molecular imaging. To enable such studies, NCRR proposes to develop and support comprehensive research resource centers equipped with state-of-the-art technologies and a team of investigators with wide-ranging but complementary expertise. These comprehensive centers, which may provide remote access to resources, will allow investigators to characterize the thousands of proteins expressed by the human genome. Scientists will be positioned to address fundamental questions that cannot be answered by examining one protein at a time. Such “postgenomic” studies may provide clues to complex disease-related processes that may be prevented or arrested with novel interventions.

MODEL DEVELOPMENT AND GENETIC MEDICINE

NCRR is also at the forefront in developing nonhuman models and tools for genetic medicine. In recent years, numerous gene-targeting and transgenic studies have produced a wealth of information on gene function and their role in development, aging, and disease processes. But the enormous volume of collected data is often unwieldy and difficult to analyze. NCRR will enhance this promising area of research by supporting a national network of resources to systematically classify and characterize genetically altered animal models and to support the development of new technologies to rapidly phenotype new mutants. With the decoding of the human genome and development of new technologies, biologic models may help unravel the causes and identify cures for such complex diseases as diabetes, hypertension and cancer.

The mouse has gained new prominence in biomedical laboratories now that scientists can readily modify the animal's genome to create transgenic and “knockout” models of human disease. In 1999, NCRR established the Mutant Mouse Regional Resource Centers to expand the nation's capacity for preserving specialized mice and distributing them to biomedical researchers. Because of the program's success and value to the scientific community, NCRR now plans to extend the scope of the mouse resource centers to an international level. Collaborations will be established with Mutant Mouse Resources at sites in Europe and Japan, thereby minimizing unplanned duplicative efforts on a global scale.

NCRR also proposes to initiate a network of Mutant Rat Regional Resource Centers—similar to the successful mouse network—to import, validate, cryopreserve, and distribute mutant rats to investigators globally. Up to three rat resource centers will be established along with a complementary informatics center to design and maintain a database of relevant data for each mutant rat included in the network, and maintain a dedicated Internet linkage among the Centers to provide investigators access the information on validated mutant rat models within the network's collection and relevant information a centralized web site and database.

Research using swine models has expanded significantly over the past five years, resulting in the need for animal production, appropriate husbandry and care, and genetic technologies related to pigs. In 2002, an NCRR-supported research team at the University of Missouri succeeded in creating the world's first “knockout” pigs—the gene function is altered so that the gene can no longer add specific sugars to the outer surface of liver cells, which, in turn, decreases the immune-mediated tissue rejection response. The knockout pigs represented a first step toward developing genetically engineered swine suitable for cross-species transplantation, or xenotransplantation, into humans. NCRR proposes to establish a National Swine Regional Resource Center with the capacity to import, cryopreserve, characterize, maintain, and distribute well-characterized specific-pathogen-free swine strains. The Resource Center will also have an R&D component to enhance the research scope and expertise of investigators there.

PREVENTION, DIAGNOSIS, AND TREATMENT

NCRR is also an ardent supporter of clinical research. The nationwide network of General Clinical Research Centers (GCRCs) provides a collection of research resources and professional research staffing for conducting state-of-the-art clinical research and career development programs to develop independent investigators. GCRCs are encouraged to reach out to investigators at nearby institutions without GCRCs and provide access to the resources of the GCRCs. NCRR also funds clinical research centers at minority institutions.

To address the public's concern about the safety of clinical research, NCRR implemented the Research Subject Advocate (RSA) program to assure that research conducted on NCRR-supported GCRCs and minority clinical research sites are in compliance with Federal laws, regulations and policies. Research Subject Advocates work closely with research subjects to help them understand the research project

for which they agreed to participate and also work closely with clinical investigators to apprise them of their ethical responsibilities to research subjects. The RSA organizes workshops to inform investigators about the several local and Federal regulations and policies that relate to clinical research. Because of the enthusiastic institutional responses to the Research Subject Advocate program, NCRR proposes to begin phasing in support for RSAs for all NIH-supported patient-oriented research at GCRC host institutions.

In addition, NCRR intends to support research to identify factors—for example, biologic, economic or cultural—which lead to health disparities and how to modulate for eliminate those factors in racial and ethnic minority Americans. Through establishing dedicated Comprehensive Centers for Health Disparities Research, NCRR support will develop the clinical research skills and translational research capacity of students, postdoctoral research fellows and faculty at minority medical schools. NCRR also will continue to encourage multidisciplinary collaborations among minority institutions and institutions with established research programs to not only accelerate the development of independent clinical research investigators but also to enhance our understanding of the factors that contribute to health disparities and how to negate them.

ENHANCEMENT OF RESEARCH CAPACITY

NCRR's purview is research infrastructure, in the broadest interpretation of the term. Insight leading to novel research approaches to prevent, treat or ameliorate disease will result from synthesis of massive amounts of molecular, genetic, and biologic data. Seamless integration of information across these data sources is a major research challenge.

NCRR will expand the advanced technology used or developed for the neuroscience testbed for BIRN to build a National Electronic Clinical Trials and Research (NECTAR) network. This effort will include designing a web based data entry approach for clinical trials and other types of clinical research, development of a host of other tools, including advanced grid technology to integrate datasets and develop tools to manipulate these datasets at distributed sites. The NECTAR network will generate heterogeneous data types which have distinct or unique requirements for data collection, storage, integration, and analysis. Initially this phase of the NECTAR network development will focus on therapeutic development networks, particularly in rare diseases. The tools developed at this stage may be readily scaled up to include, for example, collaborative clinical research across wide geographic sites, primary care physician clinical trial networks, other provider networks, and private sector partners. This infrastructure will constitute the foundation for a nation wide NECTAR-BIRN to accelerate the rate for which health research advances at the bench reach patients who are the intended benefactors of biomedical research.

The BIRN allows access to databases, bioinformatics tools, scalable computing up to the teraflop level, research resources for clinical, animal and basic research; it also includes federated databases, web-based data collection for clinical trials and access to virtual laboratories for crystallography, magnetic resonance imaging, electron microscopy. This cyberspace-based network will be intertwined with a "ground-based" network of technology-based resources. The complementary networks will continue to evolve with technologic needs and research complexities. Similarly, technologies and resources networked for human, animal and basic research will also evolve across this national infrastructure for land-based and cyber-spaced networks. In essence, as research problems become more complex, infrastructure to facilitate that research must undergo a paradigm shift.

The Institutional Development Award (IDeA) program includes two subprograms to strengthen the research infrastructure among 23 states and Puerto Rico to improve their research competitiveness for NIH grant awards. The two infrastructure-building programs—Centers of Biomedical Research Excellence (COBRE) and the Biomedical Research Infrastructure Network (BRIN)—have been in place for three and two years, respectively. In that short time span, preliminary observations are extremely encouraging. Between 1997 and 2002, the application rate for NIH grants increased 16 percent—but the number of competitive NIH grant awards increased 37 percent. The IDeA programs' impact has resulted from providing support for modern laboratories and research equipment, recruitment established investigators to lead the research effort as well as to mentor graduate students and junior faculty to become independent investigators. There has been a spinoff to small industry as well. For example, a faculty member of the COBRE in West Virginia has invented a microfluidics chip ("lab on a chip") that will enable researchers to analyze and identify proteins more rapidly, an innovation that may lead to new diagnostic strategies and treatments. Both the COBRE and BRIN programs are enthusiastically

embraced by students, mentor-faculty, and institutional leadership. In fiscal year 2004 the NCRR will develop new COBRE research centers and will develop a follow-on program to the BRIN, initially funded as a planning grant, to capitalize on state-wide networks to facilitate biomedical research efforts at undergraduate institutions and to further enhance the pipeline for promising baccalaureate and graduate students in fields relevant to biomedical research.

Finally, NCRR will further strengthen institutional biomedical research infrastructure and also design specific programs to develop the research skills of graduate students and junior faculty in both basic and clinical sciences at RCMI and IDeA institutions. Programs will be designed to enhance early career scientists to transition from a mentored research environment to an independent research career to bolster the collective research capacities of this subset of institutions. To continue to address the shrinking pool of clinical investigators, NCRR plans to expand and extend the successful Institutional Mentored Clinical Research Scholars (CRS) Program to include a consortium of minority medical schools associated with the Research Centers in Minority Institutions (RCMI) program. This cohort of investigators will be included in a dedicated network to foster their research through the Clinical Research Infrastructure initiative.

CONCLUSION

In conclusion, the health-related advances of tomorrow will depend on the availability of essential, shared research resources, including nonhuman models, advanced technologies, and tools for exploring new diagnostics, therapies, and preventive strategies. NCRR is poised to provide these essential resources to the biomedical community. As we have for more than 40 years, NCRR remains committed to providing the enabling tools and technologies that advance biomedical science and improve the health of our nation's citizens. In collaboration with the National Science Foundation, Internet2, and investigators from several universities, NCRR has become a major supporter for upgrading the infrastructure for health-related research focusing on development of a bioinformatics tool box, a more efficient clinical trials system and use Internet2 interface for the several tools and algorithms for data visualization, efficient clinical trials networks and development of grids for security, computation, and data storage.

My colleagues and I will be happy to respond to any questions you may have.

PREPARED STATEMENT OF DR. JACK WHITESCARVER

Mr. Chairman and Members of the Committee, I am pleased to present the President's budget request for the AIDS research programs of the NIH for fiscal year 2004, a sum of \$2,869,858,000 an increase of \$122,395,000 above the comparable fiscal year 2003 appropriation.

The NIH represents the largest and most significant public investment in AIDS research in the world. It supports a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated opportunistic infections and malignancies that will lead to a better understanding of the basic biology of HIV, the development of effective therapies to treat it, and the design of better interventions to prevent new infections. Perhaps no other disease so thoroughly transcends every area of clinical medicine and scientific investigation, crossing the boundaries of the NIH institutes. The Office of AIDS Research (OAR) plays a unique role at the NIH. OAR coordinates the scientific, budgetary, and policy elements of the NIH AIDS program, supported by nearly every Institute and Center; prepares an annual comprehensive trans-NIH plan and budget for all NIH-sponsored AIDS research; facilitates NIH involvement in international AIDS research activities; and identifies and facilitates scientific programs for multi-institute participation in priority areas of research.

THE WORLDWIDE PANDEMIC

HIV has already infected more than 60 million people around the world. According to a new CIA report, "The HIV/AIDS pandemic continues to spread around the world at an alarming rate, and the number of people with the disease will grow significantly by the end of the decade, as it becomes more geographically diffuse. By 2010, we estimate that five countries of strategic importance to the United States—Nigeria, Ethiopia, Russia, India, and China—collectively will have the largest number of HIV/AIDS cases on earth." A recent article in *Foreign Affairs* magazine stated, "The spread of HIV/AIDS through Eurasia, in short, will assuredly qualify as a humanitarian tragedy—but it will be much more than that. The pandemic there

stands to affect, and alter, the economic potential—and by extension, the military power—of the region's major states . . . Over the decades ahead, in other words, HIV/AIDS is set to be a factor in the very balance of power within Eurasia—and thus in the relationship between Eurasian states and the rest of the world.” Dramatic increases in HIV infection also are occurring in Eastern Europe, Central Asia, Latin America, and the Caribbean. An article in the *New York Times* recently reported another dimension to the epidemic: “As a result of HIV, the worst-hit African countries have undergone a social breakdown that is now reaching a new level: African societies’ capacity to resist famine is fast eroding. Hunger and disease have begun reinforcing each other.”

THE U.S. EPIDEMIC

The Centers for Disease Control and Prevention (CDC) recently reported that more people were diagnosed with AIDS in 2001, the latest year for which reliable statistics are available, than the previous year, or any year since 1998. After years of sharp declines, thanks largely to successful treatment with new antiretroviral therapies (ART), this report indicates a reversal in cases of AIDS in the U.S. Further, CDC reported that the rate of new HIV diagnoses, which had remained stable since 1990, also appears to be increasing. New HIV infections rose a striking 8 percent between 1999 and 2001, based on data from 25 states with mandatory HIV reporting, which does not include the two highest prevalence states of New York and California. HIV infection rates continue to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people over 50 years of age. In addition, use of ART has now been associated with a series of side effects and long-term complications that may have a negative impact on mortality rates. The appearance of multi-drug resistant strains of HIV presents an additional serious public health concern. According to CDC reports, approximately one quarter of the HIV-infected population in the United States also is infected with Hepatitis C virus (HCV). AIDS affects African Americans and Hispanics disproportionately. According to CDC figures through December 2001, approximately 64 percent of newly infected women are African American and 17 percent are Hispanic. Among newly infected men, approximately 43 percent are African American and 20 percent are Hispanic. This expanding and evolving U.S. epidemic presents new and complex scientific challenges.

COMPREHENSIVE AIDS RESEARCH PLAN AND BUDGET

To address these compelling scientific questions, the OAR develops an annual comprehensive trans-NIH AIDS research plan and budget, based on the scientific priorities and opportunities that will lead to better therapies and prevention strategies for HIV infection and AIDS. The planning process is inclusive and collaborative, involving the NIH Institutes, as well as eminent non-government experts from academia, industry, foundations, and AIDS community representatives. The Plan serves as the framework for developing the annual AIDS research budget for each Institute and Center, for determining the use of AIDS-designated dollars, and for tracking and monitoring those expenditures.

The Plan establishes the NIH AIDS scientific agenda in the areas of: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science. In addition, the plan addresses the cross-cutting areas of: Microbicides; Racial and Ethnic Minorities; Women and Girls; Prevention Science; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination. In consultation with the Director of NIH, the OAR determines the total annual AIDS research budget. Within that total, the OAR establishes the AIDS research budgets for each NIH Institute and Center, in accordance with the priorities and objectives of the Plan, at each step of the budget development process up to the Conference Committee. To accomplish this, OAR consults regularly with the Institute and Center Directors. This process allows the OAR to ensure that NIH AIDS research funds will be provided to the most compelling scientific opportunities, rather than a distribution based solely on a formula.

OAR plays a crucial role in identifying scientific areas that require focused attention and facilitating multi-Institute activities to address those needs. OAR fosters this research through a number of mechanisms, such as designating funds and supplements to jump-start or pilot program areas, sponsoring workshops or conferences to highlight a particular research topic, and sponsoring reviews or evaluations of research program areas to identify research needs.

The overarching priorities that continue to frame the NIH AIDS research agenda are: prevention research to reduce HIV transmission, including development of vaccines, microbicides, and behavioral interventions; therapeutics research to develop

simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection and its associated illnesses, malignancies, and other complications; international research, particularly to address the critical needs in developing countries; and research targeting the disproportionate impact of AIDS on minority populations in the United States. All of these efforts require a strong foundation of basic science, the bedrock of our research endeavor.

NEW CHALLENGES IN THERAPEUTICS RESEARCH

While multiple ART drug combinations continue to successfully reduce viral load and restore immune responses in many HIV-infected individuals, these regimens also can result in serious toxicities and side effects, single- and multiple drug-resistance, and other complications which make them unacceptable for some individuals. These side effects and complications appear to be increasing as HIV-infected individuals continue on drug regimens. More deaths occurring from liver failure, kidney disease, and cardiovascular complications are being observed in this patient population. NIH-sponsored research efforts continue to develop better antiretroviral drugs and treatment regimens that demonstrate less toxicity, activity in viral and cellular reservoirs, reduced development of drug resistant virus, improved pharmacodynamics and pharmacokinetics, easier compliance, and lower cost.

While the incidence of certain opportunistic infections (OIs) and malignancies has decreased with the advent of ART, the number of cases of TB, multiple drug resistant TB, and other coinfections such as Hepatitis B virus and Hepatitis C virus has increased. The development of practical and affordable treatment regimens against HIV coinfections and endemic diseases in developed and developing nations is an NIH priority.

PREVENTION RESEARCH

NIH supports a comprehensive approach to HIV prevention research that includes contributions from the biomedical, behavioral, and social sciences. Our biomedical prevention research priorities include the development of vaccines, topical microbicides, strategies to prevent mother-to-child transmission-including a better understanding of risk associated with breast-feeding-and management of sexually transmitted diseases (STDs). NIH also supports behavioral research strategies, including interventions related to drug and alcohol use. Efforts continue to identify the most appropriate intervention strategies for different populations and sub-epidemics in the United States and around the world. As a result of increased NIH funding, many new approaches to HIV vaccines are being pursued. Although production of candidate vaccines for clinical study has proceeded slowly, at least 10 new candidate vaccines will enter Phase I trials in the next 2 years. Several new combinations of products, which are expected to provide better immune responses, also will be tested in Phase I or II trials. The Dale and Betty Bumpers Vaccine Research Center, located on the NIH campus, recently launched the first Phase I clinical trial of a multi-clade, multi-gene vaccine candidate.

INTERNATIONAL RESEARCH

To address the increasing urgency of the AIDS pandemic, the OAR established an initiative and strategic plan for global research on HIV/AIDS and has significantly increased research efforts in the past several years to benefit resource- and infrastructure-poor nations. NIH supports a growing portfolio of research conducted in collaboration with investigators in developing countries. Results of this research benefit the people in the country where the research is conducted, as well as people affected by HIV/AIDS worldwide. Critical to the success of these international studies are foreign scientists who are full and equal partners in the design and conduct of collaborative studies. To that end, NIH also supports international training programs and initiatives that help build infrastructure and laboratory capacity in developing countries where the research is conducted.

WOMEN AND MINORITIES

Women experience HIV/AIDS differently from men. NIH research has demonstrated that women progress to AIDS at lower viral load levels and higher CD4 counts than men. Women also experience different clinical manifestations and complications of HIV disease. These findings may have implications for care and treatment of HIV-infected women, particularly with ART. There are many research questions that remain unanswered about specific characteristics of women and girls that might play a role in transmission, acquisition, or resistance to HIV infection during different stages of the life course.

In many U.S. urban centers, HIV seroprevalence rates mimic those found in some developing nations. These findings, along with the resurgence of STDs and associated high-risk behaviors, demonstrate the need for comprehensive strategies to decrease HIV transmission in affected vulnerable populations, and improve treatment options and treatment outcomes. OAR is directing increased resources toward research to develop new interventions that will have significant impact on these groups. These include interventions that address the co-occurrence of other STDs, hepatitis, drug abuse, and mental illness; and interventions that consider the role of culture, family, and other social factors in the transmission and prevention of these disorders in minority communities. NIH is making significant investments to improve research infrastructure and training opportunities for minorities and will continue to ensure the participation of minorities in AIDS clinical trials, as well as in natural history, epidemiologic, and prevention studies. OAR has provided additional funds to projects aimed at increasing the number of minority investigators conducting behavioral and clinical research; targeting the links between substance abuse, sexual behaviors, and HIV infection; increasing outreach education programs targeting minority physicians and at-risk populations; and expanding the portfolio of population-based research. One of these projects is a series of Training and Career Development Workshops that provide minority investigators with an opportunity to learn more about available NIH funding mechanisms and to meet and network with senior minority investigators who receive significant levels of NIH funding.

SUMMARY

The human and economic toll of the AIDS pandemic is profound. It requires a unique response that is complex, comprehensive, multi-disciplinary, and global. The NIH role in this response is fundamental and unprecedented. The diverse AIDS research portfolio demands scientific coordination and management of research funds to enhance collaboration, minimize duplication, and ensure that precious research dollars are invested in the highest priority areas of scientific opportunity. The nation's investment in AIDS research is reaping even greater dividends, as AIDS research is unraveling the mysteries surrounding many other infectious, malignant, neurologic, autoimmune, and metabolic diseases.

The authorities of the Office of AIDS Research allow NIH to pursue a united research front against the global AIDS epidemic. We are deeply grateful for the continued support this Committee has provided to our efforts.

ACTING DIRECTORS

Senator SPECTER. Thank you very much, Dr. Zerhouni.

Are there any other institutes which have acting directors at the present time?

Dr. ZERHOUNI. Yes. We have three institutes this minute. NIGMS, the General Medical Science Institute is—the Acting Director is Dr. Judy Greenberg. And she is with us today.

Senator SPECTER. And when do you expect to have a permanent director there?

Dr. ZERHOUNI. Senator, I have worked—the top priority for my first year was to complete all six—I mean, to fill all six vacancies for the six institutes that were vacant within the year. So I expect that, I hope on my first anniversary that all institutes will have new directors that have acting directors today.

Senator SPECTER. Dr. Zerhouni, the subcommittee would appreciate knowing a little more about your efforts there. There is an inevitable sense that a full-time director with that authority is necessary to move an institute along at top speed. So would you submit to us in some detail, in writing, your expectations and the progress and keep us informed as to how you are doing on full-time directors for those institutes?

Dr. ZERHOUNI. I will certainly do. And I agree with your views on that.

[The information follows:]

PROGRESS ON FULL-TIME DIRECTORS

Mr. Chairman, I consider the selection of outstanding, highly qualified scientist-administrators as directors of the various institutes to be among my highest priorities. Over the past eleven months, I have filled three of the vacancies for Directors of Institutes at NIH and have appointed:

Dr. Thomas Insel, Director, National Institute of Mental Health

Dr. T. K. Li, Director, National Institute on Alcohol Abuse and Alcoholism

Dr. Nora Volkow, Director, National Institute on Drug Abuse

Two other vacancies remain and I and my staff are working very hard to complete the searches so that I can make appointments:

—The search for the Director, National Institute of Neurological Disorders and Stroke has been prolonged, unfortunately. It started in March, 2001 and, after careful consideration, the leading candidate withdrew and took a position at a pharmaceutical company in November, 2001. The vacancy announcement was re-issued and a slate of three highly qualified candidates was sent forward, all of whom were interviewed by the Acting Director, NIH between late February and March, 2002. A candidate was offered the position at the end of March, accepted verbally and subsequently, withdrew in early April 2002.

Upon my assuming the Directorship of NIH, I discussed the situation with my senior staff and decided to reconstitute the search committee, and solicit applicants myself. This resulted in several new applicants and consideration of several previous candidates. Five candidates were interviewed and as of the time of submission of this response, I am in active discussion with my selectee. I anticipate that I will be able to name a Director for NINDS within a very short time.

—The search for the Director, National Institutes of General Medical Sciences was initiated in mid-March, 2002. The search committee interviewed a total of ten candidates between late September, 2002 and February, 2003. Of the group, I and my senior staff have interviewed three during March and early April and anticipate conducting one more interview. I anticipate that a selection will be made in the next month.

SALIVARY DIAGNOSTICS

Senator SPECTER. Dr. Zerhouni, one of the questions which we characteristically ask is the question about what progress is being made on major ailments and what could be done with greater funding. And it is obviously a very difficult question. It may be an impossible question when we ask when will a cure be found for Parkinson's. I choose Parkinson's because 5 years ago there were estimates that Parkinson's would be cured within 5 years.

Nobody can hold you to a cure time. But we would be interested in your projection on where you see NIH heading on the ailments to give us some projection as to what your expectations are. We understand that it is not possible to be scientifically precise. And then to tell us what more you can do with increased funding, what level of funding on the specific ailments would enable you to project an earlier time and by how much.

Our colleagues in the Congress are very goal-oriented. And even questions which are really not answerable with precision are pursued. So to the extent that you could give us some ideas on those questions, the subcommittee would be very appreciative.

Let me turn to Dr. Lawrence Tabak of the Dental Institute on a question which has recently come to the attention of the subcommittee on the presence of a cancer-related protein in saliva that could result in more acute, less costly ways to diagnose breast cancer in women. The question, Dr. Tabak, is, how much is being requested in the budget to pursue this line of research? And do you have any plans to conduct clinical trials in this area?

Dr. TABAK. Thank you for the question, Senator Specter. In this current fiscal year, NIDCR is expending approximately \$7 million

in the general area of salivary diagnostics. And for the next fiscal year, we hope to spend approximately \$1.5 million more to continue in this effort.

Senator SPECTER. \$1.5 million?

Dr. TABAK. Yes, sir, that is correct.

Senator SPECTER. What is the total budget of your institute?

Dr. TABAK. Currently, it is \$371 million, sir.

Senator SPECTER. Does this new test pose real promise to give an easier, better diagnosis of breast cancer?

Dr. TABAK. This and other salivary diagnostic tests do offer a great deal of promise, sir. The test to which you are referring, as you know, was worked out at the University of Mississippi. It is a test which recognizes a protein which can be found both in blood and saliva. But because of the ease of detection and the ease of sample collection in saliva, we feel that there are certain advantages for the saliva-based test.

Senator SPECTER. Dr. Tabak, if you allocated more than \$1.5 million, do you think you could get a faster result on this important test?

Dr. TABAK. Certainly, sir, resources are always welcome. But there is a point at which basic information needs to be gathered. And until that basic information is obtained, it would be premature to expend additional funds in a particular area.

Senator SPECTER. Are you saying that is the maximum amount that can be efficiently spent on that research?

Dr. TABAK. In terms of bringing this work to a full-blown clinical trial, sir, I think it would be premature. What we are now doing is termed phase-one trials to begin to understand whether or not this test is both accurate and efficacious. Once that base information is obtained, sir, then it would be appropriate to go on to larger scale trials.

Senator SPECTER. Thank you.

Senator Murray.

Senator MURRAY. Thank you very much, Mr. Chairman.

PEDIATRIC RESEARCH

Dr. Zerhouni, when you were confirmed, you and I talked about pediatric research. And I wanted to ask you today about any progress you have made. I think we have made a lot of progress on reducing gender bias, but I am still deeply concerned that we have not made much progress on making sure that we are looking at everything in terms of what happens to children.

Can you give us an update on your pediatric research initiative?

Dr. ZERHOUNI. Well, as you know, the pediatric research initiative is guided by a major document that we have been following in terms of implementation. There is no doubt in my mind that pediatric research is a priority, continues to be a priority. We have to also invest and continue to invest in the multiple areas of pediatric research.

We are, for example, invested in terms of talent and developing talent and training capabilities for pediatric research. We are continuing to make investments in many of the pediatric diseases separately. For example, we have increased our investment in mus-

cular dystrophy or increased our investment in spinal muscular atrophy. And in every category we have a disease-specific plan.

But in terms of the overall investments in pediatric research, we need to integrate the pediatric research agenda within not just the NICHD Institute, which is primarily responsible for pediatric research, but all institutes.

So I think it is work in progress. I think we are making good progress. But we will continue to consider that a priority, realizing as well, Senator, that many of the changes we need to make relate to these priority areas that I described—multidisciplinary teams that should invest in pediatric research, clinical research networks. For example, the Office of Rare Diseases is looking at establishing networks across the country to look at these rare diseases that tend to affect children.

So we are looking at a multi-pronged approach and a strategic approach in pediatric research.

FUNDING OF RESEARCH PRIORITIES

Senator MURRAY. Dr. Zerhouni, as you well know, there is a lot of misunderstanding about NIH research dollars. There is kind of this assumption out there that NIH only funds politically correct diseases or that you have to have a high-profile celebrity in order to secure any NIH funding. And I know this subcommittee under Senators Specter and Harkin have really resisted any efforts to earmark NIH dollars by disease. We can express our thoughts through report language.

But could you explain for us how you establish the priorities for NIH funding and what criteria is used in evaluating research applications?

Dr. ZERHOUNI. Certainly, Senator. This is a question that is a recurring theme, especially when any particular area feels underserved. So that when we look at the decisionmaking process, we realize that there are fundamentally several factors that come into play. One, the first and foremost is the burden of the disease as we know it through epidemiological studies. And second, the predicted future burden of disease.

For example, just as a matter of example, you look at diabetes and the rise in expenditures in diabetes, it parallels what we predict the burden of disease in diabetes is going to be. When you look at obesity research, we are now investing at an accelerated pace in obesity research because of the prediction. Even though when you look at the disease burden, per se, you cannot really decide that this is the only factor that you should look at, because the second factor is, have we made enough scientific advances to invest in the particular area with results that are likely to occur?

So we look fundamentally at the investments in terms of, A, the burden of disease; B, the priority setting in terms of science. And we get advice in that context for many more sources than any. I am very impressed with the fact that NIH receives advice from 21,000 advisors every year on every single condition that we face.

So the process is not an easy one to consider. But clearly, the patient advocacy groups are also interested in looking at how we invest. And my gratitude goes to you, because I think earmarking would not be a good direction for setting scientific priorities at

NIH. And we try to avoid that and try to not be politically correct, as you state.

Senator MURRAY. Well, I think it is really important to keep talking about how you set your criteria to the general public, because we do have a misperception constantly that if you get a high-profile person, that you get more funding. And so it makes it harder on us. And, as I said, Senator Specter has done a really good job managing that. But it is very difficult.

I think it is important that we base it on science. So I appreciate your comments.

Thank you, Mr. Chairman.

Senator SPECTER. Thank you, Senator Murray.

Dr. Zerhouni, I broach the subject of some delicacy now, which has already been communicated to you. Last year the Senate figure was cut by \$25 million because the conference committee concluded that to reach the doubling, which was an astronomical figure, was more than sufficient. We have an enormous number of complaints from other research agencies about, candidly, the favoritism that NIH gets. And we have fought those battles out.

We have heard from a number of people about directors of the institutes who have said that certain grants could not be applied or certain research could not be undertaken because the budget was cut and have attributed the \$25 million reduction, which was not a cut at all, because there was an increase of more than \$3.7 billion to the NIH budget.

It would be amazing, I think, to many of you ladies and gentlemen, how fast the information travels from what you may tell someone who is applying for a grant or you may tell someone who is concerned about more research right back to my ears. You would be surprised.

The advent of this very, very heavy increase in funding for NIH, which has come from this subcommittee, has had the reverberating effect of having this subcommittee contacted by many, many, many people, which had not been the case before we took up the cause of increasing the NIH grant. So if you do not want to make some allocation or you do not want to make a grant or you do not want to undertake some research, if you say it is because you got a cut in your budget, that is going to come back to the Congress.

We hope you do not ever have a cut in your budget. But bear in mind that these people—and I know you have a good sense of this yourself—feel so very intently about these subjects, very, very emotional, when you have a child with one of these maladies, it is just the edge of the ledge. And I know that you dedicated men and women are well aware of that. But I thought it important to make a quasi-public statement. I have not said very much on the subject in the brief remarks I have just made.

Let me turn now to the question of stem cell research. And I would like to direct this question to Dr. James Battey of the Deafness Institute and also to Dr. Allen Spiegel of the Diabetes and Digestive and Kidney Institute. Last September, this subcommittee held a hearing regarding the implementation of the Federal stem cell policy. And as you all know, back on August 9, 2001, President Bush articulated a modification of Federal policy to allow Federal funding on existing stem cell lines.

At the September 25, 2002 hearing, Dr. Curt Civin stated, "Embryonic stem cell research is crawling like a caterpillar, while NIH has listed eligible lines in its registry at 78. Only a tiny fraction of these lines are accessible and only to those persistent and patient enough to jump through a series of hoops and endure lengthy waits. I am still waiting to receive my first stem cell line."

Dr. Battey and then Dr. Spiegel, what steps has NIH taken to help people like Dr. Civin and other scientists gain access to embryonic stem cell lines? And how many are now accessible?

ACCESS TO EMBRYONIC STEM CELL LINES

Dr. BATTEY. The process of scaling up an embryonic stem cell derivation to the point where it can be distributed as a high-quality, well-characterized cell line takes about a year from start to finish. It is an expensive, time-consuming, technically demanding process that requires enormous care to maintain the cells in their state of pluripotency, which means their ability to differentiate into many different cell types, as well as to remain continuously self-renewing.

To facilitate this very expensive and time-consuming process, the NIH has awarded infrastructure grants awards to eight suppliers that have derivations on the NIH stem cell registry. And I am pleased to tell you, Mr. Senator, that between the September hearing and the hearing today, if you had a research laboratory and wanted to order cell lines, in September you could have ordered five such cell lines. And right now, you could order 11 lines today.

That effort is continuing to expand. And we expect that increasing numbers of cell lines will be widely available and actively shipped to the research community over the next 6 months to a year.

Senator SPECTER. How many stem cells are currently available?

Dr. BATTEY. You could order 11 lines today.

Senator SPECTER. Is that sufficient for the research which people want to undertake?

Dr. BATTEY. At this point in time, the fundamental challenge in the human embryonic stem cell research arena is a basic research challenge. It is a challenge to understand what growth factors, transcription factors, and other molecules regulate the ability of embryonic stem cells to differentiate into one cell type versus another. It is an understanding of the interaction between the host and the transplanted cell that allows that cell to persist for a long time within the host and to function correctly.

It is a challenge to understand how you control the cell cycle division of the cell, because once it is transplanted into a host, you do not want it to continue to be self-renewing in the same way that it was in the laboratory before it was transplanted.

These basic research questions are readily addressable with the cell lines that are currently available and will become available within the next few months to a year.

Senator SPECTER. Do we have sufficient stem cell lines for the research that people want to undertake?

Dr. BATTEY. We have sufficient cell lines to embrace the basic research challenge that is in front of us today.

Senator SPECTER. Well, is there some facet besides the "basic research challenge," which is in front of us today?

Dr. BATTEY. The major questions that confront the stem cell research community today can be addressed with the cell lines that are available.

STEM CELL INFRASTRUCTURE AWARDS

Senator SPECTER. Dr. Spiegel, would you care to amplify on Dr. Battey's answer?

Dr. SPIEGEL. I would be happy to. Thank you, Senator Specter.

Some general comments to amplify on what Dr. Battey said would include the provision of support through so-called infrastructure awards to the providers of these human embryonic stem cell lines. NCRR is funding the majority of these infrastructure awards. NIDDK is funding two of them. And this provides support to allow the distribution of these cells because they are very, very difficult to grow.

Several NIH institutes have combined to provide training courses. As Dr. Battey has emphasized, one of the rate-limiting steps here is bringing new investigators into the field. It is not trivial to learn how to grow human embryonic stem cells. And these training courses are directed at that.

A further example, which again comes out of the NIH Stem Cell Task Force, for which Dr. Zerhouni appointed Dr. Battey the Chair and on which I am pleased to serve, is an intramural NIH facility, which will be under Dr. Ron McKay and the Neurology Institute with extramural investigators as advisors. This effort will be comparing and looking critically at the different available human embryonic stem cell lines to provide information that is critical before investigators order them to work on in their own lab.

Let me then just briefly speak on NIDDK specifically. NIDDK, like many of the other NIH institutes, has invested heavily in all aspects of stem cell research. So-called adult stem cell research, animal stem cell research, because animal models are very important, as well as human embryonic stem cell research. The aggregate figure for fiscal year 2002 for NIDDK was \$58.3 million.

One particular new initiative that we undertook, based on a trans-NIDDK planning group was so-called stem cell genome anatomy projects. These span the entire spectrum of the NIDDK mission so that we have projects directed at understanding the development of cells in the bone lineage, which we do with the Arthritis Institute, in the gastrointestinal and liver lineage, in the urology and the kidney lineage, and then so-called hematopoietic stem cells.

One of our most important initiatives relating specifically to Type 1 and Type 2 diabetes is the so-called beta cell biology consortium. Of course, it is the beta cell that makes insulin, which is lacking in Type 1 diabetes and deficient in Type 2 diabetes. This consortium is looking at every avenue of approach to the development of these critical cells.

Thank you.

STEM CELLS AND MOUSE FEEDER CELLS

Senator SPECTER. Dr. Spiegel, what about the research to isolate stem cells without the use of mouse feeder cells?

Dr. SPIEGEL. Currently, to my knowledge, although there have been reports from industry about the ability to grow human embryonic stem cells absent mouse feeder cells, the lines that are in use or available that Dr. Battey referred to do use mouse feeder cells. As Dr. Battey emphasized, this is not hampering the ability to do the basic research that we need to do to really be able to understand how we can trigger in a very organized and efficient way the development of these cells into various therapeutic possibilities.

Senator SPECTER. Is it not true that research without the use of mouse feeder cells is indispensable, necessary to use those stem cells in humans?

Dr. SPIEGEL. I totally agree. The comment that I was going to make is that a critical intermediate step before anyone should contemplate—in terms of safety and every other consideration—going into human trials, would be animal models, from small animal models and eventually to non-human primate models. Here, too, the mouse feeder layer issue is not rate-limiting.

But, you are certainly correct that to go into human trials, there would be issues that would have to be addressed in terms of possible mouse viruses and other contaminating proteins.

Senator SPECTER. Should not those issues be addressed now by NIH?

Dr. SPIEGEL. I think that that is an important issue. I think that, in terms of the available lines, there are important technical developments that can be undertaken that are critical to understand what the factors are that these mouse feeder-layers are eliciting that are necessary to keep the human embryonic stem cells from differentiating spontaneously. That is really the critical issue for which they are used.

I believe that the kind of research that is being done, research that we can support, will very much address those kinds of issues. That is, after all, the goal, to really understand how to trigger development along a pathway that we want, and yet to prevent spontaneously differentiation. And such growth factor and other signaling research is being undertaken.

Dr. BATTEY. If I could, Mr. Senator. Dr. Spiegel—

Senator SPECTER. Wait just a minute. I find that very interesting, if not totally understandable. But what about the basic question of having some research without the use of mouse feeder cells? Do you not think that would be a pretty good idea with all you are doing? How many millions did you say you were spending?

Dr. SPIEGEL. The total figure for NIDDK for fiscal year 2002 was \$58.3 million.

Senator SPECTER. Well, why not some research without the mouse feeder cells? If they are to be used in humans, you are going to have to move in that direction.

Ladies and gentlemen, what I want to be sure about, and I cannot quite accomplish it in this hearing today, is that we are not making any political decision, that you are making scientific deci-

sions. That is what we expect from you scientists. That is why we are putting up \$27 billion, which is a very, very big public trust. Do you want to say something more, Dr. Battey?

MOUSE FEEDER CELLS

Dr. BATTEY. I just wanted to add to what Dr. Spiegel said. The first challenge to getting rid of the mouse feeder layer is figuring out what the mouse feeder layer is providing to the embryonic stem cells to render them able to differentiate into many different cell types and be self-renewing. And there is active research efforts to identify the factors that allow these cells to remain in that state. And when those factors are known and understood, we will be in a position to attempt to grow these cells absent a mouse feeder layer.

Senator SPECTER. Dr. Penn, let me direct a question to you with respect to spinal muscular atrophy, a genetic motor neuron disease characterized by the wasting away of skeletal muscles. It is the leading killer of infants and toddlers. Twenty-five thousand Americans have the disease with up to 1,000 new babies born with the disorder each year.

While there is a transitional research program, we are concerned about how effectively it is being put into operation. When spinal muscular atrophy was selected for this transitional research program—when was SMA selected for this transitional research program? And when will the first grants be awarded?

Dr. Penn.

SPINAL MUSCULAR ATROPHY RESEARCH

Dr. PENN. Yes, Senator. Spinal muscular atrophy actually is the leading genetic cause of infant mortality. It is not always lethal—there are three or four forms of it. In one form, it is really deadly to babies. But in several others, adults can grow and function and live with this disease.

Spinal muscular atrophy, we feel, is a great scientific opportunity, because we not only know the genetic defect, but we know something about how to try to render this disease perhaps not cured, but to help it by dealing with the genetic defects. And therefore, we did decide to move this disease toward treatments, and I must say with a lot of help from the voluntary agencies, as well as the Muscular Dystrophy Association. And this is actually part of an institute-wide effort to move in what we call translational research, dealing with the basic mechanisms of a disease and then going to treatments.

So we do have a brand-new way of pursuing working toward trying these treatments and doing clinical trials. We will go to the point of an investigational new drug application with FDA. And it has taken time to do this properly. This is so new that we have worked very hard to make it—to have a really excellent product.

Actually what we are going to do is have a contractor issue subcontracts. And the subcontracts will be directed at the group of investigators out there that have done wonders to figure out what is going on with this disease since the gene was identified in 1995.

So we will not be issuing grants. The contractor will actually call for subcontracts. We expect the whole group of investigators to

come in for these. There will then be let a contract. And they will have to achieve milestones. It is not so much reporting on what you—yes, reporting on what you have done. You have to achieve something.

There are drugs, actually drugs, that could be used in this disorder. And one of our intramural investigators, who is internationally recognized in these areas, is trying one of these drugs right now. But he is only working on cell lines from the patients. Again, we have to be very careful about using some of these things and moving to human beings.

It has taken time. But we are issuing—we have issued the requests for proposals for this contract. And we expect to have this move by the end of the summer.

Senator SPECTER. Dr. Penn, the question is, when was SMA selected for this transitional research program?

Dr. PENN. Over a year ago. It took a year and a half to get it to this point.

Senator SPECTER. Well, when will the first grants be awarded?

Dr. PENN. The first subcontracts, sir, will be awarded, I would say, this winter.

Senator SPECTER. When?

Dr. PENN. This winter, sir.

Senator SPECTER. Why is it taking so long?

Dr. PENN. To do it properly and to get our intramural program up and running with it and to make sure that we develop and design this whole program so that we would have a really excellent result.

Senator SPECTER. Well, why does it take almost 2 years, Dr. Penn?

Dr. PENN. As I said, sir, this is something brand-new for us. It is a contract-based program. And it has taken 2 years.

Senator SPECTER. It is something brand-new, but it is a contract-based program.

Dr. PENN. It is brand-new for us. And we have—we are going to have a steering committee made up of the experts, both academic and—

Senator SPECTER. You are going to have a search committee?

Dr. PENN. A steering committee, sir, to run—

Senator SPECTER. You are going to have a steering committee?

Dr. PENN. For it to run—

Senator SPECTER. Has the steering committee been appointed?

Dr. PENN. It is being appointed right now.

Senator SPECTER. Why does that take so long?

Dr. PENN. Well, we had not gotten to that phase of the exercise.

Senator SPECTER. Well, why have you not gotten to that phase?

Dr. PENN. It just took this long to do this properly. It took this long—

Senator SPECTER. Dr. Zerhouni, would you take a look at that and submit in writing—

Dr. ZERHOUNI. Yes, Senator.

Senator SPECTER [continuing]. What has happened?

Dr. ZERHOUNI. I have looked—

Senator SPECTER. I would like to have—but I am not going to take it up now.

Dr. ZERHOUNI. Fine.

Senator SPECTER. I would like to have precise answers as to when the program was adopted, as you call it a translational research program.

Dr. ZERHOUNI. Understood.

Senator SPECTER. And when a steering committee is adopted. And this subcommittee wants to examine whether there is an appropriate sense of urgency. It certainly has not satisfied a lot of parents whose children have this ailment.

Dr. ZERHOUNI. I will respond directly to you on the record, sir.

Senator SPECTER. Okay. We would appreciate it, if you would.

[The information follows:]

SPINAL MUSCULAR ATROPHY

The NIH is committed to accelerating research toward finding a treatment for SMA, and fully appreciates the sense of urgency expressed by the parents of children with this disease, as it does the concerns of the parents of children affected by the scores of other neurological disorders—many of which are genetic and are often disabling or lethal. The NINDS recently launched a comprehensive program designed to encourage and support translational research for all neurological disorders. By translational research, I mean the process of applying insights and discoveries from basic scientific inquiry to the treatment or prevention of disease; the emphasis is on those activities focused on bringing therapeutic strategies to readiness for clinical testing.

The specific, contract-based, SMA translational project to which you refer is in addition to all the other funding opportunities that are currently available for SMA research. It will use a performance-based contract mechanism to allow rapid funding of translational research, in a milestone-driven process, to identify treatments for SMA. The NINDS presented the idea for this program to its National Advisory Neurological Disorders and Stroke Council in February 2002.

The primary contract for the SMA project, which we expect to award on or about September 30 of this year, will provide overall scientific direction and organizational support for the program. A Steering Committee, drawn from academia, industry, the public, and NIH, will guide the program and play an integral oversight role for the Contractor throughout the project. A working group of the Council, including members of the proposed Steering Committee, will develop detailed recommendations for a plan for research on promising therapeutic strategies for SMA, such as drug development, gene therapy and stem cell therapy. The plan will address all the steps required, ultimately, to develop an IND—Investigational New Drug—application. The implementation of the research plan will be finalized by the Contractor, with guidance from the Steering Committee. The Steering Committee will assist the Contractor in evaluating success in accomplishing milestones, and in developing additional calls for research proposals as needed. Because the role of the Steering Committee is so integral to, and defined by, the contract, it would have been premature to establish its membership in advance of the publication of the statement of work in the request for proposals (RFP) for the SMA program; this RFP was issued on April 22, 2003. Importantly, efforts to recruit the Steering Committee are well underway, and there will be detailed recommendations for the research plan ready for presentation to the Council in September; calls for research projects can be issued in October 2003, shortly after the contract is awarded, and research projects should be underway by February 2004.

The SMA translational program is not just a novel program for SMA, but also for the NINDS. The aim is to develop treatments that will be tested in people, and we hope this effort will serve as a model for expediting therapy development for other disorders. This program will require a significant investment of resources; the contract will be awarded for four years, and NINDS intends to fund the research subcontracts at a level of \$4.5 million per year, which we anticipate will fund up to approximately ten research subcontracts per year. The NINDS intramural program will be involved throughout the process, providing expertise in neurogenetics and SMA, and will be equipped to rapidly initiate Phase I/II clinical trials when appropriate. For all of these reasons, careful planning has been essential.

Senator SPECTER. Senator Harkin.

Senator HARKIN. Thank you, Mr. Chairman. I have an interest in SMA, also. I have met with families in Iowa about this. And I am concerned, as Senator Specter, that the leading cause of infant mortality is something that—

Senator SPECTER. You ladies and gentlemen would be amazed with how many families we have met with with SMA and the other ailments.

Senator HARKIN. Yes. I started meeting with them maybe a couple years ago in Iowa or something. And this is something I had not even known about before. And now I just—now we find out that it is the leading cause of infant mortality. And we just have not done that much research on it. So I agree with you, we have to push hard on that. We have to get this thing moving. And I do not know why it has not by now. So I agree with the chairman on this, that we have to find out about that.

Senator SPECTER. Well, there is one fellow who suffers from Parkinson's, who has an hourglass. Whenever he sees me, he turns the hourglass. And the ticking sands are going through the hourglass on every hour of his life. And these parents come to us with SMA and other ailments.

I am about to go through a fairly long list of questions. We are going to take a little more time today, because we want to know what the sense of urgency is as to how these issues are being addressed.

These people come to us and say, you are giving NIH all the money. What is happening? I do not like to hear talk of long periods of time on appointing steering committees.

Senator Harkin.

Senator HARKIN. Thank you again, Mr. Chairman.

I understand that you, in my absence—I was unavoidably absent from here a little bit—that you did cover the issue of stem cell research. And I just again want to buttress what you have said and hope that we can move ahead aggressively in this area, too. I understand that has been covered. So I will not go into that.

The only thing that I just wanted to cover with you, Dr. Zerhouni, was just basically broader picture of the funding of NIH. We, as you know, basically just finished the doubling over 5 years. Senator Specter and I are both, with his leadership and with my support, starting to get on another pathway of trying to get it up to a tripling, that is, from what we started in 1998.

To maintain that level, it seems to me we are going to have to have somewhere in the neighborhood of about 7 or 8 percent a year, if I am not mistaken, increases. And it is my understanding, also, that just to maintain and kind of keep doing what we are doing, we are going to need somewhere in that level of funding. And yet the budget request this year is a 2.5 percent request.

So how can we keep from falling back from what we have done? And how can we continue to move ahead with a fairly aggressive level of expansion of NIH basic research at 2.5 percent, or 2.6 percent, I guess it is?

Dr. ZERHOUNI. Thank you.

Senator HARKIN. I mean, my point is, you asked for 2.6 percent.

SUSTAINING RESEARCH PROGRAMS ON MODEST BUDGET INCREASES

Dr. ZERHOUNI. Thank you for your question. This is a very important consideration. Because one of the issues that we have to match with the concept of doubling is why are we doubling? And what are we trying to accomplish? And I think one of the issues that I raised was that we have evolving challenges. We have in fact stimulated in our country an incredible change in the way we do biomedical research. And we are in the transition phase in terms of understanding the new methods of research and the new teams that need to do this research.

When you look at the 2004 budget, I worked very hard with the administration, with the Department, and with the Office of Management and Budget, when you look at the 2.6 percent overall, and we worked so that the effect on our research would be about 7.5 percent overall. And the reason for that is because we have essentially used one-time expenditures that related to building the infrastructures that we needed for biodefense research and other one-time items and reinvested it in research.

So for 2004, the impact on the research portfolio in terms of growth is greater than the 2.6 percent, Senator.

Senator HARKIN. Well, I want to delve into that. In fiscal year 2003, Congress funded more than \$300 million for extramural construction with allergies and infectious diseases, bioterrorism.

Dr. ZERHOUNI. \$375 million.

Senator HARKIN. \$375 million?

Dr. ZERHOUNI. Yes.

Senator HARKIN. I think you can argue that was probably a one-time expense.

Dr. ZERHOUNI. Correct.

Senator HARKIN. But if I look at the extramural facilities renovation and construction program, going back just the last few years, this is an ongoing funding stream that this committee has funded, under different chairmanships here. We have all been supporting extramural construction and renovation. We know that some of the labs around the United States are deficient. They need to be upgraded. I am sure Senator Specter has visited, as I have. And so we embarked on this, also, a few years of making a funding stream every year available.

So how can you say that this is a one-time expense? I could see saying that the \$300-and-some million that we put in last year was a one-time expense for bioterrorism. But we have an ongoing extramural renovation and construction program that last year was \$119 million, aside from that \$300-and-some million. It was \$110 million the year before. Now it was \$75 million a year for a few years before that. But then we bumped it up, because we saw the need out there. And now in fiscal year 2004, we are requesting zero dollars.

To me, that is not a one-time expense. It is an ongoing commitment that we have to rebuild and modernize our laboratory infrastructure in the United States.

FUNDING COMMITMENT TO EXTRAMURAL CONSTRUCTION

Dr. ZERHOUNI. For the 2004 year, what we tried to do was to preserve and maintain the momentum in what is the most critical resource, and that is people applying for grants and getting support so that the teams of the scientists that we have stimulated continue to be stimulated. So we had to make hard choices, Senator. And that is one of them.

Senator HARKIN. But if we make the choice here to continue to fund extramural construction, then you will not have that money for research, will you? It will be down to 2.6 percent.

Dr. ZERHOUNI. That is—

Senator HARKIN. If we keep the level of funding—

Dr. ZERHOUNI. In each category the same per year, you are correct. You are correct, Senator.

Senator HARKIN. Dr. Zerhouni, are you advising us that we should zero out all funding for renovation and building of laboratory facilities?

Dr. ZERHOUNI. For the year 2004, because of the portfolio of construction that we had to do and that we had to continue to fund, we thought that the best strategy to maintain the research momentum so that we can invest it in programs that relate to diseases was to make that choice and—

Senator HARKIN. For next year.

Dr. ZERHOUNI. For next year. Correct.

Senator HARKIN. Well, then, Dr. Zerhouni, let me carry this one step further. The President's budget documents call for a 1.9 percent increase in 2005, a 2 percent increase in 2006, and 2.2 percent in 2007. So carrying this logic forward, then for the next 3 years, we will be asked to zero out any funding for extramural construction and renovation, if that is the case. So it may be so next year. We may be looking at 4 or 5 years here—

Dr. ZERHOUNI. Right.

Senator HARKIN [continuing]. Of zeroing out any—I do not—I can only speak for myself, but to me that is unacceptable. We cannot do that. And so I just—you know, this idea that somehow we are going to squeeze out of this and get a 7 percent for basic research and to make sure we keep the grant funding going out at that level, it does not square with what we have to do with extramural construction.

So I—maybe you might do it 1 year. I do not think you can. I think we just cannot go to zero funding for 1 year. We can cut out the \$300-and-some million, because that was a one-time expenditure for bioterrorism. But then there is the underlying program that I do not think that we can cut out. So I just wanted to make that point. I know what you are trying to do, but I do not think it fits. And we are simply going to have to come up with that extra money. And I am going to keep proposing that the President has to put that in his budget next year.

Thank you, Dr. Zerhouni.

Thank you, Mr. Chairman.

Senator SPECTER. Thank you, Senator Harkin.

Dr. Zerhouni, I am going to go over a series of questions. We have been asked to have separate hearings on many of the insti-

tutes. And that is not possible, given all of the difficult schedules. We have been asked to have a separate hearing on tuberous sclerosis, where scientists have reportedly isolated the genes responsible for this disease that affects all of the body's organs.

I would like you to submit in writing and in some detail how much NIH is currently investing in research on tuberous sclerosis, and how that research is being coordinated among the various institutes involved.

[The information follows:]

TUBEROUS SCLEROSIS COMPLEX

The NIH reported actual funding for tuberous sclerosis research in fiscal year 2002 was \$6.1 million; the fiscal year 2003 estimated funding is \$6.4 million. While the National Institute of Neurological Disorders and Stroke—NINDS—is the lead institute for research on tuberous sclerosis complex, TSC, several other institutes conduct and support TSC research, which is reflective of the multiple organs affected. The National Cancer Institute—NCI; the National Heart, Lung, and Blood Institute—NHLBI; and the National Institute of Diabetes and Digestive and Kidney Diseases—NIDDK, support TSC research. Funding by Institute is summarized in the table that follows:

	Fiscal years		
	2002 actual	2003 estimate	2004 estimate
NCI	\$638,000	\$657,000	\$677,000
NHLBI	2,140,000	2,279,000	2,336,000
NIDDK	717,000	700,000	700,000
NINDS	2,596,000	2,803,000	2,859,000
OD	30,000
Total	6,121,000	6,439,000	6,572,000

The systems affected in TSC are quite distinct, and therefore, much of the research supported may be unique to a particular institute's mission, for example, NINDS to investigate the development of epilepsy and autism in children with tuberous sclerosis; NCI for studies to examine what causes skin tumors to develop in patients with TSC; and NHLBI to study the molecular and cellular basis for the development of lymphangioleiomyomatosis—LAM—a severe destructive lung disease, in patients with tuberous sclerosis complex. However, we recognize the value in tracking and coordinating the TSC research that NIH supports, as well as identifying potential partnering opportunities, and on this NINDS has the lead. Coordination is achieved in many ways, not the least of which is regular communication among the program directors who manage the TSC portfolio in each institute. In addition, NINDS is coordinating input from several institutes, extramural researchers, and the advocacy community in developing the NIH research plan for tuberous sclerosis. For example, program staff from NIDDK and the National Institute of Arthritis and Musculoskeletal and Skin Diseases—NIAMS—participated in the September 2002 NINDS-sponsored workshop on TSC research, the proceedings of which are providing the framework for the research plan, and these institutes, along with the National Institute of Child Health and Human Development—NICHD, NHLBI, and NCI, are being consulted in the development of the NIH TSC research plan.

Senator SPECTER. There is another subject matter of scleroderma, where there has been a tremendous amount of interest. And there is significant vascular and autoimmune components to scleroderma. And the question is whether there are other institutes, aside from the National Institute of Arthritis, Musculoskeletal, and Skin Disorders or the National Heart, Lung, and Blood Institute, that you would recommend scleroderma researchers pursue to find experiments aimed at finding a cure.

Since the leading cause of death in scleroderma patients is through pulmonary hypertension and its effects on heart function,

should grants on pulmonary hypertension that encompass issues unique to scleroderma patients be directed at—and this question goes to Dr. Katz and Dr. Lenfant. Should those research grants be directed at NHLBI, instead of NIAMS?

These questions are so complicated that I have to read them, which is not my style.

What do you think, Dr. Lenfant? Are you willing to defer that to another agency, or should they be directed to your agency? I would appreciate as much brevity as you can bring here, because there are quite a few more questions. And we need to finish this hearing by 11. Actually, we need to finish this hearing by 10:45.

SCLERODERMA RESEARCH

Dr. LENFANT. Senator, in view of the complexity of this condition, I think the research must be conducted by the two institutes. And it is so happens that Dr. Katz and I work very well on many conditions besides this one. And I am quite confident that this cooperation, should it continue, it will be the best way to handle that condition.

Senator SPECTER. How are you doing, Dr. Lenfant, on finding a cure for scleroderma?

Dr. LENFANT. Scleroderma, or systemic sclerosis, is of considerable interest to the NHLBI because of the lung problems that so often accompany it. Indeed, 8 out of 10 patients with scleroderma eventually develop some degree of lung disease, and interstitial pulmonary fibrosis (scarring) is now the leading cause of death among such patients. Since 1999, the NHLBI has supported the Scleroderma Lung Study, a clinical trial to evaluate treatment with cyclophosphamide, a drug that has effects on inflammation and the immune system. The goal is to determine whether cyclophosphamide helps stabilize or improve measures of lung function; the trial will also assess changes in quality of life, activity, and shortness of breath. A positive outcome of this trial would be of great importance by offering a scientific basis for treatment. Similarly, a negative result, demonstrating no benefit from cyclophosphamide therapy, would provide an important basis for avoiding a hazardous and expensive therapy that is now being used in many patients.

SCLERODERMA

Senator SPECTER. Dr. Katz, how close do you think you are coming to finding a cure for scleroderma?

Dr. KATZ. We are pursuing every scientific opportunity possible in scleroderma research and working with the community as well as with our colleagues at NHLBI in this area, which includes pulmonary fibrosis. We are pursuing research on blood vessel abnormalities genetic controlled fibrosis, as well as other genetic dimensions of scleroderma. So we are pursuing—

Senator SPECTER. Is it a realistic question to ask you how close you are to a cure?

Dr. KATZ. Yes, sir. It is a realistic question.

Senator SPECTER. Can you give me a realistic answer?

Dr. KATZ. I cannot give you a date, if that is what you are looking for. But I—

Senator SPECTER. Can you give me a time frame, a ballpark?

Dr. KATZ. I would hope that in the next 5 years we will have some better information on the complexity of this disease.

Senator SPECTER. Sometime within the next 5 years we would have better information on the complexity of the disease.

Dr. KATZ. Right.

Senator SPECTER. I would like you to supplement that in writing, focusing on my question, please.

Dr. KATZ. I would be happy to.

[The information follows:]

SCLERODERMA

I am very pleased to tell you that research on scleroderma is at a very important and promising juncture. We have a solid foundation of grants in our portfolio, we have very powerful research tools to apply to scleroderma, and we are building on significant research advances in our understanding of scleroderma. Examples of recent advances include identifying a genetic marker for scleroderma in two populations; basic research that identified defective microfibrils in cultured fibroblasts from people with scleroderma; and the determination that the risk of having scleroderma increases significantly (on the order of 10 to 27 times) if a family member has scleroderma. These are just highlights of progress. With a look to the future, I am very optimistic that within the next 5 years we will have much better information on the complexity of scleroderma. My optimism is based on the multi-pronged approach that we have taken in research on scleroderma, including the ongoing, 5-year, multicenter clinical trial that is seeking to determine the efficacy of oral collagen in the treatment of scleroderma; the funding that the NIAMS provides for two Specialized Centers of Research focused on scleroderma that will enhance translational research; support for the National Family Registry for Scleroderma that will provide vitally important information on the genetic/family dimensions of this disorder; and the outcomes of the 10 new research grants that the NIAMS funded in fiscal year 2001 as the result of a special solicitation. We can expect that research findings will begin to emerge from these grants over the next few years and will contribute significantly to our understanding of the complexity of scleroderma. In addition, I would note that scleroderma is an autoimmune disease, and the knowledge base in this area is progressing at a rapid pace. Findings that we learn from one autoimmune disease can be very useful in informing us about other autoimmune diseases. So if we look broadly, advances in genetics and autoimmunity will accelerate the pace of progress in scleroderma and many other diseases. We know that medical research is an investment, and I believe that the investments we have made over the last few years will provide critical, key pieces of the multi-dimensional, challenging puzzle that scleroderma represents.

Senator SPECTER. Dr. Zerhouni, we are having a lot of comments on the Muscular Dystrophy Care Act, which called for the creation of multiple centers of excellence, signed into law in 2001. That was before your watch. The subcommittee on three occasions has said that a minimum of three such centers should be funded. A request for proposals has finally gone out to organize the centers. But the only assurance of the scientific community is that two centers will be funded.

I would like you to submit in writing an answer to the question, why only two? And what funding level is projected for these centers?

[The information follows:]

MUSCULAR DYSTROPHY

The NIH has been actively engaged in implementing the mandates of the MD-CARE Act, including efforts to establish research centers for muscular dystrophy. Specifically, in the Fall of 2002, the NIH issued two Requests for Applications (RFAs) in this area. The first solicited applications for up to three awards for Muscular Dystrophy Cooperative Research Centers, and the second solicited applications

for up to five awards for Developmental Planning Grants for future centers. During fiscal year 2003, following peer review, we will make grant awards in response to these two RFAs; the number of grants actually awarded, up to the specified numbers, will depend on scientific merit. In fiscal year 2004, we plan to re-issue the RFA for Cooperative Research Centers, and expect to fund up to two additional meritorious centers in fiscal year 2005. Subject to the number of applications we receive and the results of scientific peer review, the combined solicitations could result in funding up to a total of five MD cooperative centers.

We anticipate that the total costs for each center will be approximately \$1.5 million for 5 years. If the combined solicitations result in funding a total of five MD cooperative centers, the total costs of all centers for 5 years is estimated at \$37.5 million.

Senator SPECTER. A question to the Cancer Institute to be responded to by Dr. von Eschenbach. On June 21, 2001, we held a hearing on blood cancers. And Dr. Klausner, then the Director of the Cancer Institute, testified that Gleevec has shown remarkable results in treating chronic leukemia. The question is: Why is Gleevec only effective on this particular form of cancer? And in what specific ways would Federal funding of stem cell research expedite the treatment and cures of blood cancer?

GLEEVEC

Dr. von Eschenbach, would stem cells be helpful there, stem cell research?

Dr. VON ESCHENBACH. Thank you, Senator. As you are well aware, there has been a great deal of research with regard to adult stem cells, and particularly in their application therapeutically in support of the treatment of blood cancers. The issue of Gleevec, that is a very important story. Because one of the wonderful things that we have seen as a result of the progress made in using a drug like Gleevec, targeted to a specific genetic defect in leukemias, the understanding of how that drug works in that pathway is now being extended to a whole variety of other cancers. Gleevec is being used in prostate cancer and it is being used in other childhood cancers. So the return on investment of Gleevec is going far beyond the blood cancers.

Senator SPECTER. Dr. Insel, the prevalence of autism is increasing, with the disease affecting, as we understand it, some 500,000 people in this country at a cost of \$13 billion annually. Autism advocates are requesting the NIH expand its research portfolio as well to finance a tissue bank program that would enhance resources and provide centralized tracking of research projects among all autism research participants.

What are your plans to develop a tissue bank? And how much has autism research increased since the NIH doubling began?

AUTISM RESEARCH

Dr. INSEL. Thank you, Senator. The interest in the autism tissue bank has increased greatly in the last few months. We held a workshop just in the last 6 weeks, bringing—

Senator SPECTER. Greatly? Greatly?

Dr. INSEL. Yes.

Senator SPECTER. How much?

Dr. INSEL. In terms of the interest? There is a wide—

Senator SPECTER. Increase in funding is the question.

Dr. INSEL. I was saying interest in the tissue bank. The workshop that we held 6 weeks ago brought in people from around the country who are experts in autism. There is a plan to roll out the specifics at the next Interagency Autism Coordinating Committee meeting.

Senator SPECTER. Is a tissue bank now being developed?

Dr. INSEL. We anticipate it will be public by July, the first week in July.

Senator SPECTER. And how much has autism research increased?

Dr. INSEL. In 1998, the NIH budget for autism was \$26,889,000. In 2002, it was \$73,850,000.

Senator SPECTER. Dr. Fauci, let us come back to smallpox one more time. The Federal Government is not recommending vaccination for the public. But HHS has stated that it will try to accommodate members of the public who want to be vaccinated. As the program is projected this year, the public has two options. First, enrolling in ongoing clinical trials; or second, for those who want to be vaccinated but who do not meet the trial criteria, HHS has proposed that it will allow vaccinations under an investigational new drug approach, which will require informed consent.

Now this is because the new vaccine has not yet been licensed. Once the new vaccine is licensed in 2004, concluding that it will be at that time, the only way the public will be able to get it is from HHS.

My question to you is, vaccination for the general public is at the impetus of the individual. Do you think this is sufficient, or should there be a national vaccination strategy for the general public as opposed to waiting for the individual to come forward?

NATIONAL VACCINATION PROGRAM

Dr. FAUCI. Mr. Chairman, given the current threat assessment, I think a national vaccine program for the general public, beyond just someone coming and asking for it, is not necessary at this time. The first priority, as you know, is to vaccinate the core smallpox response team and ultimately the first responders.

But given the current threat assessment, if we get that core group vaccinated, which we hopefully will, then in the event of an attack, the logistic capability of vaccinating anyone who is within the range of a contact would be much easier than it is right now. So the combination of the Department of Homeland Security and HHS have come to the judgment that we do not need to implement a pre-event program for the general public at this time.

Senator SPECTER. Dr. Fauci, I hope you are right.

Dr. FAUCI. I hope so.

Senator SPECTER. We have gone back and forth. We have had quite a number of hearings on the subject. We have talked about our grandchildren. There is no precise, cannot be a precise, evaluation of what the risk is of a smallpox attack, try to use that as a biological warfare weapon. People who have taken the vaccine with some bad results. People do not like the risk. Pretty tough to undertake a risk from the vaccination when there is no identifiable risk of bioterrorism in the field.

Dr. FAUCI. Right.

Senator SPECTER. But at the moment, the policy is sort of—perhaps it is not drifting along, but it is pretty hard to formulate it with precision. But I respect your conclusion that the policy has been thought through. And you have decided to do no more. But we all hope you are right that we do not find a bioterrorism attack and insufficient cautions having been taken.

Dr. FAUCI. Excuse me, sir. In the event of an attack, there is a response capability that we are building on right now that would very likely, almost certainly, be able to protect the country. The reason that the program has not been recommended for the public is because the threat assessment of an attack is balanced against the known toxicities of the currently available Dry Vax, and it is felt that a preemptive total vaccination of the Nation is not necessary.

This will change if one of two things happen. If the threat assessment changes and we feel the threat is greater. And what we are striving for in the next couple of years is a smallpox vaccine that has many fewer toxicities or adverse events. If we had the attenuated vaccine at the current time, I believe there would be a good deal more flexibility in the broad general recommendations for the general public.

Senator SPECTER. Well, thank you very much, ladies and gentlemen. This is the longest hearing we have had in awhile. We are into the third hour. And it is hard to attract the attention of Senators for very long around here, given the problem of the war in Iraq and what we are going to do with North Korea and how we are going to handle the Middle East and what we are going to do with terrorism and what we are going to do with double taxation of dividends, probably the foremost question on the minds of everybody in this room today. I mean, not the foremost question on the minds of everybody in this room today.

We appreciate what you are doing. There are going to be questions submitted for the record. And when Senator Taylor calls you up and brings issues to your attention, she is speaking for the whole Congress. She does not speak for just herself.

She does not speak just for me. She does not speak for Senator Harkin and me or this subcommittee or the full Appropriations Committee or the Senate. She speaks for the whole Congress.

We have become a lightning rod for inquiries and demands. You have no idea how many irate parents we see, or irate children we see for interest in their parents. So if we convey a sense that we are looking for a greater sense of urgency, if you get that message today, you are right. But we do know that you are in the trenches doing very, very important work. And we have a tougher issue now than we have ever had before on finding the money for NIH and the CDC. But we are going to plug away. And we look for your continued success.

ADDITIONAL COMMITTEE QUESTIONS

There will be some additional questions which will be submitted for your response in the record.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED TO THE NATIONAL INSTITUTES OF HEALTH

QUESTIONS SUBMITTED BY SENATOR ARLEN SPECTER

PANCREATIC CANCER

Question. Director von Eschenbach, this Subcommittee has taken a keen interest in the status of pancreatic cancer research at your Institute. Pancreatic cancer is the now the 4th leading cause of cancer death for men and women in this country. It also has the highest mortality rate making it the cancer you are most likely to die from, if you are diagnosed with this disease, because of the lack of reliable diagnostics.

I would like for you to update the Subcommittee on the status of a number of pancreatic cancer initiatives:

Last year's report expressed the strong intent of this Committee that the NCI fund at least five Pancreatic Cancer Specialized Program of Research Excellence (SPORE) grants by fiscal year 2004. Will you be following the Committee's intent—as expressed in last years report language—to fund five Pancreatic Cancer SPORE Grants by fiscal year 2004?

Answer. In fiscal year 2004 NCI expects to fund three pancreatic cancer SPORE grants. The NCI announced a special initiative to enhance and promote translational research in pancreatic cancer and received fourteen pancreatic SPORes applications. Thirteen of these applications were reviewed by a Special Emphasis Panel following general peer-review principles established by the NIH. Only three of these SPORE applications were found to have sufficient scientific merit to be considered for funding by the NCI. No definitive decisions can be presented at this time since our funding recommendations will undergo a second level of review by the National Cancer Advisory Board at the next meeting in June 2003. We anticipate these three meritorious applications will be funded as P20 Development awards. We are hopeful these preliminary programs will jump start the field and serve as a foundation to develop additional strong researchers and programs in this field.

Question. How many of the meritorious individual projects from non-funded SPORE Grants and program project applications does the NCI intend to fund in fiscal year 2004?

Answer. Four projects from the remaining applications were considered by the peer review as highly scientifically meritorious. These applications will be recommended for submission to our R01 grant mechanism for individual funding.

Question. I compliment the NCI's past efforts to increase the paucity of researchers through extending the payline for grants that were 100 percent relevant to pancreatic cancer. I understand that this initiative may have been the single most important action taken by the NCI to finally give pancreatic cancer the support that it needs, yet it was discontinued after just one year. Why was this important payline initiative discontinued?

Answer. Extending the payline for applications that were 100 percent relevant to pancreatic cancer enabled the NCI to fund only three additional pancreatic cancer research projects in fiscal year 2002. The NCI discontinued the extended payline for pancreatic cancer applications in fiscal year 2003 and agreed to use a mechanism for exception funding to include grants that meet only 50 percent relevancy. The NCI remains firmly committed to increasing the amount of research focused on pancreatic cancer. Therefore, the NCI is granting pancreatic cancer applications higher priority for exception funding, even those with only 50 percent relevance to the disease. We are hopeful that this mechanism will significantly increase the number of meritorious grants that will impact on pancreatic cancer.

Question. Do you have plans to reinstate this extended payline, and what are the estimated costs to continue it for a period of five years?

Answer. Since extending the payline for pancreatic cancer applications reduced the number of better scoring applications that the NCI could fund, the NCI does not intend to reinstate the extended payline. This decision is not made on basis of cost but rather a strategic effort to encourage meritorious research relevant to pancreatic cancer.

Question. If not, how do you intend to develop the critical mass of researchers needed for pancreatic cancer?

Answer. In its recently released strategic plan for addressing the recommendations of the Pancreatic Cancer Progress Review Group (<http://prg.cancer.gov/pancreatic/pancreatic.pdf>), the NCI lays out a multi-faceted approach for developing a critical mass of pancreatic cancer researchers. The Institute has implemented some of the strategies in the plan already. These include:

- Granting special consideration to pancreatic cancer applications beyond the payline, even those with only 50 percent relevance to the disease.
- Soliciting and promoting applications for SPORes in pancreatic cancer. The top-scoring applications will undergo a required second level of review by the National Cancer Advisory Board in June.
- Informing investigators of new funding opportunities in areas of particular relevance to pancreatic cancer, such as host-tumor interactions, the tumor micro-environment, and nanotechnology development for early detection.

NCI plans to put additional strategies in place in fiscal year 2003 and fiscal year 2004, but actual implementation will depend upon a final determination that these strategies are feasible and sound, and the receipt of high-quality applications from the research community. These strategies include:

- Expanding the Transition Career Development Award (K22) to extend the funding period and include all scientists.
- Increasing the number of pancreatic cancer research mentors through the National Research Service Award program.

Question. It is my understanding that the NCI is continuing to make good on its commitment to implement the report of the Pancreatic Cancer Progress Review Group (PRG)—which is a national agenda for the research needed on pancreatic cancer. I have been told that since the PRG Report came out in February 2001, the NCI has been moving forward to implement the suggestions raised in the report, and that most recently the NCI has developed a “Strategic Plan for Addressing the Recommendations of the Pancreatic Cancer Progress Review Group” to further detail and prioritize the research needed on this disease. With the President’s proposed NIH increase of roughly 2.6 percent for fiscal year 2004, how many of the strategies identified in the “NCI Strategic Plan” can actually be put into place next year, and which ones do you plan to implement?

Answer. The NCI has already implemented some of the strategies in its pancreatic cancer plan. These strategies include:

- Granting special consideration to pancreatic cancer applications beyond the payline, even those with only 50 percent relevance to the disease.
- Soliciting and promoting applications for Specialized Programs of Research Excellence (SPORes) in pancreatic cancer.
- Funding the development of new pancreatic cancer mouse models.
- Funding phase 1 and phase 2 studies for chemoprevention of pancreatic cancer.
- Holding a state-of-the-science meeting on management of pancreatic cancer symptoms.

NCI plans to put additional strategies in place this year and next, but actual implementation will depend upon a final determination that these strategies are feasible and sound, and the receipt of high-quality applications from the research community. These strategies include:

- Funding the development of nanotechnologies that use small samples for early detection of pancreatic cancer.
- Identifying markers for early detection of pancreatic cancer through NCI’s Center for Proteomics.
- Funding research on normal pancreas biology and pathogenesis of pancreatic cancer (with NIDDK).
- Expanding NCI’s cohort consortium to include pancreatic cancer.
- Supporting large case-control studies in HMOs to improve understanding of pancreatic cancer risk factors.

Question. I know the request was made before you came to the NCI, but in the fiscal year 2002 report, this Committee specifically requested that the NCI develop a professional judgment budget due April 1, 2002 for research on pancreatic cancer for the next five years. The goal here was to ascertain how much the NCI is actually spending on pancreatic cancer and compare the current funding level to what is actually needed to make some inroads on this disease, which has a 99 percent mortality rate, making it the cancer you are most likely to die from, if you are diagnosed with this disease. While I am delighted to hear that movement is being made on the findings of the Pancreatic Cancer Progress Review Group, we have not received the Five-Year Professional Judgment Budget to implement these recommendations. When might we receive it?

Answer. Over the past several years, NCI has convened Progress Review Groups (PRGs) on several types of cancer, and the reports generated by these groups have formed the basis of expanded and intensified research in these areas. Completed PRG reports have identified gaps in research in breast, prostate, colo-rectal, brain, pancreatic, hematologic, lung, and gynecologic cancers. As with all other PRGs, NCI developed an implementation plan to move forward with the recommendations for

pancreatic cancer research in a prioritized fashion. This was done with participation by outside scientists and advocates who also participated in the PRG itself.

NCI announced a 10-point plan of action that allows NCI to take immediate steps to address the gaps in pancreatic cancer research. Some strategies have already been implemented such as granting special consideration to pancreatic cancer applications beyond the payline and funding Specialized Programs of Research Excellence (SPORes) in pancreatic research. The plan's approach involves expanding existing programs, as well as developing new initiatives. Additional strategies are being considered, including funding the development of mechanisms for early detection and expanding proteomics research.

We estimate that we will spend \$38 million on pancreatic cancer research in fiscal year 2004. The preparation of a Professional Judgement Budget will take into account the implementation of these programs and their expected expenditures and increases over the next five years. Subsequent initiatives will be included in a rolling forward budget plan as reflected in our Bypass Budget.

PROTEOMIC PATTERNS

Question. In last years report, this Committee encouraged the NCI to "rapidly identify predictive proteomic patterns relevant to pancreatic cancer" and "to develop and implement methods for rapid case ascertainment." Can you please provide us with the status of progress in both of these areas including what has been developed and implemented?

Answer. The body's 30,000 or so genes carry the blueprint for making proteins, of which all living matter is made. Each protein has a particular shape and function that determine its role in the body. NCI has an extensive research program in proteomics, the study of protein shape, function, and patterns of expression, in hopes of developing better prevention, screening, and treatment options.

There has been a joint effort including the Food and Drug Administration (FDA), the NCI Clinical Proteomics Program, and Correllogic Systems Inc. which has brought together two scientific disciplines: proteomics and artificial intelligence computer programs.

Last year, there was an exciting announcement that with a preliminary diagnostic test, which could be completed in 30 minutes using blood that can be obtained from a finger stick, researchers were able to differentiate between serum samples taken from patients with ovarian cancer and those from unaffected individuals. Further study is continuing to confirm the sensitivity and accuracy of this technique as a diagnostic tool. The hope is that by combining the proteomic approach with other methods of ovarian cancer diagnosis, such as ultrasound, its accuracy can be further improved. This new diagnostic concept is potentially applicable to any type of disease and is now being tested on pancreatic, prostate, lung and breast cancer.

NCI has made significant progress in the early detection of pancreas cancer using serum proteomic patterns. We are pleased to have already made progress in the application of this technology to pancreatic cancer. Scientists tested 350 plasma samples from the University of Minnesota. The sample groups were (a) unaffected, (b) diabetes only, (c) pancreatitis only and (d) pancreatic cancer. NCI researchers discovered a serum proteomic pattern that was greater than 95 percent sensitive and specific in the classification of pancreas cancer compared to the other non cancer groups. Currently there is no other reliable test for pancreas cancer. We are now moving forward to validation of these preliminary results in a larger population of patients with and without pancreatic cancer. At the same time we are applying this technology to other cancers. If validated in larger series serum, proteomics could constitute a new approach to the early diagnosis of pancreatic cancer.

COMPREHENSIVE CANCER CENTER PROGRAM

Cancer is a disease that affects families of all backgrounds in all parts of the country. However, cancer affects more families in my state than most others. We hold the unfortunate distinction of ranking among the top five in the nation in rates of multiple myeloma and oral, prostate, pancreatic, and esophageal cancer. We are also not far behind in regard to cervical and larynx cancer.

Through the significant investment this Subcommittee has made in cancer research, we have enabled scientists from across the country to expand our basic understanding of cell growth and death and to develop effective forms of treatment and prevention. Much of this work was accomplished in NCI-designated comprehensive cancer centers. I am troubled that these centers tend to cluster in the Northeast and along the Pacific Coast, and bear little correlation to cancer incidence or mortality rates. In fact, only three of the fifteen states with the highest cancer mortality rates have a comprehensive cancer center. While we should continue to fund the

best and brightest in their efforts to find cures for cancer, I believe the current concentration of comprehensive cancer centers deprives us of gaining valuable knowledge in the parts of the country where cancer is most prevalent.

Question. Director Zerhouni and Director von Eschenbach, I would like to hear your plans for how you intend to grow the comprehensive cancer center program and how you intend to ensure that areas with high cancer rates receive the full attention of these centers.

Answer. At the present time, NCI has 60 clinical and comprehensive cancer centers. They have a wide geographic distribution and leverage the extraordinary talents and resources of major medical centers. These spheres of influence go far beyond their geographic location as a Center of Excellence of cancer treatment.

Over the years, the NCI has worked closely with a number of smaller institutions in underrepresented areas through the P20 planning grant program. At the present time, six centers are recipients of planning grants. Four of these are in states that currently have no cancer center and a fifth serves a primarily minority population. We are developing mechanisms to promote consortium centers in areas where one institution does not have the capability to apply independently, with concordant revision of NCI requirements to accommodate their unique structure. In at least one state, such a consortium has received legislative support and funding.

The NCI's Special Populations Network program is establishing a robust and sustainable infrastructure to promote cancer awareness within minority and medically underserved communities, and launching more research and cancer control activities aimed at specific population subgroups. The current Special Populations Networks consists of 18 projects in 15 states across the United States. Initial projects were begun after funding was awarded in April 2000 to groups that addressed ways of building relationships between large institutions and community groups. During the first year, cancer awareness projects were implemented in the community and project plans were developed. In the second and third years, partnerships between the project and NCI sponsored groups should enhance minority training and minority participation in cancer trials. In the last two years of these awards, full-fledged investigator-initiated research grant applications will be developed based on the initiative projects.

The NCI is also considering other options to improve access of patients in underserved areas to the benefits of cancer research. One such concept is that of a Regional Enhancement and Cancer Community Health (REACH) initiative, which would pair smaller institutions in these areas as formal partners with existing NCI designated centers for collaborative research activities and delivery of cutting edge care. As currently envisioned, this would involve providing small grants to the smaller centers for encouragement of research, as well as some form of NCI designation. An additional alternative might be to provide moderate support for the existing affiliate networks already established by the centers. These networks are primarily focused on clinical care but additional support could be provided to specifically foster the more extensive delivery of clinical trials into the community setting.

Finally, through the emphasis of the NCI on the "Discovery, Development, Delivery" continuum, we anticipate that links between existing Cancer Centers, their affiliates and partners in research, and the state, municipal and private organizations within their communities will continue to expand. These links, once firmly established, should result in a more unified approach to the conquest of cancer, and a more uniform delivery of the benefits of cancer research into the community. NCI is actively seeking mechanisms to foster both the vertical integration (i.e. from the cancer centers through the community layers they serve) and the horizontal integration (i.e. across cancer centers and a nationwide network of public and private partners) of the benefits of cancer research.

SJÖGREN'S SYNDROME

Question. Some progress has been made regarding Sjögren's syndrome at the NIAID. However, the NIAMS conducts research on closely related diseases such as lupus, scleroderma and rheumatoid arthritis. Are you conducting research on Sjögren's syndrome and are you coordinating this research with other Institutes at the NIH?

Answer. In collaboration with the NIAID and the NIDCR, the NIAMS supports research on Sjögren's syndrome and other autoimmune diseases that ranges from basic science investigations to genetic studies to prevention research. The NIH Autoimmune Diseases Coordinating Committee, of which the NIAMS is an active member, helps ensure the coordination of effort among various Federal and private entities that conduct autoimmunity research, education, and outreach. The NIAMS funds work to better understand the molecular basis of autoimmune diseases such

as Sjögren's syndrome; to identify genes that predispose individuals to autoimmunity; and to develop animal models which will provide insights into the human form of diseases such as Sjögren's.

STEM CELL RESEARCH

Concerns have been raised by some in the scientific community that not all NIH institutes are aggressively pursuing a stem cell research agenda.

Question. Would you please submit for the record how each of your institutes and centers has been implementing the embryonic stem cell research policy?

Answer. In November 2001, NIH issued NOT-OD-02-005 Notice of Criteria for Federal Funding of Research on Existing Human Embryonic Stem Cells (hESCs) and Establishment of NIH Human Embryonic Stem Cell Registry. This notice describes how federal funds can be used to support research in human embryonic stem cells that meet the criteria established by the President. This Notice also references the NIH Stem Cell Registry—a registry that only lists those human embryonic stem cell lines that meet the eligibility criteria. All NIH institutes comply with points described in the Notice and for those that support human embryonic stem cell research, only support human embryonic stem cell research that uses cell lines listed on the NIH Stem Cell Registry. In addition, NIH has a Stem Cell Implementation Committee with representatives from the NIH Institutes that assists with implementation. This Committee works in tandem with the NIH Stem Cell Task Force to ensure that policy and major research initiatives are communicated to all Institutes and provide a means for inter-Institute cooperation and exchange.

Complimenting these NIH-wide implementation efforts are many Institute-specific Program Announcements (PAs), Requests for Applications (RFAs), scientific workshops, and outreach efforts to encourage and support research on human embryonic stem cells. The NIH-wide and Institute-specific initiatives are described for each Institute with portfolios relevant to human embryonic stem cells:

The National Institute on Aging (NIA) is encouraging and supporting research on human embryonic stem cells through a number of Program Announcements, Requests for Applications, Requests for Proposals, and workshops. NIA is co-sponsoring with other NIH Institutes PA 02-054 Short-Term Courses in Human Embryonic Stem Cell Culture Techniques, PAR 02-023 Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Award, and PA-02-025 Plasticity of Human Stem Cells in the Nervous System. In addition, PAR 03-056 NIA Pilot Research Grant Program specifically encourages stem cell research pilot projects and NIA has issued a Request For Proposal (RFP) 260-03-16 on Characterization of Human Embryonic Stem Cell Lines to establish a contract to develop, maintain, and distribute data on the properties of undifferentiated human embryonic stem cell lines. The NIA intramural program is supporting one of the six intramural labs conducting research on human embryonic stem cells. Within NIA, a Stem Cell Working Group meets regularly to disseminate policy information on receipt, tracking, review and administration of grants involving human embryonic stem cell lines, as well as to plan and implement activities involving support of human embryonic stem cell research. In May 2003, NIA is hosting a meeting on Stem Cells and Aging to promote exchange and enhance research among NIA stem cell research grantees.

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is encouraging research on human embryonic stem cells and has issued an RFA 02-010 on Alcohol and Stem Cells that encompasses research objectives that include human embryonic stem cell research.

The National Institute of Allergy and Infectious Diseases (NIAID) is working to ensure that the scientific community has every opportunity to advance research into the potential of human embryonic stem cells in accordance with federal policy. NIAID is co-supporting with other NIH institutes PA 02-054 Short-Term Courses in Human Embryonic Stem Cell Culture Techniques and PAR 02-069 Career Enhancement Award for Stem Cell Research. In addition, new research grant mechanisms are available to support human embryonic stem cell research: PA 02-038 NIAID-Investigator-Initiated Small Research Grants (R03) and PAS-02-160 Application of Exploratory/Developmental Technologies to NIAID-Funded Research (R21). NIAID also accepts and supports requests for administrative supplements to add human embryonic stem cell research to an existing NIAID grant.

The National Institute on Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is encouraging research on human embryonic stem cells through several Program Announcements and Requests for Applications with research objectives that could encompass the use of human embryonic stem cells. These initiatives include: PA 03-009 High Risk Rheumatic And Musculoskeletal And Skin Diseases Research; RFA 02-003 Basic And Applied Stem Cell Research For Arthritis And Mus-

culoskeletal Diseases; PA 02-136 Precursor Cells in Skeletal Muscle Repair and Hypertrophy; and PAR 02-030 NIAMS Small Grant Program for New Investigators. In addition, administrative supplements to an existing NIAMS grant may be requested for the addition of studies of human embryonic stem cells.

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is fully aware of the policies and procedures governing the funding and use of human embryonic stem cell research and takes the necessary steps to keep grantees informed. Scientific workshops are held and talks are presented to a wide variety of audiences in academia and private industry, concerning tissue engineering, biomaterials, sensors and other areas of research that may include human embryonic stem cells. Recent outreach efforts included presentations at a PGH Engineering Tissue Growth meeting and at a meeting for BEACON, a bioengineering consortium in New England. At every appropriate outreach opportunity, human embryonic stem cells research policy is delineated to current and potential researchers. Training workshops for current and potential grantees address this issue as well. The NIBIB currently has two Requests for Applications, RFA 03-09 Development of Advanced Biomaterials and RFA 03-010 Research Opportunities in Tissue Engineering that request grant applications related to tissue engineering, which may include human embryonic stem cell research.

The National Cancer Institute (NCI) actively encourages research on human embryonic stem cells and widely disseminates NIH policies and procedures to grantees. In addition, NCI is co-sponsoring with other NIH institutes supporting the Program Announcement, PAR 02-054 Short-Term Courses in Human Embryonic Stem Cell Culture Techniques, which provides funding to develop, conduct, evaluate, and disseminate short-term courses on laboratory research techniques for human embryonic stem cell lines.

The National Institute of Child Health and Human Development (NICHD) actively encourages and supports research on human embryonic stem cells. The Institute has implemented the embryonic stem cell research policy through the issuance of special NICHD initiatives in the form of Requests For Applications, Program Announcements and Notices that include embryonic stem cells as potential targets for research. These include: RFA 02-018 Female Health and Egg Quality; RFA 02-029 Specialized Cooperative Centers Program in Reproductive Research; PA 01-005 Reproductive Genetics; NOT 03-005 NICHD Administrative Supplements for Human Embryonic Stem Cell Research. NICHD is also co-sponsoring with other NIH Institutes two program announcements: PAR 02-054 Short-Term Courses in Human Embryonic Stem Cell Culture Techniques, and PAR 02-023 Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Awards to help build the infrastructure and capacity to disseminate human embryonic stem cells eligible for federal research support. In addition, NICHD funded the first formal training course on human embryonic stem cells that was held at the Jackson Laboratory, Bar Harbor, Maine in August 2002. NICHD has also conducted numerous outreach presentations at scientific meeting on opportunities for NICHD research support for human embryonic stem cell research.

The National Institute on Drug Abuse (NIDA) sponsored a two-day meeting "Stem Cells—Opportunities for Drug Abuse Research" where developmental and general neuroscientists were brought together to pursue the link between drug abuse research to stem cell research and to provide input to NIDA about research directions in this area of endeavor.

The National Institute on Deafness and Other Communication Disorders (NIDCD) is encouraging investigator-initiated projects on high risk/high impact research and administrative supplements to facilitate scientists that would like to pursue preliminary work in stem cell research. NIDCD is sponsoring RFA 02-003 on Cellular Repair Studies of the Auditory and Vestibular Systems. In addition to these research initiatives, the NIDCD Director currently serves as the Chair of the NIH Stem Cell Task Force, a group of high-ranking scientists from a number of NIH Institutes with expertise in the research area of human embryonic stem cells. NIDCD also provides staff support to the activities of the Task Force. The purpose of the Task Force is to identify obstacles to moving the stem cell research agenda forward and to develop strategies to overcoming these challenges.

The National Institute of Dental and Craniofacial Research (NIDCR) encourages and supports research on human embryonic stem cells in studies on oral, dental, and craniofacial development and the development stem cell-based treatments for the repair and regeneration of orofacial structures that have been compromised by congenital disorders, diseases, and injuries. In addition, the Institute co-supports PAR 02-054 Short-Term Courses in Human Embryonic Stem Cell Culture Techniques.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has disseminated NIH policies and procedures to grantees through development of a web-based Investigator's Guide to Human Embryonic Stem Cell Research. In addition to encouraging and supporting investigator-initiated research, NIDDK has a number of RFAs and PAs with research objectives that could encompass the use of human embryonic stem cells. This list includes: PA 01-129 Innovative and Exploratory Research in Digestive Diseases and Nutrition; PA 02-127 Pilot and Feasibility Program Related to the Kidney; PA 01-128 Pilot and Feasibility Program in Hematological Diseases; PA 01-093 NIDDK Expanded Awards for SBIR at NIDDK; and, PA 02-008 Pilot and Feasibility Programs in Diabetes Endocrinology and Metabolism. Also, NIDDK is co-supporting with other NIH institutes research training and infrastructure initiatives targeting the needs of human embryonic stem cell research. These initiatives include: PAR 02-023 Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Awards; PA 02-054 Short-Term Courses in Human Embryonic Stem Cell Culture Techniques; and, PAR 02-069 Career Enhancement Award for Stem Cell Research.

The National Institute of Environmental Health Sciences (NIEHS) actively encourages research on human embryonic stem cells and has established a stem cell research emphasis area to encourage research on organ toxicology with potential for regenerative intervention/prevention technologies. Also, the Institute has initiated working discussions with biotechnology companies to promote their development of programs in human liver stem cell research to address the major public health organ transplantation issues leading to liver failure. In addition, the Institute held a scientific meeting in November 2002 entitled "Stem Cells: Scientific Progress and Future Research Directions" that discussed the potential of human stem cell research both globally and with respect to the environmental health sciences mission of NIEHS. This spring, NIEHS is co-sponsoring the "Frontiers in Human Embryonic Stem Cells Research Training Course and a sequel symposium entitled "Embryonic Cell Biomedicine: The Journey from Mice to Patients" both of which will be held at the University of Pittsburgh.

The National Institute of General Medical Sciences (NIGMS) encourages and supports research on human embryonic stem cells. In fiscal year 2002, NIGMS supported a "Workshop on the Basic Biology of Mammalian Stem Cells" that included key scientists in the field of human embryonic stem cells. Based on this workshop, NIGMS developed the RFA 03-003 Exploratory Center Grants for Human Embryonic Stem Cell Research. In addition, NIGMS issued a Notice 03-002 for Administrative Supplements for Human Embryonic Stem Cell Research and is co-supporting with other NIH institutes the Program Announcement PAR 02-054 Short-Term Courses in Human Embryonic Stem Cell Culture Techniques.

The National Heart, Lung, and Blood Institute (NHLBI) actively encourages and supports research on human embryonic stem cells through a number of Program Announcements, Requests for Proposals, and workshops. NHLBI has invited research applications encompassing human embryonic stem cell research through the following: PA 02-017 Innovative Concepts and Approaches to Developing Functional Tissues and Organs for Heart, Vascular, Lung, and Blood Applications; PA 02-018 Basic Research on Mesenchymal Cell Biology; PA 02-019 Research on Stem Cell Biology and Cell-based Therapies for Heart, Lung, Blood, and Sleep Disorders; and PAR 03-063 NHLBI Competitive Supplements for Human Embryonic Stem Cell Research. Also, the Institute announced NOT 02-009 NHLBI Administrative Supplements for Human Embryonic Stem Cell Research that resulted in the support of several administrative supplements to current grantees to include research on human embryonic stem cells. In addition, NHLBI is co-sponsoring several initiatives with other NIH institutes including: PA 02-025 Plasticity of Human Stem Cells in the Environment of the Nervous System; PAR 02-069 Career Enhancement Award for Stem Cell Research; PAR 02-023 Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Award; and, PA 02-054 Short Term Courses in Human Embryonic Stem Cell Culture Techniques for which NHLBI serves as the coordinator and designated administrative contact for all resulting grants. NHLBI also is sponsoring BAA 03-06 and RFP 03-07 for Somatic Cell Therapy Processing Facilities and Administrative Center that could involve human embryonic stem cells and assist in preparing the cells for clinical research. In addition, the Institute also sponsored an "NHLBI Working Group: Cell-Based Therapies for Regenerative and Reporative Medicine—Vision, Scope, and Directions" in May 2002 that addressed the area of embryonic stem cells, including their future therapeutic potential.

The National Institute of Mental Health (NIMH) disseminates NIH policies and procedures to grantees through development of a web page on NIMH Support for Stem Cell Research. In addition to encouraging investigator-initiated research on human embryonic stem cells, NIMH is co-sponsoring two Program Announcements

with other NIH Institutes: PAR 02-023 Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Award and PA-02-025 Plasticity of Human Stem Cells in the Nervous System. In addition, NIMH sponsored a satellite symposium at the Society for Neuroscience Meeting (November 2002) on "Neuroscience Opportunities in Human Embryonic Stem Cell Research: An International Perspective" and is co-sponsoring an up-coming scientific workshop on "American-Swedish Network for Stem Cell Biology and Neural Repair" currently scheduled for September 2003.

The National Institute of Neurological Disorders and Stroke (NINDS) actively encourages and supports research on human embryonic stem cells. The Institute has developed an NINDS Stem Cell website to update investigators about NIH policy, funding opportunities, upcoming meetings, and other relevant information. In addition, NINDS is sponsoring PAR 02-139 NINDS Cooperative Program in Translational Research and co-supporting with other NIH Institutes PA 02-025 Plasticity of Human Stem Cells in the Environment of the Nervous System and PA 02-054 Short-Term Courses in Human Embryonic Stem Cell Techniques. The Institute has issued several Notices requesting applications for administrative supplements: NOT 02-007, NOT 02-010, NOT 03-002 NINDS Administrative Supplements for Research on Human Stem Cells. These Notices have resulted in support of several administrative supplements that allow current grantees to include and pursue research on human embryonic stems. Also, NINDS co-funded four conferences focused on stem cell research: 8th International Conference on Neural Transplantation and Repair; International Society for Stem Cell Research Meeting; Conference on Stem Cells: Origins, Fate and Functions; and, Gordon Research Conference on Neural Development.

The National Center for Research Resources (NCRR) actively encourages and supports research on human embryonic stem cells. NCRR co-supports PAR 02-023 Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Award and serves as coordinator and designated contact for all the human embryonic stem cell infrastructure grants. In addition, the Institute is supporting a Infrastructure Awardees Meeting in June 2003 that will involve all current infrastructure awardees in an exchange about obstacles and progress to date in developing the respective eligible cells lines for distribution to the scientific community.

The Fogarty International Center (FIC) has been active in conducting outreach with foreign sources of eligible human embryonic stem cell lines. FIC has coordinated the interests of the NIH with the U.S. Department of State and respective U.S. Embassies to establish dialogues with eligible stem cell providers in India, Israel, Sweden, Australia, and South Korea. These efforts have significantly contributed to the five NIH infrastructure awards made to-date to eligible foreign sources.

Question. Please share with us the steps NIH has taken to create a positive environment for human embryonic stem cells and the researchers seeking cures using this promising research tool?

Answer. Over the past 20 months, the NIH has undertaken a number of new initiatives to enable the field of human embryonic stem cell research to move forward:

Train new investigators to culture and work with human embryonic stem cell lines. Currently, there is a limited pool of scientists with the hands-on experience needed to reliably perform experiments using approved human embryonic stem cells. To address this need, the NIH issued a Program Announcement soliciting applications for "Short Term Courses in Human Embryonic Stem Cell Culture Techniques." Five applications were received in October 2002, subsequently reviewed and plans are underway to make awards to all five applications. In addition, to assist mid-career investigators in their efforts to initiate research studies, the NIH issued the Program Announcement, "Career Enhancement Award in Stem Cell Research." These grants will provide salary support as well as some support for other research costs, to allow scientists to join an established research group working with approved human embryonic stem cells for six to twenty-four months.

Provide support to scale up and characterize human embryonic stem cells eligible for Federal funding and increasing accessibility to these lines. In early Winter 2001, many of the 71 independent human embryonic stem cell derivations listed on the NIH Human Embryonic Stem Cell Registry were in the early phases of development and had not been expanded or characterized to the point where they could be readily distributed to the research community. Expanding and characterizing cells derived from human embryos are time- and resource-consuming processes. To help make these cells available to the research community, the NIH issued a Program Announcement, "Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Awards" to provide support to allowable sources of human embryonic stem cells to scale up and distribute cell lines to investigators seeking such lines. The first Infrastructure grant was awarded in April 2002. To date, eight such

awards have been issued. As a consequence of this support the number of cell lines available for widespread distribution has grown from a single cell line in Spring 2002 to eleven cell lines at present, with more anticipated in the near future.

Provide assistance to the research community wishing to use human embryonic stem cell lines in navigating the intellectual property rights (IPR) and licensing agreements or material transfer agreements that needed to be obtained with the owners of the cell lines. The human embryonic stem cells available for Federal funding are owned by private sources, not by the Federal Government. A U.S. patent exists for human embryonic stem cell lines and the techniques used to develop such lines. NIH negotiated a memorandum of understanding with the patent holder (WiCell Research Institute) in September 2001, as well as with several other sources for the use of their cells. While the NIH can only develop such agreements for the NIH intramural research program, the terms of these agreements require the provider to offer the cells under no more stringent terms to other investigators using federal funds to conduct non-commercial research.

Encourage established investigators to initiate research projects involving human embryonic stem cells. In an effort to help established investigators begin experiments using human embryonic stem cells, the NIH announced the availability of Administrative Supplements to existing NIH grants. These supplements are supporting collection of preliminary data that will lead to investigator-initiated research grant applications whose major focus is research using human embryonic stem cells. To date, 42 supplements have been awarded. In addition to these supplements, the NIH is currently supporting 13 investigator-initiated grant awards and additional applications will be considered for funding during the remainder of 2003, and in years ahead. Six NIH Intramural laboratories are currently engaged in research using human embryonic stem cell lines.

Establish an NIH Human Embryonic Stem Cell Characterization Unit. The research community has expressed a need for information on the characteristics of the available cell lines, to allow scientists to select which lines are most suitable for their intended experiments. To address this important need, the NIH intramural program is creating a Stem Cell Characterization Unit. The mission of this unit is to provide reliable and standardized data derived from assays performed on human embryonic stem cell lines available to be shipped to the research community. Performing these assays in a single laboratory will allow a direct side-by-side comparison to be made among the cell lines that are available for shipment, and will facilitate comparison with adult stem cells. These data will arm the scientific community with peer reviewed information about the properties of available lines, so scientists can make an informed choice when ordering one or more of the available cell lines. Data will be posted on a stem cell web site as soon as they have been validated. The assays performed by this Unit will be overseen by a Steering Committee comprised of leading stem cell biologists in both the extramural and NIH Intramural Research community. In a complementary effort, the Mammalian Gene Collection at NIH has established contracts to construct cDNA libraries from several human embryonic stem cell lines, and to perform expressed sequence tag (EST) sample sequencing from these libraries. These libraries will be made available to the research community, and all sequences will be deposited into readily accessible public databases.

Provide support for multidisciplinary teams of investigators to define the properties and potential of human embryonic stem cells. The research community also articulated the need for multidisciplinary, multi-investigator teams of researchers to explore the growth and maintenance, biochemical and molecular properties, and other unique properties of human embryonic stem cells. In response to a June 2002 workshop sponsored by the National Institute of General Medical Sciences, a Request for Applications to support exploratory center grants has been issued. These awards are intended to lead to Research Centers within three years of funding the exploratory center award.

Establish NIH Stem Cell Task Force. In August 2002, the NIH Stem Cell Task Force was established to oversee and coordinate the trans-NIH activities involving human embryonic stem cells, as well as other types of stem cells. Comprised of leading NIH scientists with expertise in stem cell research, the Task Force will continue to monitor the state of this rapidly evolving science, identifying barriers to research progress and addressing the needs of the research community.

Update NIH Stem Cell Web Site. The NIH continues to serve as a resource for stem cell information by hosting a web site. Scientists have access to information on stem cell funding opportunities sponsored by NIH. The web site also includes the NIH Human Embryonic Stem Cell Registry, which lists the eligible cell lines that are available for shipping to researchers.

Host NIH Stem Cell Symposium. The NIH plans to showcase its scientific progress in human embryonic stem cell research by sponsoring a scientific conference at NIH on June 12, 2003. The symposium will feature a morning plenary session with presentations from NIH-supported researchers and an afternoon session will feature workshops and poster sessions.

Question. How many RFAs related to human embryonic stem cell research has your institute sponsored and cosponsored?

Answer. Currently NIH has issued nine Requests for Applications (RFAs) related to human embryonic stem cell research. One RFA invites applications for multiple P20 Exploratory Grants that will support multi investigator teams to conduct research using human embryonic stem cells. Sponsored by the National Institute of General Medical Sciences (NIGMS), this RFA encourages and enables basic biologists with little or no prior hESC experience to work with hESC and establish the utility of hESC as a model system by supporting the development of an institutional infrastructure for research using hESC; encouraging research on the growth and maintenance requirements of hESC; identifying biochemical and molecular markers of hESC; stimulating research that will lead to a better understanding of the unique properties of hESC; and supporting pilot projects that exploit the advantages of hESC as a model system to further the study of fundamental research problems.

Additional RFAs related to hESC research include:

- Innovative Concepts and Approaches to Developing Functional Tissues and Organs for Heart, Vascular, Lung and Blood Applications. These exploratory and developmental grants are sponsored by the National Heart, Lung and Blood Institute (NHLBI).
- Basic and Applied Stem Cell Research for Arthritis and Musculoskeletal Diseases, sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).
- Stem Cells in Development/Repair of Orofacial Structures, sponsored by the National Institute of Dental and Craniofacial Research (NIDCR).
- Basic Research on Mesenchymal Cell Biology, sponsored by the National Institute on Aging (NIA) and National Heart, Lung, and Blood Institute (NHLBI).
- Comprehensive Programs in Beta Cell Biology sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).
- Cellular Repair Studies of the Auditory and Vestibular System, National Institute on Deafness and Other Communication Disorders (NIDCD).
- Research on Stem Cell Biology and Cell-Based Therapies for Heart, Lung, Blood, and Sleep Disorders (NHLBI)
- Stem Cell Research for Alcohol related Disorders, National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Question. How many Program Announcements related to human embryonic stem cell research has your institute sponsored or cosponsored?

Answer. The Following Program Announcements related to hESC have been issued by NIH:

- Short Term Courses in Human Embryonic Stem Cell Culture Techniques are supported by 11 NIH Institutes. Five awards will be made in Spring 2003.

The 11 Institutes supporting the short-term courses are:

- National Heart, Lung, and Blood Institute (NHLBI)
- National Cancer Institute (NCI)
- National Center for Research Resources (NCRR)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of General Medical Sciences (NIGMS)
- National Institute of Mental Health (NIMH)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute on Aging (NIA)
- Career Development Awards which are sponsored by NIDDK, NIAAA, NINR, NIAID and NHLBI. The announcement was made in March 1, 2002 and expires in June 1, 2005. The purpose of these awards is to provide mid-career investigators with training to use hESC in their research.
- Plasticity of Human Stem Cells in the Nervous System sponsored by NINDS, NIA, NIMH and NHLBI. The purpose of this Program Announcement is to study the fundamental properties of all classes of human stem cells, and to confirm, extend, and compare the behavior of human stem cells that are derived from different sources and ages or exposed to different regimes in vitro and in vivo.

Question. How much funding has been provided for human embryonic stem cell research in each of fiscal years 2001 and 2002?

Answer. In fiscal year 2001, no funding was provided for human embryonic stem cell research and \$10.7 million was provided for fiscal year 2002.

Question. Approximately how much funding is your institute planning to provide for human embryonic stem cell research in fiscal year 2003?

Answer. NIH estimates \$17.1 million will be provided for human embryonic stem cell research in fiscal year 2003.

Question. Please explain your plans to expand funding within your institutes for human embryonic stem cell research over the next three years?

Answer. Investigator-initiated research is the foundation of grants supported by NIH. To date, NIH is supporting only 13 investigator-initiated research grants using human embryonic stem cells but NIH anticipates a substantial number of applications over the next three years as this field of research matures and more scientists receive stem cell biology training through various training courses, such as the NIH-supported short-term training courses mentioned above or through training offered directly by eligible providers of human embryonic stem cells. Upon completion of the training, it is expected that scientists will address the basic research questions that need to be answered for the field to move forward before being used for human therapies: What are the molecular pathways that govern stem cell differentiation to a specific cell type? How can stem cell growth be regulated? How can stem cells be safely transplanted and how is cell rejection prevented? How long will the stem cell transplant continue to function? Can animal models be developed to test the efficacy of stem cells?

Question. Please identify any administrative or program hurdles that are impeding your institute from maximizing the potential of human embryonic stem cell research in helping your institute achieve its mission?

Answer. Currently, the rate limiting step of hESC research is the lack of well-trained investigators. NIH has taken steps to remedy the situation by funding five short term training courses for up to three years starting in fiscal year 2003. In addition, career enhancement awards to train scientists in the lab culturing techniques and growth methods for hESC are currently being offered for mid-career scientists who are interested in learning to work with hESCs. In addition, NIH is supporting short-term training courses to teach scientists cell culturing techniques. Currently, WiCell, UCSF and ES Cell International are providing additional stem cell training, independent of the NIH-supported short term training courses. NIH has awarded infrastructure grants to providers of hESCs which allows them to grow and culture the federally approved cell lines, making more cells available to the research community. This will enable scientists to gain easier access to the eligible stem cell lines. In June, the NIH is sponsoring a symposium to showcase NIH supported hESC research. The symposium is attracting worldwide interest. NIH believes that these activities will assist in attracting new investigators to the field and alleviate the current shortage of trained investigators.

Question. Several scientists have suggested to the Subcommittee that NIH should create new funding mechanism to support human embryonic stem cell research, given that this is such a new area of science. Are you considering creating a mechanism that requires less preliminary data?

Answer. In an effort to help established investigators begin experiments using human embryonic stem cells, the NIH is issuing Administrative Supplements to existing NIH grants. These supplements are supporting collection of preliminary data that will lead to investigator-initiated research grant applications whose major focus is research using human embryonic stem cells. In addition, NIH is providing other funding mechanisms that are used to support high risk/high impact research as a means for generating preliminary data. Also, the NIH Center for Scientific Review has implemented processes to facilitate the peer review of human embryonic stem cell grant applications. One example is informing scientific review administrators about this new field of research and the preliminary data, which is often part of an application or may be lacking in some grant applications and should not be considered a penalty.

Question. If so, when can we expect this to be announced? If not, how do you plan to spur this field?

Answer. NIH is currently implementing these initiatives. In addition, NIH is undertaking other initiatives to spur this new research field by enabling eligible stem cell providers to scale up cells for shipping, providing easier access of stem cells to researchers, becoming a source of information to the scientific community on stem cell characteristics, and providing a forum for scientists to share their data through a stem cell research symposium.

CLINICAL RESEARCH

Question. Most of this type of research takes place at academic health centers, many of which are struggling financially. I also note that you want to re-establish the Biomedical Research Support Grant program to help support academic health centers. Are you requesting funds for that purpose in this budget?

Answer. No funds are requested in fiscal year 2004 to re-establish the Biomedical Research Support Grant (BRSG) program.

Question. For the record, would you provide the Subcommittee with a description of how that program would work, and how much money it would take to adequately support the program.

Answer. No funds are requested in fiscal year 2004 to re-establish the Biomedical Research Support Grant (BRSG) program.

Question. How much does NIH devote to translating basic research into improved health care for the patient?

Answer. An integral component of NIH's mission is to communicate research results both to the lay public and health professionals. NIH works in partnership with many different organizations to communicate scientific results and health information to the medical research community, health care providers, patients, and the general public across the nation. NIH communicates basic research findings through publication in professional journals and by distributing news releases to the science and general media. NIH scientists speak to reporters to explain the significance of the research and put it into the broader context of making progress against disease. Some examples of the translation of research findings from bench-to-bedside that are provided below:

—In 2001, the National Institute of Neurological Disorders and Stroke (NINDS) launched a multi-faceted public education campaign to educate people about how to recognize stroke symptoms and to call 911 to get to a hospital quickly for treatment. Know Stroke: Know the Signs, Act in Time includes: public service advertising for radio, television and print; as well as consumer education materials that include an award-winning 8-minute film, brochures, and posters. Because stroke attacks the brain, a stroke patient often cannot act alone to call 911 and seek medical treatment. Bystanders are integral to acting quickly and getting stroke patients to the hospital.

To date, the campaign materials have derived excellent results. The television PSA garnered more than 87 million viewer impressions and hundreds of thousands of dollars worth of free broadcast time; the radio PSAs received more than 46,000 broadcasts on 272 stations; the airport dioramas were placed in 117 airports, in cities such as Atlanta, Dallas, Denver and Baltimore and received more than 800 million annual impressions; billboard advertising focused in the Southeastern United States, known as the Stroke Belt, averaged more than 800,000 daily impressions for the months they were placed; bus side advertising placed in 10 markets resulted in more than 115,000,000 over the course of three months; a matte service article has generated more than 2 million impressions and about 15,000 requests for Know Stroke brochures, and the consumer education materials developed for the campaign have been requested by thousands of nursing homes, hospitals, senior centers and other organizations. Many of these activities have been done in partnership with the American Stroke Association, a division of the American Heart Association, and the National Stroke Association, the two largest voluntary organizations serving stroke patients and their families.

—The National Diabetes Education Program (NDEP), established in 1995, is a federally-sponsored initiative that involves public and private partners to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and to prevent the onset of type 2 diabetes. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) and the Division of Diabetes Translation of the Centers for Disease Control and Prevention (CDC) jointly sponsor the program with the participation of over 200 partner organizations. The Program's target audiences include people with diabetes and their families, with special attention to Hispanics/Latinos, African Americans, Asian Americans, Pacific Islanders, and American Indians, people at risk for type 2 diabetes, especially those with pre-diabetes, health care providers, health care payers, purchasers, and policy makers. The program's main initiatives include the "Control the ABCs of Diabetes" campaign to promote the link between cardiovascular disease and diabetes and the importance of controlling blood glucose, blood pressure and cholesterol, and the "Small Steps, Big Rewards. Prevent type 2 Diabetes" campaign, designed to promote the message that diabetes can be prevented to the 16 million Ameri-

cans with pre-diabetes, a condition that puts them at high risk for developing type 2 diabetes.

- Co-sponsored by NIH and organizations such as the Maternal and Child Health Bureau, the American Academy of Pediatrics, the SIDS Alliance, and the Association of SIDS and Infant Mortality Programs, the “Back to Sleep” National Public Health Education Campaign has resulted in a 50 percent relative decrease in the rate of Sudden Infant Death Syndrome since its launch in 1994. This campaign is directed at mothers and family members of young infants, the professionals responsible for their care, and the public in general.
- The National Eye Health Education Program (NEHEP) has established public and professional education programs to help promote public awareness on how to prevent vision loss. The NEHEP comprises more than 50 public and private organizations, which plan and implement eye health education programs. The NEHEP has created educational kits on glaucoma and diabetic eye disease for health professionals and community leaders. The kits provide information and materials to educate people at high risk about eye health and the need for regular dilated eye exams. The NEHEP also has launched four national public service campaigns. Materials and messages of the campaigns have been tailored to high-risk populations.
- The National Heart, Lung, and Blood Institute supports several long-standing national programs that rely the cooperative efforts of its partners to educate the lay public and health professionals about preventing and treating some of the major chronic diseases of our time. The National High Blood Pressure Education Program (NHBPEP) is a cooperative effort among professional and voluntary health agencies, state health departments, and many community groups interested in hypertension prevention and control. At the core of the program is the NHBPEP Coordinating Committee, composed of representatives from 38 national professional, public, and voluntary health organizations and 7 federal agencies. The program aims to reduce death and disability related to high blood pressure through programs of professional, patient, and public education. The National Cholesterol Education Program (NCEP) was established to raise awareness and understanding about high blood cholesterol as a risk factor for coronary heart disease (CHD) and the benefits of lowering cholesterol levels as a means of preventing CHD. The NCEP Coordinating Committee, with its membership of more than 40 partner organizations representing major medical and health professional associations, voluntary health organizations, community programs, and governmental agencies, helps bring cholesterol information to a wide audience. The National Asthma Education and Prevention Program (NAEPP) was initiated to address the growing problem of asthma in the United States, particularly among children, African Americans, and the elderly. Through its Coordinating Committee, composed of representative from 43 partner organizations from professional medical and health associations, public and voluntary health organizations, and federal agencies, the NAEPP works to raise awareness that asthma is a serious chronic disease, ensure recognition of symptoms, and ensure appropriate diagnosis and effective control of asthma.

CLINICAL RESEARCH

Question. I have a copy of your “road map” for streamlining the process of taking research from the laboratory to the bedside. Is this still in the planning stages or have you implemented it?

Answer. A national effort, led by NIH, to re-engineer the clinical research enterprise is being planned at this time. In the course of developing this key agency priority, the Director, NIH convened a two-day meeting to develop a plan to identify the critical roadblocks and knowledge gaps that constrain rapid advances, and to conceptualize and develop far reaching solutions to build the sophisticated clinical research enterprise of the future.

In January 2003, meeting participants developed a plan to re-engineer the clinical research system over next 10 years. They recommended creation of: (1) National Clinical Research Networks, which would accrue data on clinical outcomes and quality of care at the point of service; provide an infrastructure for rapid initiation of large clinical trials; and inform patients and consumers; (2) a Translational Research Infrastructure which would facilitate the transfer of clinical research findings to the front lines of clinical care-and back; and (3) a Clinical Research Workforce which is diverse, well trained, and capable of collaborating optimally in cross-disciplinary teams.

Since that time, NIH workgroups on translational research, clinical networks and clinical training have been reviewing, consolidating, harmonizing, prioritizing, and

determining the fiscal implications of the myriad recommendations to NIH to emerge from the Clinical Research Roadmap Meeting. Workgroups are actively taking into account key national priorities, scientific opportunities, feasibility, timing, and resources. Draft suggestions for implementing the key recommendations for streamlining and updating the clinical research enterprise are being considered by agency leadership. The NIH Director, in collaboration with Institute and Center Directors, will make the final determination of which of the many key directions will be most likely to yield the most substantial benefits to the health of the American people over the course of the next century. Once agreement is reached amongst the NIH Institutes and Centers, operational plans and a timeline will be devised for implementing the new clinical research infrastructure. We look forward to keeping you up to date as these priorities develop.

Question. One of the items in this road map calls for establishing “a natural home within NIH for clinical trials of medical importance.” Last year, the Subcommittee encouraged you to establish an Office of Clinical Research to provide a central focus. So we seem to be on the same wave length. Where does that stand?

Answer. NIH views clinical research, which focuses on the causes and consequences of disease in human populations, as the key link in the pathway from basic research to improvements in health. This area of research includes the development of new technologies, mechanisms of human disease, therapeutic interventions, clinical trials, epidemiologic and behavioral studies, and outcomes and health services research. We concur with your strong interest in ensuring the advancement of clinical research. In recent years, the NIH appreciably expanded its clinical research program; for example, by establishing both intramural and extramural clinical research fellowship programs targeted to medical and dental students at the NIH; expanding the resources available for the diverse needs of the clinical research community, including attention to inpatient, outpatient, and critical care clinical research; and investing heavily in Patient-Oriented Research Career Development Awards, Mid-Career Investigator Awards in Patient-Oriented Research, Graduate Training in Clinical Investigation Awards, and Clinical Research Curriculum Awards. In addition, the NIH Loan Repayment Program has been expanded to include health professionals engaged in clinical research funded by non-profit support.

In an unprecedented effort to be responsive to the many and varied research priorities advanced by different stakeholders—practicing physicians, the pharmaceutical and biotechnology industries, researchers, health plans, and patient groups, the NIH Director has convened a series of Roadmap meetings with extramural and intramural scientists and the Institute and Center Directors to explore the scientific challenges in clinical research and the roadblocks to progress. As a result of the recommendations to emerge from these meetings, the NIH is moving forward to re-engineer the clinical research enterprise, and to develop innovative solutions to ensure the promise of a viable 21st century clinical research enterprise.

The development of any new organizational entity at this juncture in the agency's deliberations would stimulate premature closure pertaining to this complex issue affecting all NIH Institutes and Centers. As we continue to develop the NIH clinical research roadmap plan, we look forward to keeping the committee apprised of our progress in implementing these goals as this groundbreaking process continues to unfold.

INCREASED STIPEND LEVELS

In March 2001, NIH announced a commitment to increase stipend levels for Kirschstein research training awards:

The NIH supports higher stipends for NRSA recipients and therefore announces tentative targets of \$25,000 for graduate and \$45,000 for entry-level postdoctoral stipends. Future budget requests will incorporate 10 to 12 percent stipend increases until these targets are reached. After attainment of these targets, the real value of stipends will be maintained with annual cost-of-living adjustments.

Question. The Administration's fiscal year 2004 budget departs from this commitment. Can you comment on the rationale for this change in policy?

Answer. The change came about through recommendations included in a 2000 National Academy of Sciences report. In fiscal year 2003 the Senate Appropriations Committee and the Conference Committee reports asked NIH to comment on that report. The NIH remains committed to the stipend targets described in our responses on that report. The request for funds to cover a 4 percent increase in fiscal year 2004 will permit the NIH to continue to increase stipends.

APPOINTMENT OF STUDY SECTION MEMBERS

Question. What role should the Administration have in the appointment of NIH study section members?

Answer. NIH operates study section and appoints study section members primarily based on the scientific expertise needed for review of applications assigned to the specific scientific review committees. Technical evaluation and advice regarding the scientific merit of the proposed research requires that the advising panel has the appropriate collective scientific expertise. The Federal Advisory Committee Act, which regulates establishment and operation of NIH study sections, also requires that committees be “balanced” and not “inappropriately influenced by the appointing authority.” Trained NIH scientists who develop these committees have the skills and experience to ensure this balance and the presence of the appropriate scientific expertise so as to achieve fair and rigorous reviews. In addition, NIH attempts to ensure diversity (of race and ethnicity, gender, geographic distribution, small and large institutional affiliation, public and private institutional affiliation, academic and small business, etc.) on study sections.

FULLY FUNDED GRANTS

Question. In the Administration’s fiscal year 2004 budget request for NIH, 322 new grants are “fully-funded,” that is, rather than receiving funding over the 3 or 4-year lifespan of the grants, all funding for these grants would be disbursed in fiscal year 2004. Is my understanding is that this is a pilot or test that is being pushed by the Office of Management and Budget correct?

Answer. Certain grant programs, such as the Academic Research Enhancement Awards (AREA), and the James A. Shannon awards, have always been fully funded. In fiscal year 2004, NIH will increase the number of fully funded grants. NIH will undertake a study to determine the type of grants that can reasonably be fully funded from both the point of financial stewardship and scientific accountability. Other categories of grants may also be proposed for full funding.

Question. If this is to be a test, by what criteria will the success of full funding be judged?

Answer. Factors include ensuring grantee accountability for the use of Federal funds and the availability of funds for new researchers with new ideas.

Question. Currently, as grants are funded over a four-year cycle, there is annual oversight of the research being performed as non-competing continuations are awarded. Will there be less oversight if the grants are fully-funded at one time?

Answer. The overall institutional compliance responsibilities are the same for grants that are fully funded. As noted above, NIH currently has two long-standing award programs that are “fully funded.” For example, the Academic Research Enhancement Awards (AREA) program provides for a three -year-award to AREA-eligible institutions. AREA recipients are required to submit an annual progress report to NIH.

Question. As a researcher and research administrator, what is your view of fully-funded grants?

Answer. As a researcher, there are advantages with fully-funded grants in that one can plan a research project with full knowledge and control of the entire amount of the grant award. Thus, one can better plan and manage the budget for personnel, equipment and resources as these are needed to meet the milestones of the project. As a research administrator, full funding could provide additional flexibility in managing future year commitments made to NIH researchers.

Question. Are there upsides or downsides that OMB, the Department or the Congress might not be aware of?

Answer. When determining the type of grants that can reasonably be fully-funded, NIH will consider financial stewardship and scientific accountability, NIH’s goal of supporting stable numbers of new grants, impact on research priorities supported through other mechanisms of support, and the impact on new researchers entering the research arena.

TRAINING STIPENDS

Question. In March of 2001, NIH adopted a policy of increasing training stipends by 10 percent a year until appropriate stipend levels are reached. In fiscal year 2002 and fiscal year 2003, the Administration has chosen to ignore NIH’s policy and request significantly lower increases for training stipends than are necessary, and the Appropriations Committee has had to take action to ensure that stipends were increased. Here we are in fiscal year 2004, and the Administration has once again un-

derfunded training stipends. What is NIH's view of the need for a 10 percent increase in fiscal year 2004?

Answer. The NIH remains committed to the stipend targets of \$25,000 for predoctoral and \$45,000 for entry level postdoctoral Kirschstein—NRSA recipients as identified on April 30, 2001. The 10 percent annual increases specified in the 2001 NIH statement would have permitted us to reach the indicated targets by fiscal year 2006. The indicated targets could still be achieved at 4 percent annual increases, albeit not until 2011, by which point they would need to be adjusted to account for changes in the cost-of-living.

Question. What are the numbers of students supported and at what levels?

Answer. Based on distribution of research training positions to various career levels in fiscal year 2001, we estimate that the positions funded in fiscal year 2004 will be filled according to the following table.

REQUESTED FISCAL YEAR 2004 KIRSCHSTEIN—NRSA TRAINEES AND FELLOWS BY LEVEL OF TRAINING

[Full-time training positions]

Career level	Number of positions	Fiscal year 2004 est. stipend levels
Predoctoral	10,046	\$19,631
Postdoctoral:		
Years of experience:		
0	1,339	33,629
1	1,163	35,498
2	818	40,494
3	704	42,273
4	842	44,032
5	783	45,803
6	449	47,574
7	1,053	49,588
Total Postdocs	7,151	
Total Full-Time Training Positions	17,197	

Question. Is it your view that stipends are adequate and that we have enough high-quality students in the pipeline?

Answer. As indicated in my previous response, the NIH believes that Kirschstein-NRSA stipends should be adjusted upward to \$25,000 and \$45,000 for predoctoral students and entry-level postdoctorates, respectively. Stipends are not being adjusted to influence the supply or the quality of students in the pipeline. Based on recent studies, the health-related sciences continue to attract highly motivated students that score very well on national, standardized tests. Stipends are being adjusted upward as recommended by the National Academy of Sciences in recognition of increases in the cost-of-living and because of the high level of education and professional skills involved in biomedical research.

Looking at this budget proposal, I am reminded of those slow motion films of crash tests for cars. My suspicion is that, under the Administration's proposal, we are taking a \$27 billion dollar research enterprise and driving it into a brick wall at 60 miles an hour. Fiscal year 2004 is the instant that the car's bumper hits the wall, the crash dummies in the car are just starting to be thrown forward, and perhaps the hood is starting to buckle. I fear that in fiscal year 2005 and beyond we may well "total" the NIH. I didn't double the NIH over the past five years so that we could drive it into a brick wall.

EMBRYONIC STEM CELL RESEARCH

Question. Please discuss how human embryonic stem cell research fits into the mission of the NCI. Has NCI been actively encouraging research on human embryonic stem cell research in order to advance your mission?

Answer. Currently, NCI has not received any research grant applications relating to human embryonic stem cell research. We do believe that we will see basic research applications in the future.

NCI has an extensive commitment to the field of stem cell biology, including both adult and animal embryonic stem cells. This research is important in expanding our fund of knowledge that can be applied to future human embryonic stem cell research. The Institute has publicized to all of our grantees by listserv announcements the current applicable NIH policies and procedures. In fiscal year 2002, NCI spent a total of \$95 million in both animal and human adult stem cell research. NCI has also provided vital resources to the research infrastructure through its Mammalian Gene Collection program. This program works with the source of stem cells, such as the program at the University of Wisconsin-Madison, to create public resources for full-length cDNA and genomic libraries of human ES cell lines. In addition, NCI also participates in the NIH task force and implementation team that are facilitating interactions with the scientific communities.

Question. What is NCI doing to provide investigators with the training necessary to maximize the potential of these cells?

Answer. In fiscal year 2002 NCI supported training and education programs for investigators to acquire the skills and techniques necessary to grow and maintain the human embryonic stem cell (hESC) lines. NCI provided co-funding support to NHLBI for the T15 short courses in hESC culture techniques. The total funding provided was \$50,000 per year, divided among the five (5) successful applications. These five awards were made to training programs to help establish the workforce necessary to pursue this research field. These awards will develop, conduct, evaluate, and disseminate short-term courses on laboratory research techniques for human embryonic stem cell lines. The courses will include hands-on experience to improve the knowledge and skills of biomedical researchers to maintain, characterize, and utilize human embryonic stem cells in basic research studies. The courses will improve the skills of biomedical researchers in the maintenance of human embryonic stem cells in culture and their application of this research tool in basic research studies. The long-term objective of the courses is to increase the number of researchers who have both knowledge and skills in the use of human embryonic stem cells in basic research.

REGENERATIVE MEDICINE

Question. Regenerative medicine is an area of research that could be shared by government, academia and industry—a true public-private partnership. Can you outline for the Subcommittee how regenerative medicine fits into your plan for the NIH research agenda?

Answer. Regenerative medicine involves collaboration between several research fields—stem cell biology, biomolecules/biomaterials, and tissue engineering; and involves several scientific disciplines—medicine, biology and bioengineering. NIH places a high priority on supporting regenerative medicine research and is bringing together several working groups to identify research obstacles and address research opportunities for regenerative medicine especially in application to stem cell biology and biomolecules/biomaterials. This process will serve to develop an NIH roadmap for regenerative medicine with the goal of attracting more scientists to this emerging multidisciplinary field that has the potential of revolutionizing health and quality of life of millions of people.

Recent advances in stem cell research have spurred new interest in the field of regenerative medicine. Before new therapies using human embryonic stem cells (hESC) can proceed to the clinical phase, much basic research must be conducted. There is a need for validating the long-term stability of hESCs in culture and after transplantation, understanding cell cycle control and cell specialization, and evaluating cell-host interactions. In response to these needs, the NIH Stem Cell Task Force is convening a working group with representatives from government, academia and industry to develop recommendations about what steps NIH could take to help improve or develop supporting technologies and research tools in basic research of hESC biology. Topics for discussion would include assessing the needs for supporting supplies, materials, reagents, databases with broad public access; assessing needs, progress, and opportunities for characterization studies, genomic, and proteomic approaches to better define stem cell lines; determining protocols for directed differentiation of stem cells; and recommending needs for enhancing research tools to the Task Force.

SALIVARY DIAGNOSTICS

Early detection offers the best hope for cure for many serious diseases. However, many of the existing ways of diagnosing disease can be difficult, invasive, time-consuming, and expensive, so that by the time people have a test done, it may be al-

ready too late. I understand that saliva as a diagnostic tool is a promising area of research for addressing this issue.

Question. Is there, in the 2004 budget, an investment in this area of research and if there is, how much are you budgeting for saliva research?

Answer. We need to improve methods for detecting and diagnosing disease in the early stages. Unfortunately, there are also many barriers to effective diagnosis. Current methods, like blood tests and imaging technologies, are often uncomfortable, invasive, and expensive. Some diagnostic methods also carry risks themselves. Currently many diagnostic tests do not allow for real time monitoring of the state of health or disease because testing can take days or even weeks to complete.

One of the most promising lines of research for diagnostic testing involves the use of saliva. Like blood and urine, saliva can be used to detect and measure many compounds in the body. Unlike blood and urine, saliva is easy to collect in a physically non-invasive manner, and the mouth is accessible for continuous monitoring. The science of microchip technology is evolving so rapidly that it is possible to envision the day when a microchip could be attached to a patient's tooth and be capable of continuously monitoring not only specific disease conditions but also an individual's overall health status.

NIH is using its resources to make this vision a reality. In fiscal year 2002, NIDCR funded a series of grants to develop strategies to measure and analyze multiple substances in saliva quickly and simultaneously. Working in partnership with colleagues in industry and academia, these grantees are using microchip technology to develop diagnostic tests for a variety of conditions. As these studies are completed, follow-up research will be conducted to determine the efficacy of these new tools.

NIDCR will spend an estimated \$9.0 million in fiscal year 2004 on salivary diagnostics research.

Question. Is saliva being used for HIV diagnosis?

Answer. A number of companies have been working on saliva tests to measure antibodies to HIV. However, the sensitivity and specificity is lower than desired, mostly due to the fact that saliva contains low levels of immunoglobulin G. Thus, two companies are using mucosal transudate, the fluid that naturally seeps from the soft tissues of the mouth, as a diagnostic medium. The existing systems are really collection devices. The sample is sent to a laboratory, and the results are obtained after a week or two. Both companies, however, have developed rapid tests that are pending FDA approval for use in the United States. One company received FDA approval on Jan. 31, 2003 for a rapid test that utilizes a finger stick (i.e., blood sample) and provides results in 20 minutes. The same company also has an application before the FDA that uses the same technology with a sample of oral mucosal fluid. FDA approval of the oral mucosal rapid test is expected by the end of 2003.

Question. I hear people talk about the need to develop an "HIV rapid test". Can you explain what that is and are you close to accomplishing that?

Answer. An "HIV rapid test" implies that it can be conducted on site within a very short time frame without the need for specialized equipment or trained laboratory personnel. The NIDCR is working to make this vision a reality. In fiscal year 2002, the Institute funded several grants to develop technologies to measure and analyze multiple substances, including HIV, in saliva. Working in partnership with colleagues in industry, national laboratories and academia, these grantees are focusing their efforts on developing "labs on a chip", miniaturized systems about the size of a credit card for the detection of HIV and other substances. These technologies will allow real-time analysis of a large number of proteins (including antibodies to HIV), nucleic acids (DNA, RNA) and small molecules (e.g., drugs, metabolites) in oral fluids. The development of these technologies would permit fast, highly sensitive and accurate diagnosis of HIV in small amounts of saliva. To date, grantees at the University of Washington and the University of Pennsylvania working in partnership with industry have developed miniaturized prototypes for immunoassays of substances in blood. This technology is currently being adapted for the rapid diagnosis of HIV antibodies in saliva. Once these technologies are developed, they will need to be validated prior to widespread use.

CLINICAL TRIALS RESEARCH IN DENTAL AND ORAL HEALTH

This Committee appreciates the need to support definitive, high-quality clinical trials. We understand that such trials are especially critical in dental and oral health, where large numbers of Americans continue to suffer from oral diseases and disorders.

Question. Are there clinical trials in the area of oral health that need to be conducted?

Answer. Continuing scientific progress in oral health has created opportunities for state-of-the-art clinical trials to determine the effectiveness of new treatment approaches and to broaden our understanding of the link between oral health maintenance and overall health. For example, new clinical trials are underway to assess the effectiveness of periodontal treatment on control of systemic health conditions such as preterm birth. The NIDCR has taken several steps to increase the number of applications and awards for high-quality clinical trials and to enhance the oral health research community's capacity to conduct such trials.

Question. And what plans does NIH have to respond to this need?

Answer. As support for clinical trials in oral health has expanded from about \$10.8 million in fiscal year 2000 to nearly \$18 million in fiscal year 2002, NIDCR instituted a new process designed to better assist investigators to develop and conduct clinical trials. The Institute has given priority to Phase III clinical trials that are likely to have a major impact on public health policy and/or clinical practices, and that will provide important new information to practitioners and consumers.

NIDCR recently reorganized its extramural programs to delineate more clearly and to focus more prominently on the development and management of clinical trials and recruited additional program staff with expertise in clinical trials. Furthermore, a new, defined path for clinical trial applications has been established, which will assist investigators in developing and conducting trials. NIDCR has given the highest priority to Phase III clinical trials with the potential for high public impact. In addition, the Institute is using a variety of funding mechanisms to strengthen the scientific workforce through expanded training in clinical trial methods. The extramural community has been very positive about these program enhancements, as reflected in the increased number of applications and funding for clinical trials.

SMA RESEARCH BUDGET

Question. What is the budget for SMA basic research for fiscal year 2003 and fiscal year 2004?

Answer. The NIH total estimated funding for Spinal Muscular Atrophy (SMA) is \$7,351,000 in fiscal year 2003 and \$11,489,000 in fiscal year 2004.

SMA TRANSLATIONAL RESEARCH BUDGET

Question. As a result of promising breakthroughs in basic research along with the severity and incidence of this disease in newborns and infants, NIH has selected SMA as a model for translational research. What is the budget for translational research for SMA in fiscal year 2003 and fiscal year 2004?

Answer. To enhance our current research efforts on SMA, we anticipate awarding a contract for the SMA translational project on or about September 30, 2003. The contract will be awarded for four years, and the research will be conducted as subcontracts. The NINDS intends to fund these research subcontracts at a level of \$4.5 million per year, which will support up to ten research subcontracts.

IMPLEMENTATION OF SMA TRANSLATIONAL RESEARCH PROGRAM

Question. Please provide specific details on your plan of action for implementing SMA translational research?

Answer. The NINDS has developed a performance-based contract approach to allow rapid funding of translational research in a milestone-driven process to identify treatments for SMA. The members of the steering committee, selected by the NINDS Director and drawn from academia, industry, the public, and NIH, are in the process of being identified and recruited; they will guide the program and play an integral role throughout the project. During the Summer of 2003, a working group will develop recommendations for a detailed plan for research on promising therapeutic strategies, such as drug development, gene therapy and stem cell therapy, which will address all steps ultimately required to develop an IND-Investigational New Drug-application, the formal procedure usually required before a treatment can be tested in people. The primary contract for the SMA project will provide overall scientific and organizational support. Subcontracts will support individual research projects, which will be highly-targeted and milestone-driven, as is often the case in industry. The steering committee will evaluate progress toward the specified milestones and prepare calls for additional subcontracts to do the next steps along each therapy development pathway, as appropriate. The NINDS intramural program, which has substantial expertise in SMA and other neurogenetic disorders, will play an integral role throughout this effort, and is capable of performing early phase clinical trials when these become appropriate.

OVERSIGHT OF SMA TRANSLATIONAL RESEARCH

Question. Who has been appointed within the NINDS to oversee and execute the SMA translational research project? What mechanisms are in place to review the process of the project on an ongoing basis with NIH leadership and Congress?

Answer. Dr. Jill Heemskerk, an NINDS Program Director, will be the Project Officer for the SMA contract. She will receive advice from the steering committee and other NINDS staff. To allow optimal management and monitoring of research progress by the steering committee, projects will be short-term, goal-directed, and milestone-driven. The steering committee will review research progress at biannual oversight meetings; advise the Contractor in assessment of research milestones; and advise on strategies for overcoming difficulties in research progress.

Institute staff have briefed Dr. Zerhouni extensively about the project and will continue to do so. We have responded to many questions about the project, by letter and phone, from members of Congress, and will continue to keep Congress informed.

TIMELINE AND PLAN FOR SMA TRANSLATIONAL RESEARCH

Question. Please provide a timeline and strategic plan for the implementation of the translational research project and identify any potential roadblocks?

Answer. In December 2002, NINDS published a notice on the "Collaborative Program to Accelerate SMA Therapeutics Development" in the NIH Guide to Grants and Contracts to help develop the statement of work and a request for proposals. A March 23, 2003 notice in Federal Business Opportunities announced that the formal request for proposals will be issued in April, and a similar notice appeared in the NIH Guide on April 8th. We expect to award the primary contract on or about September 30, 2003. Subsequently, calls for proposals for highly-targeted research sub-projects will be issued quickly, and initial research projects should be underway in January or February 2004. Importantly, efforts to establish the steering committee are underway, and a working group should have detailed recommendations for research plans ready by the end of the summer, in time to begin issuing calls for specific research and development projects once the contract is awarded.

With regard to roadblocks, the project depends, of course, on receiving proposals that are sufficiently scientifically meritorious so that we can responsibly fund them. The most serious obstacles to success, however, are scientific. It is important to keep in mind that developing effective treatments for neurogenetic diseases such as SMA is very much on the frontier of medicine. There are very substantial scientific difficulties that must be overcome to develop a treatment for SMA.

PROMOTING AWARENESS OF AND RESEARCH ON SMA

Question. What is NINDS doing to solicit grant applications? What workshops and conferences have been organized this year and next year to increase awareness of SMA and promote research funding opportunities?

Answer. We are using both grant and contract mechanisms to enhance research on SMA. SMA research funding at NINDS increased by 21 percent from fiscal year 2001 to fiscal year 2002; SMA funding grew by more than 500 percent from fiscal year 1998—\$945,000—to fiscal year 2002—\$5.6 million. This reflects in part the stimulus provided by an NIH workshop and a request for applications—RFA—on SMA and amyotrophic lateral sclerosis—ALS—in Spring 2000. Much of the growth, however, arises from the increased scientific opportunities, and reflects the strength of the traditional investigator-initiated grant process in responding to new avenues for progress. Given the state of the science, we expect grant applications in SMA will continue to increase.

The translational project in SMA that I described is contract-based. In December 2002, NINDS published a notice on the "Collaborative Program to Accelerate SMA Therapeutics Development" in the NIH Guide for Grants and Contracts to help develop the statement of work and Request for Proposals—RFP—for this program. On March 23, 2003 and April 8, 2003 NINDS published notices in Federal Business Opportunities and the NIH Guide, respectively, that the RFP will be released in April.

Other efforts include an NINDS consortium, developed through a solicitation, to screen all FDA approved compounds for activity against neurodegenerative diseases, which included a test specific to SMA. The Institute has a program to rapidly provide supplemental funding for testing candidate treatments that emerge from this, or other efforts, in rodent models. Through a solicitation, the NINDS has also established a high throughput drug screening facility and called for proposals for disease assays, specifically listing SMA among those disease assays being sought. In recent years, we have offered solicitations in several cross-cutting areas that may provide results that are relevant to SMA, focused on areas such as gene therapy for the

nervous system, neural stem cells, and pediatric neurological diseases. The NINDS is also assisting voluntary groups in organizing a scientific conference for Spring 2004 that will, among other goals, help inform biotechnology companies and the pharmaceutical industry about opportunities to develop therapies for SMA.

PROMOTING PROFESSIONAL AND PUBLIC AWARENESS OF SMA

Question. Please identify other NIH institutes and federal agencies that NINDS is working with to promote professional and public awareness of the disease. Please describe the programs that are being developed with a timeline and list of objectives?

Answer. The NINDS has an SMA public information page with links to advocacy organizations, relevant clinical studies, and research literature. The National Library of Medicine also has an information page for SMA with many useful links. In addition, scientific workshops and the variety of research solicitations addressing or referencing SMA, as well as program staff contacts, provide outreach to the professional community. There are a number of voluntary health advocacy groups focused on SMA that undertake extensive activities to inform the public and the research community, as is appropriate to their role, and we have cooperated with these groups in various ways.

STATUS AND COSTS OF CLINICAL TRIALS FOR SMA

Question. What is the status of clinical trials for promising SMA treatments?

Answer. The NINDS is funding a grant to lay the groundwork for clinical trials in SMA by developing a consortium of investigators and by validating appropriate outcome measures. However, at this time we need to emphasize translational research to bring potential treatments to the point where clinical trials are warranted. The NINDS is addressing this need in several ways. The contract-based translational research project for SMA is, of course, an important part of that effort.

Question. What is the estimate cost per trial?

Answer. Estimating the cost of trials and the possibilities of partnering with industry depend on the specific drugs or other therapies that might be tested, so we are not yet at the point scientifically where I can give a specific answer.

Question. For FDA approved drugs, what efforts have been made to partner with the manufacturer of these drugs?

Answer. We also support a consortium of investigators to screen FDA approved drugs for potential use against neurodegenerative diseases, including SMA. We have recently developed a high-throughput drug screening facility as well, and called for proposals to develop disease-specific tests, including those focused on SMA. In addition, the NINDS intramural program will be capable of conducting clinical trials on candidate therapies that emerge from these or other efforts.

ADDITIONAL RESOURCES REQUIRED FOR SMA RESEARCH

Question. What additional resources are necessary to execute the SMA translational research project? What additional resources do you require to increase the focus of SMA research at the NIH?

Answer. We believe we have the resources to execute the SMA translational project at this time. This and all other efforts against SMA depend on the response of the research community to these efforts. The substantial increases in funded research on SMA over the last few years reflect exciting scientific advances, which have brought increases in the scientifically meritorious proposals we receive from investigators, which is very encouraging. The growth also reflects our commitment to addressing this terrible disease.

DUCHENNE MUSCULAR DYSTROPHY—NICHD INVOLVEMENT

Question. Duchenne Muscular Dystrophy is the world's most prevalent, lethal childhood genetic disorder. Only in the past year has the Child Health Institute at NIH had any involvement in this disease. Has the Child Health Institute devoted any specific, significant resources to this disease?

Answer. Since the passage of the MD-CARE Act, the NICHD has partnered with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) to support the Muscular Dystrophy Cooperative Research Centers and the Developmental Planning Grants for Muscular Dystrophy Research Centers. In addition, over the past five years, NICHD, although it does not have primary responsibility for muscular dystrophy research, has sponsored an active portfolio of grants concerned with the muscular dystrophies, muscle pathophysiology and other neuromuscular dis-

orders. NICHD, along with other NIH Institutes, also has an active role on both the NIH MD Research Task Force and the MD Coordinating Committee.

In addition, through the NICHD-sponsored network of Mental Retardation and Developmental Disabilities Research Centers, resources created under this network have been used to conduct research in some topics related to muscular dystrophy. The National Center for Medical Rehabilitation Research within NICHD has also sponsored research on muscle and neuromuscular disorders including such topics as the effect of stress on dystrophic muscle and the role of strength on child mobility. Finally, the Intramural research program at NICHD has for several years had a research focus on understanding muscle pathophysiology.

DUCHENNE MUSCULAR DYSTROPHY—CONGRESSIONAL PRIORITY

Question. Funding for DMD is approximately $\frac{1}{2500}$ of the NIH budget. This committee has held a hearing on the subject; strong report language has been attached to the Labor/HHS appropriation for three years in a row; a comprehensive muscular dystrophy authorization bill has been signed into law. Is the spending of NIAMS, NINDS, and other institutes consistent with the congressional priority that has been identified for this disease?

Answer. Yes, NIH's funding of muscular dystrophy research is consistent with Congressional priorities. Indeed, from fiscal year 2000 to fiscal year 2002, NIH funding for muscular dystrophy—MD—research has more than doubled. In fiscal year 2000, NIH funding for MD was \$12.6 million; NIH funding increased to \$21.0 million in fiscal year 2001 and to \$27.6 million in fiscal year 2002. Funding for DMD during the same period also increased from \$7.0 million in fiscal year 2000 to \$12.4 million in fiscal year 2002.

MD-CARE ACT—CENTERS OF EXCELLENCE

Question. The Muscular Dystrophy CARE Act called for the creation of multiple Centers of Excellence, and was signed into law in 2001. This committee on three occasions has said that a minimum of three such Centers should be fully funded. I understand an RFP has finally gone out to organize the Centers, but the only assurance to the scientific community is that two Centers will be funded. Why so few? What funding level is assumed for these Centers?

Answer. The NIH has been actively engaged in implementing the mandates of the MD-CARE Act, including efforts to establish research centers for muscular dystrophy; the Act did not provide for a specific number of Centers. Specifically, in the Fall of 2002, the NIH issued two Requests for Applications—RFAs—in this area. The first solicited applications for up to three awards for Muscular Dystrophy Cooperative Research Centers, and the second solicited applications for up to five awards for Developmental Planning Grants for future centers. During fiscal year 2003, following peer review, we will make grant awards in response to these two RFAs; the number of centers actually funded, up to the specified numbers, will depend on scientific merit. In fiscal year 2004, we plan to re-issue the RFA for Cooperative Research Centers, and expect to fund up to two additional meritorious centers in fiscal year 2005. Subject to the number of applications we receive and the results of scientific peer review, the combined solicitations could result in funding up to a total of five MD cooperative centers. Direct costs for the research centers can be a maximum of \$1 million per center per year, for five years.

MD-CARE ACT—CBO ESTIMATES

Question. The MD-CARE Act was scored by CBO two years ago to cost \$54 million over four years. Apparently there was a minor increase in funding during the past year, but it is exceptionally difficult to see that this Act is going to be fully funded at the current pace of NIAMS/NINDS activity. What are the prospects for full funding of this Act?

Answer. The Congressional Budget Office—CBO—estimated that implementing the MD-CARE Act—including aspects that are the responsibility of other HHS components—would cost \$4 million in fiscal year 2002 and \$56 million over the five year period of fiscal years 2002 through 2006. Of this amount, the costs of the NIH activities and of the MD Coordinating Committee, which was established by the Act, were estimated at \$2 million in fiscal year 2002, and at \$28 million total over the fiscal year 2002 to fiscal year 2006 period. From fiscal year 2001 to fiscal year 2002, NIH actual funding for muscular dystrophy research increased from \$21.0 million to \$27.6 million, an increase of \$6.6 million or 31.4 percent—considerably more than the CBO estimate for fiscal year 2002. Budget estimates for fiscal year 2003 suggest that NIH muscular dystrophy funding would increase another 13.8 percent this fiscal year to an estimated \$31.4 million. While this trend of increasing support for

MD research is dependent upon future scientific opportunities and meritorious applications, it should be evident that the NIH is fully committed to implementing the MD-CARE Act, and to defining and advancing the MD research agenda.

MUSCULAR DYSTROPHY—CINRG

Question. Has NIH ever funded translational research into muscular dystrophy—in particular, has NIH ever subsidized the only human clinical trials network (the Cooperative International Neuromuscular Research Group, or CINRG) that is testing pharmacological approaches to delay the progression of this disease?

Answer. The CINRG, with the Children's National Medical Center as its coordinating center, conducts a multicenter clinical trials program to investigate the most promising treatments for DMD and related disorders. NIH currently funds a number of researchers who serve as principal investigators at participating centers for these clinical trials. In addition, NINDS has supported clinical trials on muscular dystrophy through both its intramural and extramural programs, and welcomes proposals for translational and clinical research aimed at delaying the progression of MD and related neuromuscular diseases.

Translational research, by which we mean the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease, is a high priority for the NIH. The emphasis in translational research is squarely on projects focused on the identification and pre-clinical testing of new therapeutics. The Muscular Dystrophy Cooperative Research Centers will promote side-by-side basic, translational, and clinical research, and will be designed to accelerate the translation of fundamental advances to the clinic. In addition, in July 2002, NINDS initiated a comprehensive program designed to encourage and support translational research for all neurological disorders, complemented by specific initiatives in areas such as drug discovery, gene therapy, and stem cells. Translational research is also an area of focus in the ongoing NIH Roadmap initiative.

MUSCULAR DYSTROPHY—NIH COORDINATION

Question. DMD is untreatable and incurable, and has, throughout history, taken the lives of children in their teenage years. Because of the extraordinary burdens placed on families of children with this disease, most of the benevolence on this affliction goes to subsidize care, not research. While DMD is the #1 genetic child killer, it afflicts one out of 3,500 boys, which is not a threshold high enough to attract private drug money. Hence NIH research is the leading hope for this generation of sufferers. Yet only in the past year has NIH created a muscle biology study group—the only one devoted to the study of the largest organ of the body, out of 110 study groups in all of NIH. Scientific interest in this disease for years had been dampened and frustrated because of this structural flaw. Congress on repeated occasions has suggested that NIH coordinate its activities, and begin to fund this disease commensurate with others—on the basis of prevalence, severity, need, and scientific opportunity. Yet the process of securing adequate funding in this area has been painfully, tortuously slow—testing the limits of congressional patience and willingness to entrust the Institutes alone to designate funding priorities. What assurance can you give that this will change?

Answer. NIH has already taken numerous steps to coordinate its activities with regard to muscular dystrophy. In early 2002, NIH formed the Muscular Dystrophy Research Task Force to help guide efforts to intensify research on muscular dystrophy. The Task Force is made up of physicians, scientists, NIH professional staff, and representatives of voluntary health organizations with a focus on muscular dystrophy. The purpose of the group is to help NIH add new capabilities to the national effort to understand and treat muscular dystrophies, without duplicating existing programs. The Task Force has met twice already—in May 2002 and January 2003.

In September 2002, NINDS, NIAMS, and NICHD jointly issued the request for applications—RFA—“Muscular Dystrophy Cooperative Research Centers—MDCRC,” and in November 2002, issued another RFA, “Developmental Planning Grants for Muscular Dystrophy Research Centers.” These centers will constitute a cohesive program, the MDCRC Program, operating under guidelines for NIH cooperative agreements. The centers will promote cooperation and coordination of activities and resources across the entire MD research community.

Coordination of MD research and education activities across the entire MD community will also be greatly enhanced by the formation of the Muscular Dystrophy Coordinating Committee—MDCC, as called for in the MD-CARE Act. The MDCC has broad representation from a number of HHS agencies, including the CDC, FDA, and HRSA as well as other government agencies, MD advocacy organizations, and

the public, with an interest in MD research and education. The MDCC is tasked with developing a plan for conducting and supporting research and education on muscular dystrophy through the national research institutes. This plan is to be developed within a year of the establishment of the MDCC and will further enhance the coordination of activities and funding opportunities relevant to MD across NIH.

MUSCULAR DYSTROPHY—NIAMS EFFORTS

Question. What is the NIH doing to ensure an integrated research approach regarding Muscular Dystrophy? What specific corporate processes exist to ensure research synergies and research success? Please provide for the record NIAMS efforts in these regard.

Answer. The NIH has a strong and growing interest in research on muscular dystrophy, and a number of collaborative efforts illustrate this commitment. Over the past few years, several NIH Institutes, including the NIAMS and NINDS, have partnered to support scientific meetings and research initiatives designed to advance the field of muscular dystrophy research. Projects funded as a result of these efforts include work on several forms of the disease, including the Duchenne, facioscapulohumeral, myotonic, and limb-girdle dystrophies. To underscore the importance of expanding and intensifying programs in this field, the NIH has established a Muscular Dystrophy Research Task Force, which includes NIH scientific staff, as well as researchers, clinicians, and patient representatives. This group will help ensure that we pursue all promising opportunities to enhance muscular dystrophy research and training. It will also complement the work of the newly established inter-agency MD Coordinating Committee, which was mandated by the MD-CARE Act. Among other NIH Institutes, the NIAMS has a very active role on both the Research Task Force and the Coordinating Committee.

DUCHENNE MUSCULAR DYSTROPHY—"ROADMAPS"

Question. Are the specific Science and Technology "roadmaps" established for diseases such as Duchenne Muscular Dystrophy? What are the disciplines involved? If so, for the record, please provide these, demonstrating how they integrate multi-disciplinary sciences and technology efforts.

Answer. The "Roadmap" Action Plans being developed by Dr. Zerhouni, with input from a broad range of NIH staff and extramural scientific experts, are not disease or discipline specific, but rather take a cross-cutting approach to identify scientific challenges and roadblocks to progress. The "Roadmap" Action Plans will focus on facilitating and accelerating multi-disciplinary aspects of basic, translational, and clinical research. It is likely that several of these areas will be applicable to research on DMD. With regard to muscular dystrophy research overall, the MD Coordinating Committee—MDCC—is tasked with developing a plan for conducting and supporting research and education on muscular dystrophy through the national research institutes. This plan will be developed within a year of the establishment of the MDCC.

MUSCULAR DYSTROPHY—TRANSLATIONAL RESEARCH

Question. Has the NIH ever considered a technology maturity assessment methodology akin to the NASA technology readiness levels or TRLs? Outline for the record the means and process for determination of transition from laboratory science to clinical trial?

Answer. As was mentioned before, translational research—the transition from laboratory science to clinical trial—is the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease. There are rigorous criteria and procedures, which are unique to medical science, for determining when it is appropriate to begin a clinical trial. At the present time, the NIH is in the midst of developing Roadmap Action Plans that will identify opportunities and roadblocks, as well as establish goals, in cross-cutting, multidisciplinary areas such as translational research. We expect that, as these needs are addressed over the next several years, the rate of successful translation of scientific advances into clinical trials will increase.

MD-CARE ACT—IMPLEMENTATION

Question. Outline the specific steps and associated timetable that the Department of Health and Human Services and NIH have been on to fully implement the provisions of the MD-Care Act of 2001. The Congressional Budget office scored the MD Care Act at approximately \$54 million for implementation. What are the total resources that NIH has dedicated to implementation of this Act currently reflected in

the fiscal year 2004 President's Budget Submission? Please provide for the record fiscal year 2002 and fiscal year 2003 obligations and expenditures for muscular dystrophy. Please indicate by institute by form of MD, to include, Duchenne, Becker, Limble-Girdle etc.

Answer. In September 2002, NINDS, NIAMS, and NICHD jointly issued two RFAs related to establishing the MD Research Centers provided for in the Act. The RFA for "Muscular Dystrophy Cooperative Research Centers," will establish research centers, each of which will bring together expertise, infrastructure and resources focused on major questions about muscular dystrophy. In November 2002, another solicitation was issued for "Developmental Planning Grants for Muscular Dystrophy Research Centers." These capacity-building grants are targeted to investigators who are not yet ready to compete to establish a muscular dystrophy research center, but would like to do so eventually.

With respect to the MD Coordinating Committee called for in the Act, the public members of the MDCC have been appointed as of April 20, 2003. Nine of the 10 Federal agency members have been designated by the Secretary, HHS, and it has been recommended that the DOD be invited as a member of the MDCC, based on the establishment in fiscal year 2003 of muscular dystrophy research as a project within the DOD's Defense Health Program. Committee members have been contacted about scheduling the first meeting, which is expected to be held in July.

The NIH has also been expanding and intensifying its efforts in MD research. In fiscal year 2002, NIH funding for MD was \$27.6 million. Estimated NIH funding for MD research in fiscal year 2003 is \$31.4 million and \$32.4 million in the President's fiscal year 2004 Budget. The funding by institute follows:

	Fiscal year		
	2002 actual	2003 estimate	2004 estimate
NHLBI	\$1,099,000	\$1,170,000	\$1,200,000
NINDS	9,843,000	12,327,000	12,589,000
NICHD	599,000	600,000	600,000
NIA	1,265,000	1,300,000	1,330,000
NIAMS	11,081,000	12,000,000	12,450,000
NHGRI	2,253,000	2,413,000	2,502,000
NCRR	1,438,000	1,631,000	1,679,000
NIH	27,578,000	31,441,000	32,350,000

The NIH funding for Duchenne MD was \$12.4 million in fiscal year 2002, and the estimated funding for fiscal year 2003 is \$13.7 million. The reported funding for Duchenne MD in fiscal year 2002, fiscal year 2003, and fiscal year 2004, by institute follows:

	Fiscal year		
	2002 actual	2003 estimate	2004 estimate
NINDS	\$4,050,000	\$4,373,000	\$4,459,000
NIA	1,265,000	1,360,000	1,400,000
NIAMS	4,571,000	5,000,000	5,200,000
NHGRI	2,160,000	2,312,000	2,398,000
NCRR	384,000	430,000	454,000
OD	200,000
NIH	12,430,000	13,675,000	13,911,000

MUSCULAR DYSTROPHY RESEARCH—INFRASTRUCTURE

Question. What are the specific NIH "infrastructure" shortfalls associated with MD research? (ie. RDT&E equipment, laboratory equipment, facilities, facility improvements) Please list any unfunded requirements by institute.

Answer. The NIH's Muscular Dystrophy Research Task Force has identified a number of infrastructure priorities, including the need for multidisciplinary training programs to ensure a steady pipeline of MD researchers; the importance of developing better animal models for MD; the need to enhance bioinformatics and imaging resources; and the need for tissue repositories, DNA samples, and cell lines that can be used by the MD research community. Some of these needs will be addressed

through the Muscular Dystrophy Cooperative Research Centers that NIH is planning to fund over the next few years, while others may require novel partnerships with industry and MD voluntary organizations.

MUSCULAR DYSTROPHY RESEARCH—COOPERATION WITH DOD

Question. Is there any relationship or cooperative research activities with the Department of Defense regarding muscle or myopathies? Between NIAMS and DOD? Or any other institute and DOD?

Answer. NIAMS is aware of the Department of Defense's (DOD) involvement in muscular dystrophy research, as reflected in the fiscal year 2003 DOD Appropriation for the Defense Health Program—Public Law 107-248—in that area. As a result, NIH is recommending that the Secretary of HHS solicit a nomination for a DOD representative to the Muscular Dystrophy Coordinating Committee. This will help to foster the communication and cooperation between DOD and NIH with regard to MD activities.

MYOPATHIES RESEARCH—NIAMS AND NASA

Question. In similar fashion, is there any cooperative RDT&E between NIAMS and NASA on muscle, muscle wasting, or myopathies? Is there any significant relationship to human physiology of flight, especially for long-duration manned space flight? Have NIH institutes made use of any data from NASA regarding muscle preservation with long-duration space flight? Please provide for the record.

Answer. Research cooperation between NIAMS and NASA can be traced at least to the early 1990's, highlighted by a 1990 meeting entitled, "The Effects of Space Travel on the Musculoskeletal System" and a program announcement, which resulted in several grants. In 2000, NASA and a number of NIH institutes—including NIAMS—collaborated on the program announcement, "Earth-Based Research Relevant to the Space Environment," to encourage research applications related to biomedical effects of space flight on humans, including the effects of gravity on the musculoskeletal system. Thus far, the announcement has resulted in the award of at least one NIAMS grant, a project which may provide insights into the use of resistance exercise as a countermeasure to the loss of muscle and bone that occurs during space flight.

DUCHENNE AND BECKER DYSTROPHIES—CLINICAL TRIALS

Question. What is the status of potential clinical trials on Duchenne and Becker dystrophies? Are these efforts fully funded in the fiscal year 2004 President's Budget Submission? Where is this in NIAMS research priorities for fiscal year 2004 and the outyears? Please provide for the record the current status of research on systematic delivery of the dystrophin gene? What are the specific impediments to gene therapy in DMD/Becker? What resources are reflected in the fiscal year 2004 PB for these efforts? Provide a comprehensive list of the "critical technical issues" associated with efficiency of systemic delivery.

Answer. Although much promising research is being done in animal models of muscular dystrophy, significant work remains before the science progresses to the level where major clinical trials in humans are safe and appropriate. Recent progress in developing simple and effective tests that detect more accurately the precise genetic defects in forms of muscular dystrophy may help advance clinical research in this area. By establishing a correct genetic diagnosis, we can identify potential gene replacement strategies, and more accurately estimate risks in families with a history of the disease. In addition, the NINDS has recently funded a pilot clinical trial that will test whether the common antibiotic gentamicin has therapeutic potential for patients with both the Duchenne and limb-girdle forms of muscular dystrophy. This trial may provide new insights that will help shape the course of future clinical studies in this area. Other clinical trials are currently under development.

One potential avenue to pursue, gene therapy, which uses vectors such as viruses to deliver a replacement for the defective gene, is seeing some success in the mouse. Current issues in muscular dystrophy gene therapy include obtaining vectors in significant numbers, effective gene delivery to affected muscles, and prevention of immune reactions to the vector itself. NIH also supports promising work in animal models on the therapeutic properties of muscle stem cells to devise potential new approaches for treatment of MD. Discussions by the NIH Muscular Dystrophy Research Task Force are expected to address these issues.

DUCHENNE AND BECKER DYSTROPHIES—RESEARCH INITIATIVES

Question. What specific research initiatives exist regarding the neuropsychological aspects of DMD/Becker? What resources and institutes are associated with this effort?

Answer. NIH realizes the importance of studying and integrating research on all aspects of a disease—from the physiological to the psychological. NIH has supported research and invites proposals on the neurocognitive and neuropsychological aspects of DMD. More broadly, four NIH Institutes—NINR with NIAMS, NICHD, and NINDS—in May 2002, issued a solicitation on “Increasing Quality of Life in Mobility Disorders.” This initiative seeks applications for grants to study the psychosocial aspects of conditions with limited mobility, which could include DMD. These psychological consequences may include anxiety, depression, social isolation, and lowered self-esteem. In February 2003, NINDS also issued a Request for Information for a contract that NINDS is considering to develop a coordinated approach to defining and measuring quality of life in neurological disorders. Patients’ social and psychological condition, as well as mental well-being, are among the parameters that may be measured. In addition, NINDS funds very basic studies on the effects of MD-related proteins in brain function. These studies may provide the basis for developing studies on neuropsychological aspects of MD.

The Muscular Dystrophy Coordinating Committee, which is tasked with developing a research and education plan for muscular dystrophy, has broad representation from a number of HHS agencies, such as the CDC, FDA and HRSA, as well as other government agencies such as the Department of Education. This will ensure that all aspects of MD, including the neuropsychological aspects of the disease, are considered in developing the research and education plan.

DUCHENNE AND BECKER DYSTROPHIES—PHARMACOLOGIC APPROACHES

Question. What specific pharmacologic approaches to DMD/Becker are currently being pursued by NIH and NIAMS? What are the resource implications and institutes involved?

Answer. Several years ago, NIAMS-funded scientists successfully used the common antibiotic gentamicin to restore the function of the missing protein dystrophin in mouse models of DMD. More recently, the NINDS has funded a pilot clinical trial that will test whether gentamicin has therapeutic potential for patients with both the Duchenne and limb-girdle forms of muscular dystrophy. This trial may provide new insights that will help shape the course of future clinical studies in this area. The NINDS is also supporting work in mouse models to test the efficacy of the protein biglycan as a potential therapy for Duchenne muscular dystrophy. In addition, early advances involving enzyme inhibitors and growth factors could eventually lead to new pharmacologic treatments.

The NICHD has established a Pediatric Pharmacology Research Unit Network which could prove to be a resource for developing pharmacological approaches in this area.

DUCHENNE AND BECKER DYSTROPHIES—STEROIDS

Question. Has the NIH developed a consensus statement regarding steroids in DMD/Becker? What is the progress here and target dates for such a statement? How is NIAMS participating in this?

Answer. In the spring of 2000, several NIH Institutes, including NIAMS and NINDS, sponsored a scientific workshop on “Therapeutic Approaches for Duchenne Muscular Dystrophy.” The goals of this workshop were to address key questions in improving treatments for DMD, and identify areas of needed scientific knowledge, impediments, and critical next steps to promote effective therapies. One of the areas covered in the workshop was the use of steroids in treating DMD patients, specifically the lack of guidelines for use and concerns about side effects in children. Subsequent to this workshop, the American Academy of Neurology—AAN—charged a Practice Parameters Committee with looking at this treatment approach and developing clinical guidelines. The AAN is expected to publish these guidelines in the next few months.

MD CARE ACT—COOPERATIVE RESEARCH CENTERS

Question. The MD Care Act mandated the creation of coordinated research centers in muscular dystrophy research, and suggested a budget of \$54 million. Would you verify for the record that the NIH has indeed responded to this by requesting applications for “Muscular Dystrophy Cooperative Research Centers?” Additionally, please detail your goal of funding 2 to 3 centers at the cost of \$1 million direct costs

each for 5 years a total of about \$15–21 million over 5 years. Is this currently reflected in the fiscal year 2004 President's Budget Submit?

Answer. The CBO estimate of \$56 million for implementation of the MD-CARE Act encompasses more than just the creation of research centers; it is an estimate for implementing all aspects of the Act, including those outside of NIH.

As one of the first steps in implementing the Act, NIH issued two requests for applications related to Muscular Dystrophy Research Centers. In September 2002, NIH issued an RFA entitled "Muscular Dystrophy Cooperative Research Centers," to establish research centers, each of which will bring together expertise, infrastructure and resources focused on major questions about muscular dystrophy. In fiscal year 2003, following peer review and selection of applications of the highest merit, NIH will fund up to three centers. In November 2002, NIH issued a second RFA for "Developmental Planning Grants for Muscular Dystrophy Research Centers." These grants, which will be awarded in fiscal year 2003, are targeted to investigators who are not ready to establish a muscular dystrophy research center but would like to do so eventually. Since the President's fiscal year 2004 budget reflects commitments from awards made in fiscal year 2003, the Centers are reflected in the fiscal year 2004 budget.

In fiscal year 2004, we plan to reissue the RFA for Cooperative Research Centers, and expect to fund up to two additional meritorious centers in fiscal year 2005. Direct costs for the research centers can be a maximum of \$1 million per center per year, for five years.

MD COOPERATIVE RESEARCH CENTERS—RESOURCE CORES

Question. The committee understands that a second round of competitive awards is anticipated in late 2004, with funding shared between NINDS, NICHD, and NIAMS. Please outline for the record the concept of "Scientific Research Resource Cores." Does this include the Muscular Dystrophy Cooperative Research Centers grant mechanism? Does this initiative ensure that the very best support infrastructures are present and enable the nation-wide muscular dystrophy research community some advantage?

Answer. In fiscal year 2004, we plan to re-issue the RFA for Muscular Dystrophy Cooperative Research Centers, and expect to fund up to two additional centers in fiscal year 2005. At present, NIAMS and NINDS are committed to funding centers of the highest scientific merit through this follow-up initiative. The Scientific Research Resource Cores that will be funded as part of these new centers are expected to serve the national muscular dystrophy research community, in addition to supporting research within the centers. These resource cores will foster multidisciplinary collaborations across departments at a single institution, as well as among investigators at several institutions, through the sharing of novel research tools. Examples of scientific cores include, but are not limited to, tissue and DNA repositories, medical imaging, special animal facilities, and bioinformatics. Investigators at the cooperative research centers are expected to promote the use of the core facilities among researchers within the parent institution and among scientists at other institutions.

MD RESEARCH RESOURCE CORES—ACCESS AND FUNDING

Question. A successful competitive clinical trial network could accept clinical trials for promising therapeutic approaches from muscular dystrophy investigators that are not formally part of one of the two or three funded MDCRCs. Likewise, a successful gene vector or stem cell core facility could produce these critical reagents for laboratories throughout the country. Is the potential increased work load of a successful Scientific Research Resource Cores planned to be funded by the NIH via administrative supplements? Please outline your plans and the funding profiles for record for fiscal year 2004 and the outyears.

Answer. It is expected that an MDCRC will be able not only to accommodate the research ideas and needs of participating scientists, but also to be responsive to other muscular dystrophy research enterprises that may not have direct connections to the center. Cooperation is a key part of the MDCRC's name; the centers are designed to both foster research, and to share knowledge and resources with the muscular dystrophy community at large.

In fiscal year 2004, we plan to reissue the RFA for Cooperative Research Centers, and expect to fund up to two additional meritorious centers in fiscal year 2005. Direct costs for the research centers can be a maximum of \$1 million per center per year, for five years. The Scientific Research Resource Cores will be funded as part of these centers. In general, administrative supplements are awarded to already funded researchers in response to identified needs and opportunities within the

scope of the original grant award. Since the center grants have not yet been awarded, any discussion of supplements would be premature.

MD COOPERATIVE RESEARCH CENTERS—FUNDING

Question. It appears that innovative and novel mechanisms that they have put into place for executing the congressionally directed muscular dystrophy cooperative research centers. Please outline for the record the anticipated funding levels and implementation dates for three competitive centers, and evidence of implementation of the innovative Scientific Research Resource Cores via administrative supplements.

Answer. As stated in the recent solicitations for muscular dystrophy cooperative research centers and for developmental planning grants for future centers, the NIH expects to fund up to three research centers and up to five planning grants in fiscal year 2003. In fiscal year 2004, we plan to re-issue the RFA for Muscular Dystrophy Cooperative Research Centers. Direct costs for the research centers can be a maximum of \$1 million per center per year, for five years. The Scientific Research Resource Cores, which will be funded as part of these new centers, are expected to serve the national muscular dystrophy research community, in addition to supporting research within the centers.

NIH TUBEROUS SCLEROSIS FUNDING

Question. How much is NIH currently investing in research on tuberous sclerosis complex (TSC)?

Answer. The NIH reported actual funding for TSC research in fiscal year 2002 was \$6,121,000. The fiscal year 2003 estimated funding is \$6,439,000.

INVESTMENT IN TUBEROUS SCLEROSIS BY INSTITUTES

Question. Since tuberous sclerosis can affect all of the body's organ systems, which institutes are currently supporting this research, and how much is each institute investing?

Answer. The National Cancer Institute—NCI; National Heart, Lung, and Blood Institute—NHLBI; National Institute of Diabetes and Digestive and Kidney Diseases—NIDDK; and National Institute of Neurological Disorders and Stroke—NINDS support TSC research. Funding by Institute is summarized in the table that follows.

	Fiscal year		
	2002 actual	2003 estimate	2004 estimate
NCI	\$638,000	\$657,000	\$677,000
NHLBI	2,140,000	2,279,000	2,336,000
NIDDK	717,000	700,000	700,000
NINDS	2,596,000	2,803,000	2,859,000
OD	30,000
Total	6,121,000	6,439,000	6,572,000

COORDINATION OF TUBEROUS SCLEROSIS RESEARCH

Question. Has there been any attempt to coordinate research on tuberous sclerosis among the institutes involved?

Answer. Yes. The Program Director at NINDS who manages the TSC research portfolio is in regular contact with his counterparts at other Institutes. In addition, program staff from the National Institute of Arthritis and Musculoskeletal and Skin Diseases—NIAMS and NIDDK participated in the September 2002 NINDS-sponsored workshop on TSC research, and these institutes, along with the National Institute of Child Health and Human Development—NICHD, NHLBI, and NCI, are being consulted in the development of the NIH TSC research plan.

TUBEROUS SCLEROSIS RESEARCH PLAN AND REPORT

Question. On September 19–22, 2002, NIH, the Office of Rare Disorders and the Tuberous Sclerosis Alliance sponsored a research conference entitled New Perspectives in Tuberous Sclerosis Complex. In the fiscal year 2003 Senate report the Committee asked to receive a progress report on efforts to develop a research plan. When can we expect to receive this report, and how will it affect future research on tuberous sclerosis?

Answer. In response to a joint resolution of Congress, passed in 2001, NIH is preparing a five-year TSC research plan. Efforts are currently underway, led by NINDS, to craft the recommendations that emerged from the September 2002 conference into a formal research plan. NIH expects to finalize the plan and then submit a report to Congress in June 2003. This plan will help guide the development of NIH initiatives related to TSC and provide a framework that will allow the NIH Institutes and research and advocacy communities to coordinate their efforts to advance TSC research.

PAIN RESEARCH

Question. Chronic pain affects anywhere from 35–110 million individuals per year, and is the most common reason consumers seek health care, accounting for 20–30 percent of doctor visits and 10 percent of prescriptions sold.

The NIH Pain Research Consortium has been in existence since 1996. Can you please provide this Committee with evidence of its activities over the past three years, and its planned activities for fiscal year 2004?

Answer. The NIH Pain Research Consortium was established in 1996 to enhance pain research and promote collaboration among researchers across the many NIH Institutes and Centers that have programs and activities addressing pain. Since its inception, the Consortium has been co-chaired by the Director of the National Institute of Dental and Craniofacial Research (NIDCR) and Director of the National Institute of Neurological Disorders and Stroke (NINDS), and most recently the Director of the National Institute of Nursing Research (NINR) has joined as the third co-chair. The working membership of the Consortium has been comprised of the key representatives of the Institutes, Centers (ICs) and Offices conducting and sponsoring pain research and programs at the NIH. It is designed to promote pain research and to increase awareness in the various NIH ICs in order to stimulate collaborative research initiatives, to coordinate both intramural and extramural research programs, to foster and maintain contact with research and patient communities, and to ensure that the results of NIH-supported pain research are widely communicated.

In its first few years the Consortium:

- Sponsored the symposium “New Directions in Pain Research,” which brought together scientists within the mainstream of pain research and exposed them to the work of investigators who do not normally focus on pain. In this way, the symposium brought new ideas, methodologies and techniques to pain researchers, where novel approaches to understanding and treating pain are greatly needed. Summary reports from the meeting appeared in the journals *Neuron* and *Science*.
- Sponsored the Symposium “Gender and Pain,” which covered subjects such as the differing impact of the sex hormones testosterone and estrogen on pain, brain imaging of nerve pathways involved in the pain response, and efforts to identify genes that affect pain sensitivity. This meeting received a great deal of media attention, and thus information dissemination on the differing responses to pain and current research.
- Established a Pain Research Consortium website on the NIH web that included information on the consortium’s mission, its membership, activities being coordinated both intramurally and extramurally, conference proceeding and collaborative funding announcements, among other things.
- Developed a number of multi-institute supported Program Announcements and Requests For Applications in the area of pain research, that were also listed on the website.
- Gave rise on the NIH campus to the formation of the Pain Interest Group, which sponsors seminars, informal discussions and communication via subscription to a list accessible to members of the NIH community.

In addition to these efforts, a number of institute-initiated efforts have been ongoing. Examples include:

- In an effort to enhance the pain consult services within the NIH Clinical Center, the highly successful Pain and Palliative Care Service was established under the direction of a nationally recognized pain clinician, Ann Berger, RN, MD.
- Similarly, the NIDCR-directed Pain Research Clinic accounts for the vast majority of translational pain research done intramurally at NIH and has influenced the field of pain research through training and the scientific productivity of its senior investigators.
- The NIH-FDA Analgesic Drug Development workshop attracted 250 registrants, resulted in a FDA Advisory Committee hearing in July to develop new criteria

for multi-dose studies and claims structure for drugs indicated for Rheumatoid Arthritis and Osteoarthritis, and has catalyzed the first revision of the analgesic drug development process in nearly two decades.

—The NIAMS-led Osteoarthritis Initiative resulted in greater than \$50 million in funding, with significant contributions from the pharmaceutical industry, to develop improved clinical trials methods, identification of biomarkers, and an innovative format for future clinical trials for this disease.

More recently, efforts are underway to capitalize and build upon these above activities and to reinvigorate the Consortium. Over the last six years, several changes of leadership in the NIDCR and the NINDS have resulted in a number of changes in individual co-chairs, and, as noted, NINR has joined as the third co-chair. Drs. Lawrence Tabak, Audrey Penn, and Patricia Grady, the current co-chairs of the Consortium, with the support of NIH Director, Dr. Elias Zerhouni, are facilitating the necessary efforts to see the Consortium reach its full potential to catalyze activities both intra- and extramurally in pain research.

To this end, each Institute and Center Director, as well as the central NIH Office Directors, have been contacted and asked to reaffirm their commitment to the pain Consortium as members, and to update their liaisons to the Consortium. In addition, invitations to participate in the Consortium have been extended to NIH's sister agencies, including the Food and Drug Administration, and to pain researchers in the Department of Defense and the Veteran's Administration. An organizational meeting of the revitalized Consortium has been scheduled by the co-chairs to convene on June 10, 2003 to collectively frame the scope and activities of this group for the future, and update the scientific agenda for NIH pain research. Plans for the Consortium, which will address current IC activities as well as those for fiscal year 2004 and beyond, include catalyzing additional multi-institute supported research efforts within both the extramural and intramural programs, including more highly integrated, multi-institute sponsored PAs and RFAs in the area of pain research. The website for the Consortium will also be enhanced to make it an interactive source of more comprehensive information on pain and pain research for its various stakeholders, e.g., pain researchers; patients and patient advocate groups, professional associations, the public, and the media, among others.

Question. According to pain advocacy groups, the NIH has difficulty in accurately accounting for its expenditures in pain and symptom management. Past estimates indicate that the NIH spends less than 2 percent of its total budget on primary pain care research. The American Pain Foundation maintains that in a conversation with the NIH Office of Budget last summer, that office indicated that the NIH spent \$124 million on pain-related projects in fiscal year 2000, with an increase to \$134.9 million in fiscal year 2001. However, other sources believe that those figures may exaggerate the actual expenditures because they included grant figures where pain was an underlying or secondary focus in the study.

Can you prepare for this Committee an accurate accounting of the NIH's intramural and extramural activity in pain and symptom management research, to include detailed information and accounting on the projects that are primarily addressing pain issues from across the institutes and centers?

Answer. Thirteen of the NIH organizations have reported support for pain-related research, as detailed in the following table and narrative descriptions:

NATIONAL INSTITUTES OF HEALTH; FISCAL YEAR 2002 ACTUAL OBLIGATIONS; PAIN CONDITIONS, CHRONIC

[In millions of dollars]

Participating ICs	Extramural research	Intramural research	Fiscal year total
NCI	10.6	0.4	11.0
NHLBI	10.3	10.3
NIDCR	21.4	5.1	26.5
NINDS	47.7	1.4	49.1
NICHHD	4.8	1.1	5.9
NIA	1.8	0.7	2.5
NIAMS	6.6	6.6
NIMH	5.9	5.9
NIDA	22.6	0.4	23.0
NINR	10.9	10.9
NCRR	11.4	11.4
NCCAM	9.0	9.0

NATIONAL INSTITUTES OF HEALTH; FISCAL YEAR 2002 ACTUAL OBLIGATIONS; PAIN CONDITIONS,
CHRONIC—Continued

[In millions of dollars]

Participating ICs	Extramural research	Intramural research	Fiscal year total
OD	1.9	1.9
NIH	164.9	9.1	174.0

The National Cancer Institute (NCI)

NCI supports clinical trials on secondary or indirect pain-related research where pain alleviation is a factor in determining patient quality of life during the patient's experimental treatment and care. Pain assessment/pain management research grants investigate how to overcome cultural barriers between providers and patients to better manage cancer related pain. These studies consider gender differences in the effectiveness of similar pain medications. NCI researchers are also developing new methods of pain measurement that are computerized for ease of patient use at the provider site or in the patient's home. Other complementary and alternative medicine pain relief research includes: hypnosis for postoperative breast surgery pain, massage for short-term relief from pain in advanced stage cancer patients, and acupuncture or acupressure for pain relief in advanced pancreatic cancer patients.

Other NCI research examines the biological or molecular basis of pain. Researchers are studying cellular proteins that may be elevated in cancer cells to activate the pain response in humans or animal models. NCI has several ongoing studies on the reduction of therapy-induced pain. These include studies on reversing opioid related constipation as well as determination of initial dosing rates to minimize the pain associated with use of photodynamic therapy for treatment of certain skin cancers. There are several phase II clinical trials underway on therapy induced pain in advanced stage cancers, including a study of radionuclides for metastatic prostate cancer tumors ablation, arsenic trioxide for pain relief of advanced prostate cancer, and radiation as a palliative care measure in advanced lung cancers. NCI is also funding pharmaceutical research on new delivery systems for natural delta-9-tetrahydrocannabinol (THC) to alleviate the marked loss of appetite and weight in cancer and AIDS patients.

Emerging evidence from several groups reveals that the capsaicin receptor (a biologic molecule involved in pain sensation) is modulated not only by compounds like capsaicin but also by signaling pathways such as protein kinase C. NCI is actively investigating the regulation of other (vanilloid) receptors by protein kinase C as well as the design of molecules that can manipulate the protein kinase C pathway to obtain useful therapeutic outcomes, such as modulation of pain.

The National Heart, Lung and Blood Institute (NHLBI)

NHLBI supports research on the management of painful episodes associated with sickle cell disease (SCD). Its current portfolio includes a study to ascertain the impact of acute and chronic pain events on health care utilization among adults with SCD, as well as an examination of the relationship between sickle cell pain, mood, and stress in adolescent and adult patients. The NHLBI is also funding a 5-year follow-up of adult patients who participated in a landmark clinical trial that established the usefulness of the drug hydroxyurea in preventing complications of SCD. The goal of the follow-up study is to assess the continuing effectiveness of hydroxyurea in decreasing rates of painful sickle cell episodes and improving quality of life.

The National Institute of Dental and Craniofacial Research (NIDCR)

The history of pain research at NIH began over five decades ago when the NIDCR recognized many Americans' association of dentistry with pain. Since that time, NIDCR, in conjunction with other NIH Institutes, has built a comprehensive portfolio of pain research. Its scientists and grantees have made important contributions to define the basic neurocircuitry of pain, as well as translating this understanding into improved treatments that benefit millions of Americans.

The NIDCR has established relevant research programs initiatives in both its intra- and extra-mural components. NIDCR scientists have long studied oral-facial pain, not only because of its importance in oral disease, but also because it provides an accessible model of pain elsewhere in the body. These investigations have greatly enriched our understanding of the basic mechanisms of pain perception and modulation and have helped delineate the complex pathways and multiple transmitters

that convey pain signals. The NIDCR recognizes that a unique opportunity now exists, with the emergence of genomic, proteomic, and other powerful, information-generating technologies, to define in greater detail the genetic and molecular basis of pain. This basic research will serve as the pipeline for new strategies in pain management, allowing future clinicians to more selectively and efficiently control the pain process.

NIDCR grantees are defining biological factors that might account for differences in pain perception. Novel imaging techniques that track the “mu-opioid” system, have revealed that people vary both in their capacity to produce mu-opioid receptors and in their ability to release the anti-pain chemicals themselves. Researchers found that at matched levels of pain intensity, men and women differ in the degree and direction of the mu-opioid response in distinct areas of the brain. Variability in the mu-opioid system appears to determine the emotional and sensory aspects of a painful experience may also help to explain why some people are more prone to chronic pain conditions or do not benefit from certain anti-pain medications. While the neurocircuitry involved in each of these processes is extraordinarily complex and inadequately understood, these initial imaging studies of pain perception offer an important starting point to further explore human perception and diversity.

In preliminary animal studies, NIDCR scientists have demonstrated a treatment approach that selectively controls the chronic pain associated with tissue damage and recurrent inflammation. This discovery builds upon laboratory studies of the cell-surface protein vanilloid receptor I, known by the unrelated acronym TRPV1. Researchers have isolated a TRPV1-binding compound, which in animal studies selectively eliminates an entire class of pain-sensing neurons from the peripheral nervous system. This compound, known as resiniferatoxin (RTX), killed certain neurons, and blocked inflammatory pain, hyperalgesia, and thermal pain sensation. Importantly, the animals maintained their ability to sense pain and remained well coordinated, an indication that RTX did not affect proprioceptive nerves in the muscles and joints. These NIDCR researchers have yielded in just over a year of work a novel approach to pain management. This finding has important implications for the field of pain research, as well as the potential to impact American public health. Additional studies are under way that will move RTX and related compounds into human clinical trials.

The National Institute of Neurological Disorders and Stroke (NINDS)

NINDS supports a broad range of research focused on both understanding the causes and mechanisms of pain and on developing effective treatments for pain. Our portfolio includes research on the unique roles in processing and regulating pain that are played by different areas of the nervous system including: the peripheral nervous system, spinal cord, brainstem, and cerebral cortex. The portfolio also includes research aimed at gaining a better understanding of the different neurotransmitter systems involved in mediating pain. The NINDS supports research on a wide variety of pain conditions, including: neuropathic pain, visceral pain, pelvic pain, causalgia, painful peripheral neuropathies, cancer pain, back pain, muscle pain, migraine and other types of headache pain, post-surgical pain, and inflammatory pain. Research on the mechanisms of anesthesia and analgesia is another area funded by NINDS. The NINDS supports a number of clinical studies aimed at testing the effectiveness of different types of treatments (both drug and non-drug) for several pain conditions. For example, one clinical trial is comparing the effectiveness of either a drug or cognitive behavioral therapy for treatment of chronic tension-type headaches. Another clinical study is examining whether behavioral changes (e.g., changes in diet and exercise) can prevent the pain associated with peripheral neuropathy in individuals who have Impaired Glucose Tolerance, a condition of impaired glucose metabolism. Finally, the NINDS supports training programs at both the pre- and post-doctoral level with the goal of giving young scientists and physician-scientists a broad experience in the pharmacological, pathological, and molecular biological methods of pain research.

National Institute of Child Health and Human Development (NICHD)

Chronic pain is a secondary condition in persons with disabilities. Currently funded research on the management of chronic pain explores the efficacy of innovative non-pharmacologic therapies, such as virtual reality analgesia in children with cerebral palsy and burns. Cognitive restructuring, relaxation training and hypnotic analgesia are pain-management approaches being investigated in persons with cerebral palsy, multiple sclerosis, acquired amputation, and spinal cord injury. Research focused on the biomechanics of wheelchair propulsion may reduce shoulder pain and increase the mobility of wheelchair users.

In the area of reproductive health, several investigators are studying pharmacologic treatments for the pelvic pain associated with vulvodynia, endometriosis, dysmenorrhea and hysterectomy. Other pain research examines the effects of epidural analgesia, used commonly to reduce pain in labor. There is evidence that suggests epidural analgesia may also prolong labor, influence the position of the fetus during labor and increase the likelihood of a high-risk cesarean delivery. Pre-term infants are subjected to many painful procedures in the NICU environment. The long-term neurodevelopmental effects of early exposure to pain and the effects of the sedatives and opioid analgesics used to reduce neonatal pain are the focus of other NICHD-supported research.

National Institute on Aging (NIA)

It has been estimated that chronic pain affects approximately half of older adults living at home, and may cause significant disruption of physical, psychosocial, and cognitive function. Management of pain is also of particular concern in older surgical patients, Alzheimer's patients and other patients with diminished cognitive capacity, as well as in end-of-life care. NIA extramural studies include a study of pain management in hip fracture patients and the potential problem of overlooking pain symptoms in patients who experience delirium as well as an investigation of chronic low back pain and its effect on physical, psychosocial, and cognitive function in a group of adults over age 65. Another extramural study is examining the possible effects of a multidisciplinary palliative care consultation on pain management, dyspnea, and anxiety in a group of seriously ill, hospitalized older patients. A new study will research the effect that identifying pre-visit concerns of older adult patients has on improved health status for the primary outcomes of pain and physical function. There is also a study to understand the major determinants of post-operative outcomes and improve functional recovery of elderly surgical patients, including the relationship between improved pain management and improved daily functioning.

NIA has two intramural studies of pain. The first is a study of chronic musculoskeletal pain in hereditary disorders of connective tissue, such as Ehlers-Danlos syndrome and Stickler syndrome, that examines the efficacy of the use of the "Mindfulness-Based Stress Reduction Program" in the relief of chronic pain. The second is an epidemiologic study of the impact of pain and other symptoms of chronic diseases on the daily lives and functioning of older disabled women, which is specifically investigating whether musculoskeletal pain increases the risk for falls and other adverse health outcomes and if the risk can be reduced through the use of analgesic medications.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

The mandate of the NIAMS is broad and diverse, focusing on the whole array of diseases that affect the muscles, joints, bones, and skin. Many of these diseases are chronic, and are also accompanied by significant pain. The origin of pain and effective strategies for pain management are areas of research supported by the NIAMS. The NIAMS pain research portfolio includes a significant number of studies on fibromyalgia, a complex and chronic disorder that is characterized by widespread musculoskeletal pain, fatigue, and multiple tender points. "Tender points" refers to tenderness that occurs in localized areas, particularly in the neck, spine, shoulders, and hips. The NIAMS supported studies related to fibromyalgia and pain include efforts to identify the central factors causing fibromyalgia; research on the changes that occur in the nervous and the hormonal systems in people with fibromyalgia; and a study that is using chronic low back pain as a model for fibromyalgia. Additional research topics include: exploring the roles of sex hormones, stress, and pain in fibromyalgia; work on the employment and health status of women with fibromyalgia; and adaptation to pain and stress in fibromyalgia. Other studies are focusing on rheumatoid arthritis and exploring the value of coping skills training for early rheumatoid arthritis as well as the roles of stress and adaptation to rheumatoid arthritis. Also, the NIAMS has teamed with the NIH Office of Research on Women's Health in funding a new Specialized Center of Research on gender differences in sensitivity to pain.

National Institute of Mental Health (NIMH)

In keeping with the NIMH's mission, over one-half of the pain research NIMH supports is devoted to examining the relationship between pain and mood states. Examples of this work include studying the effects of anxiety on pain perception, and research evaluating depression as a consequence of pain. The NIMH portfolio also includes research on the basic neurophysiology of pain, including both central and peripheral nervous system mechanisms. NIMH also supports studies of the relevant receptors, neurons, neurotransmitters, and neuropeptides implicated in pain.

NIMH-funded work also investigates the efficacy of psychosocial interventions in alleviating and preventing chronic pain. Thirty percent of the pain research funded by NIMH focuses specifically on children and elderly populations.

National Institute on Drug Abuse (NIDA)

The National Institute on Drug Abuse (NIDA) has a comprehensive research portfolio that looks at all aspects of drug abuse and addiction and includes a significant pain and analgesia research program. NIDA's interest in this area stems from the fact that many analgesics also have abuse potential and research on drug abuse and addiction is relevant to pain issues. Thus, NIDA supports the development of treatments for chronic pain, including the use of opioids (e.g. morphine, oxycodone, fentanyl, codeine) as well as finding alternatives to opioids. Innovative research funded by NIDA includes a device using transcutaneous electrical nerve stimulation (TENS) that was developed through NIDA's Small Business Innovation Research (SBIR) program. TENS stimulates certain nerves in the skin, and this activation inhibits pain. This device is now FDA approved and commercially available. NIDA also supports research on treating some severe forms of pain, such as cancer pain, using transplanted cells from the pituitary gland that produce opioids. Initial work in this area showed that implanting these cells into the spinal cord reduces pain in rats. Researchers are now looking at the use of this technique in monkeys. Another technology using "targeted neurotoxins" is being developed in animal models by several NIDA researchers. This technology is expected to reduce chronic pain by eliminating specific chronic pain fibers in the spinal cord. NIDCR has been examining specific targeted agents acting on ion channels in pain-sensing neurons that have shown potential as a clinical pain treatment. NIDA is partnering with NIDCR in completing toxicology studies on this agent and getting FDA approval for clinical trials in the treatment in cancer patients.

National Institute of Nursing Research (NINR)

Nursing research focuses on ethnically and culturally sensitive interventions for pain prevention, assessment, management, and treatment. Emphases include end-of-life pain management and interventions that help people manage their own pain caused by chronic diseases, such as arthritis. NINR also focuses on the interaction of pain, the immune system, and illness at biological and cognitive levels. NINR supports research on non-pharmacologic interventions to reduce pain, including exercise, music and art therapy, and biofeedback, as well as the improving clinicians' ability to assess pain in those unable to express the level of pain they experience, including infants and cognitively impaired elderly.

Research findings have set a new direction for pain research. For the first time, the influence of gender on pain relief was demonstrated. Study results showed that Kappa opioids, when used for acute pain, are more effective in women than men and have fewer side effects than stronger drugs, such as morphine. The role of hormones on the effectiveness of treatment is currently under study. NINR also conducts research on the importance of pain relief in improving the immune systems response to metastasis following surgery. In an animal model, researchers found that if morphine is provided before and after surgery, the immune system is less depressed, which suggests that pain relief improves resistance to the spread of cancer. Other research findings suggest that exercise helps fibromyalgia patients, who typically have both localized and widespread pain. Patients participating in muscle strengthening achieved the greatest benefit without significant exercise-induced flare-ups in pain.

National Center for Research Resources (NCRR)

NCRR develops and supports critical research technologies and resources that underpin and advance health related research supported by the NIH and other research organizations. Research is carried out through support from the four NCRR divisions: Biomedical Technology, Clinical Research, Comparative Medicine, and Research Infrastructure. The Division of Biomedical Technology supports research resources that enable investigators to do basic research on the biochemistry and physiology of pain. NCRR's Division of Clinical Research supports General Clinical Research Centers where researchers are studying the clinical aspects of pain, including: drug testing and development, gender differences in pain, and pain associated with specific diseases. The Division of Comparative Medicine supports research on pain treatments in animal models, including a mouse model of analgesic regimens for surgery. Finally, the Division of Research Infrastructure supports studies on musculoskeletal pain and pain in children.

National Center for Complementary and Alternative Medicine (NCCAM)

NCCAM supports an extramural pain research portfolio that involves extensive testing of complementary and alternative (CAM) therapies, such as acupuncture, chiropractic medicine, and yoga, to determine their efficacy in preventing and treating pain associated with a variety of conditions and diseases. For example, in a partnership with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NCCAM is supporting a large clinical trial to determine the efficacy of acupuncture in treating pain and functional limitations imposed by degenerative arthritis of the knee. At the Northwestern Health Sciences University, investigators are comparing chiropractic spinal manipulation, prescription medication, and self-care advice for neck pain, while at Harvard University investigators are evaluating the placebo effect and its role in treating repetitive strain injury. One of NCCAM's major research interests is to study how alternative therapies, primarily botanicals, interact with other medications. At the Fred Hutchinson Cancer Research Center researchers are studying how St. John's wort, a popular herb taken as an antidepressant, interacts with pain relieving opioids in the context of cancer pain therapy. In addition, NCCAM-supported researchers at the Johns Hopkins University Center for Complementary and Alternative Medicine are developing an animal model to study the reduction of cancer pain using herbal medicines that appear to contain anti-inflammatory properties. To help ensure a cadre of clinical investigators in the field of CAM research, including pain research, NCCAM has also awarded a grant to the Palmer Chiropractic University to develop a curriculum on research methodologies for chiropractors.

Office of the Director (OD)

The Office of Research on Women's Health co-funded a total of \$1.9 million in pain research projects in the areas of: lower back pain, sex differences that influence pain, cellular mechanisms of neuropathic pain, pain management in temporomandibular disorders, and chronic pain conditions that predominantly affect women.

SCLERODERMA

Question. There is significant vascular and autoimmune component to scleroderma, are there other institutes aside from the NIAMS at the NIH that you would recommend scleroderma researchers pursue to fund experiments aimed at finding a cure? For example, since the leading cause of death in scleroderma patients is through pulmonary hypertension and its effects on heart function, should grants on pulmonary hypertension that encompass issues unique to scleroderma patients be directed to the NHLBI instead of the NIAMS?

Answer. Research on scleroderma is of interest to a number of NIH components. This is one of the strengths of the NIH—that we study diseases from a variety of perspectives. These efforts are complementary, not duplicative. To give an illustration, not an comprehensive list, in the case of scleroderma, the NIAMS is the lead Institute with interests in connective tissue and skin involvement. Other researchers interested in particular aspects of scleroderma include those supported by the National Heart, Lung, and Blood Institute (for example, work on pulmonary fibrosis, pulmonary hypertension, and vascular involvement), the National Institute of Diabetes and Digestive and Kidney Diseases (for example, work on the gastrointestinal tract and kidney function), the National Institute of Allergy and Infectious Diseases (for example, work on autoimmunity), and the NIH Office of Research on Women's Health (because scleroderma affects more women than men). As well, the National Center on Minority Health and Health Disparities also has an interest because of the increased incidence of scleroderma in Native Americans. This means that researchers interested in studying scleroderma should first consider what particular dimension they wish to pursue and contact the relevant Program Director within that Institute. The NIH web site includes links to the individual web sites of each Institute, so this is an effective way to identify the appropriate Program Director for the particular area of interest. I do want to underscore the close collaboration and collegial spirit that we have at the NIH—we team together to sponsor solicitations and to support research in targeted areas as well as jointly sponsor scientific meetings. All of this means that the NIH is able to bring a wealth of experience and complementary interests to a disease like scleroderma.

Question. In your opinion is there sufficient infrastructure (i.e., enough scientists in the field) to support a significant increase in scleroderma funding? Aside from funding more grants specific to scleroderma research, how would the NIH propose increasing interest in the field?

Answer. The issue of infrastructure is of significance to all scientific disciplines and diseases, and the NIH is actively working to address all of the dimensions of

infrastructure. When we look specifically at scleroderma, I am pleased to tell you that this is an area that is the focus of a broad array of research efforts, and I want to cite highlights of several investments. First, the NIAMS made a significant commitment to boosting research on scleroderma when the Institute issued a special solicitation for research applications in fiscal year 2000. This successful solicitation resulted in the funding of ten new research grants totaling more than \$2 million. These included both basic and clinical studies, and we were joined by the NIH Office of Research on Women's Health in co-funding two of the grants. The NIAMS also currently funds two Specialized Centers of Research in Scleroderma—one at the University of Texas Health Science Center and one at the University of Tennessee. Specialized Centers of Research (SCORs) increase the transfer of basic research findings into clinical practice by conducting basic and clinical studies under one roof. These SCORs focus only on scleroderma, and they serve as a national resource for researchers studying scleroderma. In addition, the NIAMS established a national Scleroderma Family Registry and DNA Repository for scleroderma in June 2001 with the goal of identifying susceptibility genes. We believe these investments will provide critically important information on the causes of scleroderma and help us to develop improved treatments. In addition, through Dr. Zerhouni's Roadmap Initiative, infrastructure will be strengthened to facilitate clinical research across the spectrum of clinical diseases.

With regard to increasing interest in the field, scleroderma is an autoimmune disease—a broad category of diseases in which the body's immune system attacks the body's own tissues as if they were foreign invaders, causing significant damage to target organs. The whole field of autoimmunity is currently exploding with activity and newly launched initiatives. Information that we learn from studying one autoimmune disease will provide valuable information for all autoimmune diseases. It is my opinion—and the goal of the NIAMS—that the significant, ongoing work on scleroderma as well as the broad interest in autoimmunity will be of great benefit for affected patients and their families and care givers.

Question. There is strong scientific support for the NIH's "roadmap" meetings with scientists from various disciplines to identify major cross-cutting biomedical challenges that the NIH could help address. How can representatives from the scleroderma community fit into one or several of these meetings to accelerate promising clinical opportunities and better enable new pathways to discovery for scleroderma and other illnesses?

Answer. There is great excitement at the NIH as well as in the voluntary and professional communities about the newly launched NIH Roadmap Initiative and what it will mean to medical research. The NIH is committed to the participation of all of the voluntary and professional groups in this process. Opportunities range from serving as a member on one of the Working Groups that are just being formed, to providing comments through other venues such as public representatives serving on Institute National Advisory Councils or meetings of the NIH Director's Council of Public Representatives. As well, as the Roadmap Initiative moves forward, there will be opportunities to review draft recommendations from the many components of the Initiative as information is posted on the NIH Website and comments sought. I can assure you that NIH is seeking very broad input on this new Initiative, and will welcome the participation and thoughts of members of the scleroderma community as well as all of the other constituent communities.

Question. Approximately what percentage of scleroderma-related grants or requests for funding did the NIH fund last year compared to the last five years?

Answer. NIAMS is the lead Institute at NIH for funding research on scleroderma, and the Institute has undertaken several initiatives over the past 5 years to increase funding in this area. The total NIAMS spending for scleroderma research has grown from \$4 million in fiscal year 1998 to over \$10 million in fiscal year 2002—an increase of 155 percent. NIH-wide, funding for scleroderma research has grown to a total of \$15.1 million in fiscal year 2002.

As mentioned previously, the NIAMS has recently increased efforts to expand the scleroderma portfolio including co-sponsoring a conference on "Emerging Opportunities in Scleroderma Research," which led to the funding of a very successful special solicitation; support for two Specialized Centers of Research on scleroderma to enhance translational research; and support for the development of a national scleroderma family registry and DNA repository, with the overall objective of identifying genes that influence susceptibility to the disease.

VASCULAR DISEASE

Question. There seems to be evidence that vascular diseases—including stroke, high blood pressure, and diabetes—are associated with an increased risk of Alz-

heimer's disease. Some promising initial studies suggest that cholesterol-lowering drugs and changes in diet could reduce that risk. Are you conducting any research along these lines?

Answer. A growing body of evidence suggests that some vascular conditions may be associated with an increased risk of cognitive impairment and/or Alzheimer's disease (AD), and such findings suggest that interventions to treat or prevent these conditions, particularly cholesterol-lowering drugs or dietary changes, could also be used to treat or prevent AD. For example, recent results from a biracial (African American and white) population-based community study in Chicago have suggested that dietary intake of vitamin E can decrease the risk of cognitive impairment and AD and that intake of dietary fats may increase or decrease risk of AD depending on the type of fat, while several epidemiological studies have suggested that individuals who take cholesterol-lowering drugs known as statins may have a reduced risk of cognitive impairment or AD.

The NIA is currently conducting several clinical studies of cholesterol-lowering drugs and dietary modifications for AD treatment or prevention. For example, recent results from the Framingham Heart Study indicate that high blood levels of the amino acid homocysteine, a known risk factor for cardiovascular and cerebrovascular disease, may also be a risk factor for AD. The Alzheimer's Disease Cooperative Study (ADCS) will soon begin a clinical trial to determine whether lowering homocysteine using a combination of vitamins B6 and B12 and folic acid can modify progression of AD over a one-year period. Several other studies using various antioxidants to prevent or treat AD are ongoing. The NIA has also initiated a clinical trial through the ADCS to determine whether the cholesterol-lowering drug simvastatin can slow the progression of AD in people who have mild to moderate disease. Studies using another statin drug, lovastatin, are ongoing or planned.

In addition, the NIA supports a number of basic studies elucidating the mechanisms of interventions that ameliorate both vascular and cognitive dysfunction. These include animal studies on the effects of cholesterol and cholesterol-lowering drugs on cognition. The Institute has provided support to several long-term cardiovascular health studies, including the Framingham Study, the Honolulu Heart Study, and the Cardiovascular Health Study, to explore links between vascular disease and cognitive impairment. We are also working with the National Heart, Lung, and Blood Institute to identify potential areas of collaboration in both epidemiologic studies and clinical trials.

DIABETES AND HYPERTENSION

Question. Within the next 30 years, minorities will make up one-fourth of the elderly population. (16 percent today) Some studies suggest that the two diseases that are most common in minority populations—namely diabetes and hypertension—are associated with an increased risk of Alzheimer's disease. Are you pursuing any research in this area?

Answer. The NIA supports a number of epidemiological studies that are looking for risk and protective factors for AD, including diabetes and cardiovascular disease, in minority populations. For example, the Sacramento Area Latino Study on Aging (SALSA), a study of nearly 1,800 community dwelling Latinos, primarily Mexican Americans aged 60 and above, has recently reported that risk of dementia was nearly 8 times higher in those individuals with both type 2 diabetes mellitus and stroke. In a community-based sample of African Americans in Indianapolis, the investigators found that use of antihypertensive medications was associated with preservation of cognitive function in older adults.

The need to understand the driving factors behind persistent black-white health disparities in cardiovascular disease, cerebrovascular disease, and overall longevity has led to the development of the HANDLS (Healthy Aging in Neighborhoods of Diversity across the Lifespan) study, a community-based research effort focusing on evaluating health disparities in socioeconomically diverse African-Americans and Whites in Baltimore. This multidisciplinary project will assess physical, genetic, demographic, psychosocial, and psychophysiological parameters over a 20-year period. It will also employ novel research tools to improve participation rates and retention. HANDLS researchers will investigate the longitudinal effects of socioeconomic status and race on the development of cerebrovascular disease and cardiovascular disease, as well as changes in psychophysiology, cognitive performance, strength and physical functioning, health services utilization, and nutrition, and their influences on one another and on the development of cardiovascular, cerebrovascular, and cognitive decline.

ALZHEIMER'S DISEASE

Question. In your testimony you talk about the remarkable strides that have been made in understanding Alzheimer's disease. How quickly can we expect some of that new information to be put into the hands of physicians who are treating Alzheimer's patients? Along the same lines, do you feel that there are sufficient clinical researchers trained to translate all of this new knowledge into treatments and better patient care?

Answer. NIA is currently conducting 18 clinical trials, seven of which are large-scale prevention trials. These trials are testing agents such as estrogen, anti-inflammatory drugs, and anti-oxidants for their effects on slowing progress of the disease, delaying AD's onset, or preventing the disease altogether. Other intervention trials are assessing the effects of various compounds on the behavioral symptoms (agitation, aggression, and sleep disorders) of people with AD. In addition, the NIA has a contract in place to facilitate testing of potential new therapeutic compounds in animals. This contract mechanism has now been in place for 8 years and has yielded several potentially promising compounds. So far, two of the drugs that have been tested, AIT-082 and phenserine, have entered human clinical trials.

Although I cannot predict when potential treatments will be available to physicians treating AD patients, I am hopeful that the ability to support clinical trials directed at the multiple molecular targets identified by recent research advances will lead to positive results in the not-too-distant future.

Expanding the numbers of AD-focused clinical researchers has long been a priority of the NIA. Opportunities for clinical research training exist throughout NIA's 29 AD Centers, as well as through the Alzheimer's Disease Cooperative Study. Many of our program project grants have also provided an avenue for training young physician-scientists. An important aspect of each of these mechanisms is the exposure of basic scientists to clinical research; a number of these "clinically-trained" basic scientists are now making important advances in the clinical arena. NIA has also initiated the Markey Training Program, which provides support for supervised research and study for clinically trained professionals who wish to redirect their careers toward research on Alzheimer's disease. In fiscal year 2002, six investigators received Markey Awards.

Efforts are ongoing to find better ways to encourage and facilitate entry of clinicians into research careers (e.g., public/private collaborations, Beeson scholarships for training in geriatric research). Dr. Judy Salerno, NIA Deputy Director, has been leading a major effort, in collaboration with members of the National Advisory Council on Aging, to identify issues that affect the numbers of clinicians entering or remaining in research careers. Related to this effort, a symposium was held in November 2002 in Bethesda entitled "Finding Synergy: Advancing the Development of Physician-Investigators in Aging and Geriatrics" at which experts in the field shared their views of what would be needed to increase the numbers of clinical researchers.

WOMEN'S HEART EDUCATION

Question. I am concerned that heart disease remains the leading cause of death of women in the United States, yet many women do not realize this fact. I hear that you have been working with the fashion industry in your Women's Heart Health Campaign to increase women's knowledge about their No. 1 killer. Please tell the Committee about this initiative.

Answer. The NHLBI launched a new campaign, *The Heart Truth*, last September to convey the message "Heart disease is not just a man's disease—it's the No. 1 killer of women." The Institute unveiled the Red Dress Project as part of the campaign during Mercedes-Benz Fashion Week, February 7–14, 2003, in New York. Fashion Week is a twice-yearly event in which top fashion designers in the United States unveil their new garment lines for the following season. It garners attention from media in the United States and around the world, including editors from most daily newspapers, women's magazine editors/writers, and broadcasters such as Entertainment Tonight and local network affiliates. The Red Dress Project provides a platform to promote the messages of the campaign via the slogan "heart disease doesn't care what you wear." Nineteen red dresses were contributed by leading fashion designers from either vintage or current collections and showcased throughout Fashion Week. A Red Dress Pin, specially designed for *The Heart Truth* campaign by a leading accessory designer, was introduced as the national symbol for women and heart disease.

First Lady Laura Bush wore the Red Dress Pin during her visit to the Red Dress Project display in New York on Valentine's Day. She appeared on *Good Morning America*, *Today*, and *The Early Show* to promote awareness of women and heart dis-

ease. On February 21, in the Great Hall of the Hubert H. Humphrey Building, U.S. Department of Health and Human Services Secretary Tommy G. Thompson presented The Red Dress Project and designated the third Friday of February as Women's Heart Day. The Red Dress Project is the cover story of the May 2003 issue of *Prevention* magazine and has been featured in *People* magazine and *Newsweek*. A national tour of the Red Dress Project is also being developed, as well as plans to disseminate *The Heart Truth* messages and Red Dress Pin through channels that will reach a diverse population of women.

PARITY

Question. Dr. Insel, as you know there has been a lot of discussion during the last several years concerning the issue of mental health parity—that is, the requirement that health insurance coverage for mental disorders be provided on the same basis as that provided for coverage of so-called physical disorders. What is your view of that?

Answer. As you know, the President has come out in support of parity coverage for mental disorders. Mental disorders are real and devastating illnesses. They account for a large proportion of the disability caused by all medical illnesses. Research supported by NIMH shows that the increase in cost to provide parity coverage for mental disorders can be limited, but not treating them would be very costly.

MEN AND DEPRESSION PROGRAM

Question. I note that NIMH has recently launched—with the help of the Surgeon General of the United States—a major public campaign focused on men and depression. Can you tell me why you've done that?

Answer. Depression is a treatable medical disorder that causes terrible suffering for its victims and is the cause of many of the Nation's 30,000 suicides each year. A major obstacle to getting people into treatment, however, is the stigma that accompanies admitting that you're depressed and that you need help—and this is especially true of men, including men who have suffered trauma. To help men recognize the signs of depression and to guide them toward more information and sources of assistance, the NIMH recently launched the "Real Men/Real Depression" public education campaign.

Question. Isn't it true that far more women than men develop depression?

Answer. Yes, more women than men are diagnosed with depression, but men do have depression and are less likely to seek treatment. One indication of the importance of this campaign is that four times as many men as women die by suicide. Figures from the Centers for Disease Control and Prevention and the 2000 census show that more than 70 percent of all suicide victims are white males.

Question. What do you hope to accomplish with this?

Answer. The NIMH estimates that more than 6 million American men suffer from depression every year. We are trying to overcome the barriers that prevent these men from seeking help, and we are hoping to reduce the number of suicides in this country as a result of this effort. We already appear to be having success, based on the many thousands of e-mails and letters asking for help or more information that we have received to date—not only from depressed men, but from their friends, their family members, their co-workers, and others who care about them.

BUDGET REQUEST

Question. For fiscal year 2004, the President is proposing \$1.382 billion for scientific and clinical research at NIMH. This is \$41 million over the fiscal year 2003 appropriation of \$1.341 billion—a 3 percent increase. This is barely enough to cover inflation and below expected increases in the cost of conducting clinical research. The Subcommittee is concerned that this funding request could prevent NIMH from sustaining the ongoing multi-year research grants that have been initiated over the past 2–3 years. What would be the impact of holding increases at NIMH to 3 percent this year? Would NIMH be able to continue ongoing, multi-year research programs such as the plan on mood disorders and bipolar disorder? Can you provide us with an estimate of the number of qualified grant proposals that you would expect to be unable to fund if NIMH's budget is held to a 3 percent increase in fiscal year 2004?

Answer. Under the proposed 3 percent increase for NIMH's fiscal year 2004 budget, the Institute will honor its commitments to ongoing grants that have been funded over the past several years. The proposed budget provides funds to proceed on schedule in addressing the scientific priorities identified in The Strategic Plan for Mood Disorders Research. In fiscal year 2004, the NIMH estimates receiving a total

of 2,535 applications for research project grants (RPGs). At the fiscal year 2004 President's Budget level, NIMH would fund an estimated 636 of these applications while the remaining 1,899 RPGs would be unfunded. This is a success rate of 25 percent and is consistent with NIMH success rates over the last few years

RESEARCH

Question. While steady funding increases have been achieved in the area of severe mental illness research, research on these illnesses remains underfunded, given the severe burden that these diseases present to the nation's public health. A 1996 independent study by the World Bank and World Health Organization (DALY: Disability Adjusted Life Years) found that four of the top ten causes of disability worldwide are severe mental illnesses: major depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder. But using the most recent estimates from NIH, research on mental illness lags far behind other diseases relative to public health costs, lost productivity, disability, etc.

What efforts are underway at NIMH to focus greater attention and resources on promising research at the basic, clinical, and services levels on severe mental illness such as schizophrenia, bipolar disorder and major depression?

Answer. NIMH maintains energetic communications, public liaison/outreach, and public education programs, all of which are designed to draw attention to the opportunities and payoff of research on mental and behavioral disorders. The Institute's award-winning home page presents a wealth of information, (www.nimh.nih.gov) about mental disorders and recent progress in NIMH sponsored research. The page receives approximately 10 million hits per month from the public as well as members of the scientific and clinical communities. In April, NIMH launched a new mass media campaign, Real Men. Real Depression., which is focused on the leading cause of disability adjusted life years in the United States. The campaign features real men—that is, not actors—describing in everyday language what it felt like for them to be depressed. They talk about their confusion and concern for their ability to care for their families, about their jobs, about plans and hopes that are so easily shattered by depression. They talk about the difficulty of acknowledging that they were depressed and the struggle to force themselves to get help—help that is available largely because of NIMH-sponsored research.

TREATMENTS

Question. In the last decade, many new treatments and services have been developed and proven for severe mental illnesses such as schizophrenia. Yet most individuals with these illnesses receive extremely poor treatment. What efforts are underway (or ongoing) to ensure that the improved treatment interventions being developed now will be effectively disseminated to providers and made available to the people who so desperately need these treatments?

Answer. NIMH supports research on testing the best methods for dissemination of knowledge, whether in the form of evidence-based reports, algorithms, or guidelines. In addition to building a stronger base for understanding what are the best methods for sharing information, we also are engaged in research that seeks to determine how information is translated into sustained practice, or more simply put, how to get individuals, practitioners, and health care systems to adopt effective research-based practices. Examples of some of the grants we currently fund include studies that examine the use of depression guidelines in primary care settings, and the use of practice guidelines by physicians to improve care for hospitalized youth with aggression and impulsivity. Another project examines the use of the internet in educating families on care issues related to schizophrenia, while another applies technology for physicians' use with decision making in prescribing medications in community mental health clinics. Examples of program activities that occurred during 2002 include:

- Two workshops on diffusion of evidence based practices in state mental health systems
- Workshop on special issues in disseminating research findings for child and adolescent mental health
- Initiation of new grants mechanisms that increase the capability of providing centers to evaluate the delivery of their interventions and improve their practices; and expedited submission, review and funding of applications where evaluation of changes being made in a delivery system requires time sensitive research.

Question. How is NIMH collaborating with SAMHSA and the Center for Mental Health Services (CMHS) on these efforts?

Answer. The Science to Service Initiative that involves SAMHSA Centers and NIH institutes (NIMH, NIDA, and NIAAA) has as one of its goals the exchange of evidence-based practices that can be implemented by SAMHSA in natural settings, and then further researched by NIH as treatment and services questions arise from the practice field. NIMH is the principal source of support for mental health services research in the DHHS. In the past 22 months, we have been able to increase the number of services research applications by 45 percent. We are providing technical assistance to former SAMHSA grantees through workshops and individual consultations and working closely with CMHS staff members. Through co-sponsored activities we are working together to build the capacity of state mental health agencies and other “natural treatment settings” to conduct research on the treatment they are providing, to evaluate its effectiveness and to examine factors that will increase readiness for adoption of research-based care.

SERVICES RESEARCH

Question. Administration is returning agencies to their core mission, meaning that NIMH, rather than the Substance Abuse and Mental Health Services Administration, will be conducting services research on mental health issues.

To what degree is NIMH prepared to assume greater responsibility with respect to services research?

Answer. NIMH is the principal source of support for mental health services research in the DHHS. In the past 22 months, we have been able to increase the number of services research applications by 45 percent. We are providing technical assistance to former SAMHSA grantees through workshops and individual consultations and working closely with CMHS staff members. The Science to Service Initiative that involves SAMHSA Centers and NIH institutes (NIMH, NIDA, and NIAAA) has as one of its goals the exchange of evidence-based practices that can be implemented by SAMHSA in natural settings, and then further researched by NIH as treatment and services questions arise from the practice field.

Question. People with mental illnesses often have conditions besides a mental health diagnosis. To reflect the real world in which mental health services are delivered, how will NIMH services research address people with multiple diagnosis?

Answer. To insure rigor and maximize the possibility of detecting a treatment effect, randomized, controlled clinical trials—the traditional “gold standard” for medical research—have excluded anyone with a comorbid mental disorder, substance use disorder, general medical illness or other conditions ranging from pregnancy to active suicidality. Thus, the typical clinical trial for an antidepressant would be conducted with a relatively small, highly homogenous number of outpatients or, less frequently, inpatients, usually in an academic health center. The major outcome criterion would be a decrement on a behavioral rating scale such as the Hamilton Depression Scale.

In real life, of course, the patient who typically appears in a psychiatrist’s office is quite unlike the patient enrolled in the traditional clinical trial. Accordingly, while the NIMH will continue to fund the traditional form of clinical trial, the Institute’s researchers also are adapting to the changing nature of treatments, patients, and the health care environment. In order to help clinicians provide optimal care to patients, research today also involves trials with larger sample sizes and with fewer exclusion criteria; trials are being conducted not only in academic clinics but also in more real world settings including managed care settings; and outcomes are assessed not only on the basis of symptom reduction but also on measures of functional rehabilitation, the end result that is of greatest interest to families and patients as well as employers and others who pay for treatment. This new type of trial—often called an “effectiveness” trial—need not give up any of the traditional and indispensable emphasis on rigor. In trials of both pharmacotherapies and psychotherapies, the information sought should be geared toward helping clinical decision-making in real world settings and should demonstrate compelling types of functional outcomes. From a methodological perspective, new analytic techniques are being developed that allow clinical investigators and services researchers to move away from linear patterns and account for the complex interactions that occur in the real world.

Question. Research at NIH focuses on randomized, clinical trials, despite the fact that many other proven research methods are more conducive to services research (such as multi-site research or analysis of nationally representative data sets such as the Census Bureau’s Current Population Survey or the National Health Interview Survey). To what degree will NIMH utilize these other methods?

Answer. NIMH supports a wide array of research designs and methods, not just randomized clinical trials. Researchers have the freedom to use the best techniques

available to address the questions they are asking. This might involve using statistics to analyze large national data sets as in studies of risk factors for depression in children, or the use of interviews and qualitative techniques for research questions that require more context to understand. Other studies require control of variables to get at causation; thus randomized clinical trials are appropriate. Epidemiologic studies are also conducted in which surveys are the basic tools used. In summary, no one approach is used-the research question asked dictates the method to be used.

SCHIZOPHRENIA

Question. Schizophrenia is the most devastating mental illness, affecting approximately 2.2 million American adults, or 1.1 percent of the population age 18 and older. Scientists still do not know the specific causes of schizophrenia; like many other medical illnesses such as cancer or diabetes, schizophrenia seems to be caused by a combination of problems including genetic vulnerability and environmental factors that occur during a person's development. While newer treatments for schizophrenia such as atypical anti-psychotic medications are proving effective, these treatments are largely palliative and help patients live with, rather than recover, from the illness.

Given the enormous public health burden associated with schizophrenia and the demand for new treatments, what is NIMH doing to assure that the research base studying schizophrenia is strengthened and expanded?

Answer. Recognizing that schizophrenia is among the most serious public health problems facing Americans, the NIMH has increased the proportion of its budget devoted to this and other related neurodevelopmental disorders from 16 percent to 23 percent in the last five years. Reflecting the higher priority afforded this severe illness within NIMH, new initiatives have been launched that balance the need to focus on discovering the fundamental cause of the disease so a cure might be possible, with the need to improve treatments for patients who are suffering today.

Efforts to understand the etiology of schizophrenia and other devastating mental illnesses are grounded in the neurosciences. For example, the NIMH Human Genetics Initiative is in the process of collecting biological materials on over 17,000 individuals to create a national scientific resource of DNA for broad use by investigators in the scientific community. Such samples help to identify risk genes associated with schizophrenia and shed light on the mechanisms malfunctioning in the brain. The Research Centers of Excellence (Silvio Conte Centers for the Neuroscience of Mental Disorders) have been established to develop and follow new leads generated by genetic and other basic studies in order to clarify abnormalities in brain functioning associated with major psychiatric illnesses. Over half of these Centers focus on schizophrenia, including two new centers (Mt Sinai, in New York City, and the University of North Carolina, Chapel Hill) that have been funded in the last fiscal year.

BIPOLOAR DISORDER

Question. Bipolar disorder, or manic depression, is a serious brain disorder that causes extreme shifts in mood, energy and functioning. It affects 2.3 million adult Americans, or 1.2 percent of the population. Currently, there is no cure for bipolar disorder. While it can be a highly treatable and manageable illness, most of the approved treatments are indications associated with medications that were developed for other illnesses (anti-convulsants for epilepsy and anti-depressants). In 1997, Congress requested NIMH to undertake a national research plan on bipolar disorder. This request resulted in the current research plan on mood disorders at NIMH. Can you please update the Subcommittee on the mood disorders research plan and what NIMH is learning about the causes and new treatments for bipolar disorder?

Answer. NIMH completed the Strategic Plan for Mood Disorders last year and is now in the process of implementing the highest priority recommendations for new research on the nature, course, treatment, and prevention of these disorders. In addition, we are systematically monitoring and evaluating the ongoing research activities in each of the Divisions from neuroscience to services, to ensure movement toward our goals.

In 1998 NIMH initiated funding of the STEP-BD program (Systematic Treatment Enhancement Program for Bipolar Disorder), a multisite study of bipolar disorder that is now following nearly 3,000 individuals receiving care for bipolar disorder in 18 centers across the United States. The budget for STEP-BD is approximately \$25,000,000. This study is providing unique information on the course of bipolar disorder and on targets for treatment. We have learned, for example, that even under

optimized treatment conditions about 5 percent of people with bipolar disorder will experience a relapse during the course of a year. Significantly, and counter to expectations, 80 percent of these relapses are depression, not mania, thus highlighting the need for safe and effective treatments for bipolar depression. Studies have been initiated to explore the value of rational strategies of combination treatment targeting bipolar depression. One of the benefits of large studies, such as STEP-BD is they provide training grounds and engender interest for new studies in bipolar illness. In fiscal year 2003 NIMH will be funding the first center specifically targeting interventions in bipolar illness in adolescents and adults—this new center is established at one of the primary sites of the STEP-BD study.

With an increased awareness that bipolar disorder also affects children and adolescents, NIMH has recently funded two multisite trials to study the benefits of medications for youths with this disorder.

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

PARKINSON'S

Question. Dr. Zerhouni, I appreciate that you have focused some of your attention on Parkinson's disease during your first year as director and that you and your staff have developed a "matrix" that outlines future NIH-funded research on Parkinson's. This matrix follows the release in 2000 of the NIH Parkinson's Disease Research Agenda. As you know, I have been concerned that funding for PD research during the past few years has increased at a rate below the overall percentage increase for NIH, despite the professional judgment estimates included in the Research Agenda. Please explain what the NIH is doing to fully implement the Research Agenda as well as the matrix.

In addition, the President's proposed budget for fiscal year 2004 includes \$35 million for "Roadmap Funding." The Budget describes its purpose "as an additional effort to accelerate fundamental discovery and translation of that new knowledge into preventive and therapeutic strategies." Will you be focusing on any particular diseases when you implement the Roadmap, and will Parkinson's disease be one of the diseases you will choose?

Answer. With regard to funding, NIH funding for Parkinson's disease research has been growing much more rapidly than the growth of the overall NIH budget, which of course has been very significant. During the first four years of the doubling effort—fiscal years 1999 through 2002—actual NIH funding for Parkinson's disease research rose approximately 92 percent, while the overall NIH budget rose by a very generous 72 percent. To fully appreciate this increase, it is critical to recognize that in fiscal year 1998—the "base" year of the doubling—NIH had just increased its funding of Parkinson's disease research by 23 percent over fiscal year 1997, while the overall NIH budget increased only 7.2 percent in that time frame.

More importantly, the NIH Parkinson's Disease Research Agenda and its updates encompass every research area critical to Parkinson's disease—genetics, environmental factors, cell death and survival, pharmacological treatments, deep brain stimulation, gene therapy, stem cell research, and the non-motor effects of Parkinson's—and the NIH is addressing every scientific aspect of that Agenda. This includes hundreds of research grants and contracts, at all levels of research, from basic through translational to clinical, including major clinical trials. We are following all plausible strategies to develop therapies, including drugs, surgery and cell transplantation. We have also held several scientific meetings since the original Agenda was developed to adjust to the changing scientific landscape, and to make sure that all scientific opportunities are pursued. This includes a "summit" of Parkinson's disease researchers that I convened in July 2002 to identify roadblocks that might be impeding progress. The Summit was very successful in identifying roadblocks, and NIH staff has drafted a matrix of short-to-long term, and low-to-high risk action items designed to target these issues. NIH is actively addressing these action items, both through enhanced support of individual Institute and Center efforts, and through improved coordination and collaboration with the research and voluntary Parkinson's communities.

The Roadmap initiatives, being developed with input from a broad range of NIH staff and extramural scientific experts, are not disease or discipline specific, but rather take a cross-cutting approach to identify scientific challenges and roadblocks to progress. Driven by the enormous convergence in fundamental research approaches and technologies across diseases, organs and biological systems, the Roadmap will focus on facilitating and accelerating multi-disciplinary aspects of basic, translational, and clinical research. Roadmap initiatives will exploit new unprece-

mented opportunities and technologies that will accelerate progress in disease areas across the 27 Institutes and Centers of the NIH. The exact nature of the progress will differ with each disease depending on our current knowledge of the disorder. Some diseases, which are in need of further basic research, will be aided by initiatives supporting portions of the Roadmap such as New Pathways to Discovery. Other diseases will benefit from Roadmap efforts aimed at optimal translation of discoveries into clinical reality, such as Clinical Trial Networks.

NATIONAL LIBRARY OF MEDICINE

Question. The NLM and its Center for Biotechnology Information have made a major contribution to the fight against disease. To maximize this contribution, this committee has supported the design of a new facility. How is that going, and are you ready to initiate construction if funds are made available?

Answer. The design of the National Center for Biotechnology Information is expected to be complete by August-September 2003 at which time the NIH, in consultation with the HHS Office of Facility Management and Policy, will develop a plan for scheduling and financing this project while considering other demands and priorities.

QUESTIONS SUBMITTED BY SENATOR PETE V. DOMENICI

MENTAL ILLNESS RESEARCH

Question. Dr. Zerhouni, can you please update the Subcommittee on efforts underway at NIH and NIMH to focus greater attention and resources on promising research at the basic, clinical, and services levels on severe mental illness such as schizophrenia, bipolar disorder and major depression to ensure that advances rapidly translate into better treatment for individuals living with these illnesses?

Answer. At NIMH extensive efforts are underway to translate basic science findings (from genetics, structural and functional brain imaging, analysis of human post-mortem brain specimens, etc.) to an enhanced understanding of the causes (etiology and pathophysiology) of the major mental disorders. In the past few years significant progress has been made in identifying risk genes, refining disease phenotypes (characterizing more homogeneous subpopulations of patients), and implicating particular brain molecules, cells, circuits and structures as key players in these processes. The goal of these investigations is to develop more specific treatments and, ultimately, curative and preventive interventions. NIMH established a Clinical Neuroscience Research Branch in 1999 specifically to address these issues of translational science and, in the past several years, has significantly expanded its "flagship" translational program—The Silvio Conte Centers for the Neuroscience of Mental Disorders (currently 13 Centers are funded at an annual cost of \$24 million).

Carefully controlled, randomized, double-blind trials remain a cornerstone of clinical research sponsored by the NIMH. As practitioners are well aware, however, such studies cannot be the end of treatment research but a beginning. Clinical treatment research must adapt to the changing nature of treatments, patients, and the health care environment. Accordingly, NIMH has launched a series of clinical effectiveness trials that are characterized by large sample sizes and few exclusion criteria; to ensure the generalizability of findings, these trials occur not only in academic clinics but also in more real world settings including primary care settings. The approach also calls for aggressive dissemination of results. Four large-scale, multi-site clinical effectiveness trials include: (1) Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) to investigate strategies for managing bipolar disorder, (2) Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) to study the effectiveness of the new atypical antipsychotics in schizophrenia and Alzheimer's disease, (3) Sequenced Treatment Alternatives to Relieve Depression (STAR*D) to develop algorithms for managing especially difficult to treat depression, and (4) Treatment of Adolescents with Depression Study (TADS). In mid-fiscal year 2003, all of these trials are well on their way to attaining the targeted number of research participants. Through the network of research centers participating in these effectiveness trials, NIMH is creating an infrastructure for future clinical research involving direct comparisons of treatments and their benefits to different populations that can be conducted independently of pharmaceutical companies.

Recognizing that much of the screening for mental illness and treatment is provided in other than specialty settings, NIMH continues to gain a better understanding of cost and financing associated with care in three different settings: juve-

nile justice system, school systems, and primary care. Use of non-traditional settings offer an opportunity to learn new ways of treating and managing co-existing addiction and mental illness problems through the use of non-specialty care providers working with the less numerous specialty providers. Research is also exploring preferences of individuals with mental disorders or combined disorders to seek treatment in general health care, or social services settings and determining if access to treatment in a preferred setting improves seeking treatment, staying in treatment, and adherence to treatment plans.

SCHIZOPHRENIA RESEARCH

Question. Schizophrenia is the most devastating mental illness, affecting approximately 2.2 million American adults, or 1.1 percent of the population age 18 and older. Schizophrenia interferes with a person's ability to think clearly, make decisions, and relate to others. Scientists still do not know the specific causes of schizophrenia, but research has shown that the brains of people with schizophrenia are different, as a group, from the brains of people without the illness. While newer treatments for schizophrenia (including atypical anti-psychotic medications) are proving much more effective in treating both the positive and negative symptoms of schizophrenia, these treatments are largely palliative and help patients better live with, rather than recover from the illness.

Given the enormous public health burden associated with schizophrenia and the need for new treatments, what is NIMH doing to ensure that schizophrenia research becomes a higher priority within the agency?

Answer. Recognizing that schizophrenia is among the most serious public health problems facing Americans, the NIMH has increased the proportion of its budget devoted to this and other related neurodevelopmental disorders from 16 percent to 23 percent in the last five years. Reflecting the higher priority afforded this severe illness within NIMH, new initiatives have been launched that balance the need to focus on discovering the fundamental cause of the disease so a cure might be possible, with the need to improve treatments for patients who are suffering today.

Efforts to understand the etiology of schizophrenia and other devastating mental illnesses are grounded in the neurosciences. For example, the NIMH Human Genetics Initiative is in the process of collecting biological materials on over 17,000 individuals to create a national scientific resource of DNA for broad use by investigators in the scientific community. Such samples help to identify risk genes associated with schizophrenia and shed light on the mechanisms malfunctioning in the brain. The Research Centers of Excellence (Silvio Conte Centers for the Neuroscience of Mental Disorders) have been established to develop and follow new leads generated by genetic and other basic studies in order to clarify abnormalities in brain functioning associated with major psychiatric illnesses. Over half of these Centers focus on schizophrenia, including two new centers (Mt Sinai and University of North Carolina, Chapel Hill) that have been funded in the last fiscal year.

Although the delusions and hallucinations of schizophrenia are often treated effectively by available medications, research indicates that impairments in cognition (memory, planning, abstract thinking) are most associated with disability in this illness. Unfortunately, available medicines do little to reverse this aspect of schizophrenia. To address this problem, NIMH has launched a Schizophrenia Treatment Development Initiative focused on both developing new drug treatments to remedy cognitive impairments. With the cooperation of the FDA, this initiative will develop standard measures and methods to test new drugs that target cognition in schizophrenia in order to provide the pharmaceutical industry with guidelines for drug registration and hence, enhanced incentives to invest in developing treatments for this aspect of schizophrenia. To jumpstart this effort, in fiscal year 2004 NIMH will establish a new clinical trials network focused on collaborating with industry to identify and test new agents for cognition in schizophrenia.

In addition to the large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, which is designed to determine the long-term effects and usefulness of antipsychotic medications in a broad cross-section of persons with schizophrenia, NIMH is conducting a range of studies concerned with how to best use available treatments for schizophrenia. These include clinical trials of combination medication strategies. Recognizing that medication adherence is a crucial issue for many patients, active efforts to stimulate research on this problem have yielded a series of new studies designed to develop and test adherence-oriented intervention. Finally, rehabilitation-oriented studies are encouraged and supported to develop new approaches to enhancing patient skills and functioning.

Question. Dr. Insel, as you know, NIMH has been criticized in the past for failing to maintain an appropriate focus on severe mental illness in its portfolio. Over the years, concern has been expressed that basic scientific and clinical research on schizophrenia, bipolar disorder and other severe mental illnesses remain low priorities at NIMH. In order to challenge and rebut these criticisms, would you support a requirement for NIMH to provide an accounting of new and existing research grants broken down by specific illnesses?

Answer. First, let me make clear that direct support for research of so-called “serious mental disorders,” such as schizophrenia, is a priority at NIMH. It is the lead Federal agency responsible for supporting research on mental and behavioral disorders. The goal of NIMH’s portfolio of research on mental illness is to better understand, treat, prevent, and ultimately cure mental illness. This requires both direct and indirect approaches, which may not be apparent in accounting for spending by disease.

Basic research, the relevance of which might not be immediately apparent, can produce knowledge critical for understanding mental illness. For example, studies of the brains of songbirds, brought the unexpected and startling news that adult brains can regenerate new nerve cells, a finding that completely changed scientists’ thinking about the possibility for brain repair. Similarly, in October 2000, Dr. Eric Kandel, an NIMH grantee, won the Nobel Prize for Medicine based on his work with sea slugs, in recognition that this research had profoundly increased understanding of brain function and medication effects in humans. Both scientists have accelerated our understanding of brain processes important for mental illness.

Over the years, Congress has expressed interest that NIMH take responsibility for many areas beyond mental illness including HIV/AIDS risk behaviors, violence, gambling, and many others. Nevertheless, NIMH has a strong and abiding commitment to a core focus on severe mental illnesses. Indeed, NIMH has launched four large-scale, public health oriented clinical trials in major disease conditions, including bipolar (manic depressive) illness; schizophrenia/Alzheimer disease; treatment-resistant depression; and major depression in adolescents. These trials investigate “real world” effectiveness of mental health treatments, and because they are carried out in community settings they do not exclude people because they have a co-occurring substance abuse disorder or other problems. Unlike typical short-term pharmaceutical trials, people with these disorders live in the community, and NIMH is committed to assuring that treatment interventions will work where the patient lives.

NIMH is supporting many new activities with a focus on severe mental illnesses, and has increased the percentage of its overall research portfolio in this area. One major new initiative, for example, will look at the cognitive deficits associated with schizophrenia. The deficits that make it very difficult for people affected by the disease to be employed or otherwise function fully in society. This is an effort to develop new insights into the neurobiology of attention, working memory, and other fundamental cognitive processes in order to identify and test potential therapeutic agents targeting cognitive deficits in schizophrenia. As a part of this effort focused on schizophrenia, NIMH is establishing an expert Schizophrenia Cognition Measurement Development Group. Without measurement consensus, the Food and Drug Administration cannot recognize cognition as a valid treatment endpoint for industry-sponsored research and drug registration. Since cognitive impairment, rather than delusions and hallucinations, may be the major determinant of functional outcome in people with schizophrenia, this is an extremely important effort. NIMH also will support a Cognition Treatment Network to identify, evaluate, and acquire pharmacological agents to treat cognitive deficits in schizophrenia and related psychoses.

In summary, the goal of NIMH’s portfolio of research on mental illness is to better understand, treat, prevent, and ultimately cure mental illness. While the NIMH has significantly increased the percentage of its portfolio devoted specifically to studies related to severe and persistent mental illnesses, it continues to honor its mission and responsibility to support basic biomedical and behavioral research that will elucidate the underlying causes of these disorders. A strict focus on specific diseases would make this very difficult, if not impossible, and would certainly hamper scientific progress.

QUESTIONS SUBMITTED TO THE SOCIAL SECURITY ADMINISTRATION

QUESTIONS SUBMITTED BY SENATOR ARLEN SPECTER

Question. Commissioner, since 1997 the General Accounting Office (GAO) has included the Supplemental Security Income program in its list of programs that are at high risk for waste, fraud and mismanagement. Thanks to the Agency's dedicated effort, GAO's 2003 High Risk Update did not include the Supplemental Security Income program. However, as indicated by your Corrective Action Plan, additional steps can be taken to continue to strengthen program oversight and reduce the incidence of erroneous payments.

What specific actions are supported in the fiscal year 2004 budget request to prevent the occurrence of erroneous payments in the SSI program and strengthen program oversight?

Answer. The President's fiscal year 2004 budget includes appropriation language requiring the Social Security Administration (SSA) to spend no less than \$1.446 billion of the Limitation on Administrative Expenses (LAE) for program integrity activities, including continuing disability reviews (CDR), non-disability redeterminations of eligibility in the Supplemental Security Income (SSI) program, and overpayment workloads. This language will ensure adequate resources for these three important and cost-effective workloads that reduce erroneous payments, within the overall SSA request of \$8.53 billion. The fiscal year 2004 program integrity investment will return lifetime program savings of more than \$10 billion. The three key activities are:

- Continuing Disability Reviews.*—SSA conducts periodic reviews to ensure that only those beneficiaries who are truly disabled continue to receive benefits.
- SSI Redeterminations.*—Experience has shown that the most powerful tool SSA has to detect and prevent improper payments in the SSI program is to perform periodic reviews of the non-disability factors of eligibility for SSI.
- Overpayment Collections.*—Prompt processing of the Agency's debt collection workload is an important element of sound financial management and program stewardship. Having sufficient administrative resources will allow SSA to process substantial overpayment workloads and move forward as quickly as possible to implement new tools of prevention, detection and collection.

SSA's substantial program integrity initiatives result in significant benefits to the Government in terms of detecting and collecting overpayments. Without these program integrity efforts, the Agency would pay out billions of trust fund and general fund dollars in erroneous payments. Experience has shown a \$9-to-\$1 return on for investments in CDRs and a \$7-to-\$1 return for investments in SSI redeterminations. Because these activities pay for themselves, many times over, resources to support them shouldn't compete with resources needed for service delivery; and the President's budget proposes funding them through adjustments to discretionary spending caps.

The fiscal year 2004 budget also supports a number of initiatives to prevent and collect erroneous payments in the SSI program and strengthen program oversight, including piloting an automated monthly wage reporting system using voice recognition and touch-tone phone technology, testing electronic access to records of financial institutions, and implementing cross program recovery, credit bureau referrals, and Treasury Department administrative offset.

SSA's fiscal year 2004 budget also contains a legislative proposal to apply the same requirements now in effect for reviewing title II initial disability allowances to title XVI adult disability allowances. Preeffectuation reviews have a high rate of return on investment, would strengthen the integrity of the SSI program and help assure the American people that their tax dollars are going only to individuals who are truly disabled under the law.

Question. How will this budget request fully utilize all of the tools provided by Congress for preventing and collecting erroneous payments, in particular those authorized by the Foster Care Independence Act of 1999? Also, if erroneous payment prevention and collection authorities currently available are not being fully utilized, is it because of a lack of resources available to the SSA? If not, what is preventing SSA from fully utilizing these authorities and what steps are being taken to overcome those barriers to full implementation?

Answer. SSA has a vigorous program for developing all debt prevention and collection tools authorized by Congress. The Agency's program encompasses the authorities granted by the Foster Care Independence Act (FCIA) of 1999, authorities given by other laws, and self-initiated projects. SSA's strategy for implementing all of the tools is to use its available resources first to develop those that yield the most

savings or that can be easily integrated into the existing debt management framework.

The authorities granted by FCIA are: access to financial institutions, credit bureau reporting, administrative offset, establishing overpayments on the records of representative payees of deceased beneficiaries, Federal salary offset, private collection agencies, and interest charging. Authorities granted by other laws include mandatory cross program recovery and administrative wage garnishment.

DEBT PREVENTION

The top two reasons for SSI overpayment errors are unreported wages and unreported bank accounts with substantial assets. In the past, SSA has focused on the detection of errors in payments already made. Initiatives either planned or underway offer substantial promise as a means to preventing error.

—*Automated Monthly Wage Reporting Using Voice Recognition and Touch-Tone Phone Technology.*—The Monthly Wage Reporting Pilot using voice recognition and touch-tone phone technology is one of the steps SSA is exploring to facilitate wage reporting and reduce the incidence of erroneous overpayments in the SSI program. Each year we detect approximately \$500 million in overpayments due to wages. Over half this amount is due to the failure to report changes to SSA. SSI recipients are required to report whenever there is a change in their income or the income of a devisor (a spouse or parents of a child under the age of 18 living in the same household but not receiving SSI). Some individuals report changes as required, but many do not. Currently, few SSI recipients have access to the Internet. Therefore, we are testing a new automated telephone reporting system that could quickly process large numbers of wage reports. We will ask approximately 4,000 people to use this new system to report wages once a month for a 6-month period, May through October 2003. We will then verify the wage amounts to determine if they reported accurately. If this test is a success, automated monthly wage reporting will be rolled out nationwide.

—*Access to Financial Institutions.*—SSA will test a process using authority granted by FCIA to access the records of financial institutions. Use of this tool during the initial claims process will provide access to information on unreported income or assets. Similarly, use of the tool during the SSI redetermination process and periodically throughout the life of a SSI recipient's entitlement will provide information regarding a recipient's assets in relationship to limits affecting eligibility. SSA is currently working to finalize the rules for publication, which will enable SSA to proceed with a proof of concept to test the capability of electronic access of financial records later this year. If the proof of concept is successful, SSA will develop plans for a phased rollout of the new business process.

DEBT COLLECTION

SSA is constantly striving to improve its debt management program. Since 1992, when the Agency implemented Tax Refund Offset (TRO) to collect delinquent title II overpayments, SSA has put in place eleven different improvements. These improvements include two major expansions to the TRO program, credit bureau reporting and administrative offset for delinquent title II overpayments and a streamlined remittance process that uses state-of-the-art equipment. In addition, SSA worked with Treasury's Financial Management Service to implement Benefit Payment Offset and the Federal Payment Levy Program, whereby Social Security benefits are offset or levied as collection toward delinquent tax and non-tax debts owed by beneficiaries to other Federal agencies.

—*Recent Initiatives.*—In keeping with its developmental strategy, SSA implemented mandatory cross program recovery in 2002 because of its promise of large debt collections. In fact cross program recovery has enabled SSA to collect over \$50 million in SSI debt in less than one year. SSA also implemented credit bureau reporting and administrative offset in 2002 because those tools could be integrated easily into the existing debt management system.

—*Current Initiative.*—SSA also is developing administrative wage garnishment (AWG), which was authorized by the Debt Collection Improvement Act. We believe AWG has the potential to yield the largest amount of collections of all the remaining tools. We estimate this tool will yield \$105 million in the first five years of its use (\$80 million in title II collections and \$25 million in title XVI collections).

—*Future Initiatives.*—When SSA completes its work on AWG, it will move on to a pair of debt collection tools authorized by FCIA: establishing overpayments on the records of representative payees of deceased beneficiaries and Federal salary offset. Although these two tools will yield direct collections from payment

sources such as tax refunds, other Federal payments and Federal salaries, they will not approach the collection potential of AWG, and that is why they will be developed after garnishment.

Implementation of interest charging and use of private collection agencies will follow the completion of Federal salary offset and the establishment of overpayments on the records of representative payees.

FULL UTILIZATION OF FCIA TOOLS

Debt management represents one of the many different areas requiring resources. In fact, SSA has a multitude of initiatives spanning all aspects of its business process. The Agency must prioritize projects and choose the order in which they are developed.

SSA has a process for determining the priority of initiatives. This process is manifested in SSA's Information Technology plan, where projects are assessed based on their return on investment and other critical factors. Based on this rigorous examination of projects, SSA is focusing first on monthly wage reporting, access to financial information and administrative wage garnishment.

Question. The "Justification of Estimates for Appropriations Committees" for the fiscal year 2004 budget request for Social Security Administration (SSA) states that: "The Ticket to Work Program is up and running in 33 States and the District of Columbia and will be expanded to all States and U.S. territories in 2003."

Specifically, how much funding is available within the fiscal year 2004 request for the Limitation for Administrative Expenses account to support implementation of the Ticket to Work program and what activities are supported?

Answer. SSA's fiscal year 2004 LAE account includes \$39 million to fund the following activities in support of the Ticket to Work program:

- Benefits Planning and Assistance Cooperative Agreements (\$23 million).*—Benefits planning, assistance and outreach (BPAO) cooperative agreements are intended to ensure that these community based services are available in every state, the District of Columbia and every U.S. territory. The law authorizes \$23 million to be appropriated each year through 2004 for this purpose, and SSA's fiscal year 2004 budget includes funding in this amount (including costs of related training and technical assistance).
- Protection and Advocacy Grants (\$7 million).*—The 1999 Ticket to Work Legislation authorizes \$7 million to be appropriated each year through 2004 for Protection and Advocacy (P&A) grants. These grants will be used to provide advice to beneficiaries and to provide an avenue for resolving disputes. Consistent with the \$7 million authorization, we plan to spend \$7 million (including costs of support services such as training and technical assistance) for P&A in fiscal year 2004.
- Program Manager Contract (\$9 million).*—The Program Manager contract was awarded to Maximus Inc. in fiscal year 2000 at a total cost of \$56 million covering the period September 29, 2000 through September 30, 2005. Maximus is a private Virginia based organization that will help SSA manage the over-all Ticket to Work program. Phase IV of the contract is funded in fiscal year 2004 at \$9.4 million.

In addition SSA's administrative budget supports other Return to Work activities such as:

- The Ticket to Work and Work Incentives Advisory Panel advises the Commissioner of SSA, the President, and Congress on issues related to work incentives for people with disabilities.
- Other administrative costs include quality assurance contracts, notices, miscellaneous printing costs such as public education materials and reference guides, postage, training, travel, and systems enhancements.
- Nationwide training and outreach efforts to build employment support expertise in SSA's field offices. SSA also is looking at its current incentives as they pertain to young people with disabilities who are making the transition from school to work and to disabled individuals with more challenging rehabilitation issues.

Question. How much funding from other sources support the program within the fiscal year 2004 budget request?

Answer. SSA's fiscal year 2004 budget includes program funding to cover outcome and milestone payments made to Employment Networks (EN) under the Ticket to Work program. Milestone payments are provided to ENs based on a beneficiary's successful achievement of prescribed work activity. Outcome payments are made once an individual's benefit payments cease due to work activity and earnings. For fiscal year 2004, we have budgeted \$25 million in each program—Social Security (OASDI) and Supplemental Security Income—to cover Ticket payments. In addition,

SSA provides reimbursement payments to State Vocational Rehabilitation (VR) agencies, which elect to be paid under this system and not as ENs, when they are successful in rehabilitating disability beneficiaries. The budget includes an estimated \$73 million to cover OASDI VR reimbursement payments and \$75 million to cover SSI reimbursement payments in fiscal year 2004.

In addition, SSA's fiscal year 2004 section 1110 research budget request, funded through the SSI appropriation, includes \$5.2 million for evaluation of the Ticket to Work and Self-Sufficiency Program. This project will identify the most promising components of the Ticket to Work initiative, the most efficient incentive structure for the program, the refinements necessary to improve Ticket outcomes, and the individuals most likely to benefit from the program. It also will examine the adequacy of incentives in delivering services under the program for hard-to-serve beneficiaries.

SSA's fiscal year 2004 budget for research and demonstration projects also funds several other projects that support the return-to-work initiative and the Ticket to Work program's goal of transitioning disabled individuals into the workforce, including the Youth Transition Process Demonstration, the Early Intervention Demonstration, and evaluation of the Disability Program Navigator project with the Department of Labor.

Question. Now that the SSA has roughly one year of experience with Social Security and SSI disability recipients receiving Tickets for VR services, what trends are evident in terms of the choices consumers are making whether to utilize their ticket, the characteristics of participating individuals, the organizational characteristics of selected Employment Networks (including VR agencies), the way in which such Employment Networks are paid and the employment outcomes for participating individuals?

Answer. Our early information reveals that a fairly diverse group of beneficiaries have made the decision to assign Tickets to providers and to begin employment. So far, the profile of beneficiaries who have assigned Tickets closely tracks the profile of Ticket-eligible beneficiaries with regard to type of benefit, sex, type of disability and time on the rolls. One interesting trend we will be watching is that younger beneficiaries, those under age 40, are assigning Tickets at a much higher rate than older beneficiaries are.

With respect to providers, approximately 85 percent of individuals participating in the Ticket program have assigned their Tickets to the State VR agencies; of these, about 60 percent are new clients to VR. VR agencies have elected to receive payment under the traditional cost reimbursement program for 95 percent of these beneficiaries. ENs with Tickets assigned to them include traditional employment service providers in the public and private sectors, and such non-traditional providers as employers, colleges, employment agencies and job placement services, hospitals, faith-based organizations and Department of Labor One-Stop centers.

As of May 8, 2003, about 4 million Tickets have been mailed, and more than 16,000 have been assigned to ENs or VR agencies. Although we have information regarding payments to providers, it is still too early to draw broad conclusions regarding the employment outcomes of beneficiaries participating in the Ticket program. We will be evaluating the Ticket program to identify its most promising components, refinements needed to improve Ticket outcomes, and the individuals most likely to benefit from the program, as well as to assess the program's cost effectiveness. Nevertheless, many Ticket participants are now working, and we are pleased to learn the success stories from individuals whose receipt of the Ticket has provided them the opportunity to return to productive employment.

By the end of this year, the Ticket-to-Work program will be available in all 50 States. I truly believe that we're entering a new era for people with disabilities—an era of new attitudes, new possibilities, and new hopes. Many people want to work, and this program helps them do that:

- Arizonian, Bob Q., used his Ticket, set up an appointment with an employment network, and is now working as a marketing designer for the real estate industry.
- Didi A. credits the Ticket-to-Work program for helping to provide the motivation that brought her to Arizona Bridge to Independent Living (ABIL). Using her Ticket, she met with a job counselor who prepared her for work. Last September, Didi accepted a position with the Arizona State Government.
- Vera L. has the longest recorded employment of the Ticket Program, more than a year. Vera works 40 hours a week as a personal assistant and has already received a raise.

Question. Through what means has SSA informed eligible beneficiaries and recipients, employers, service providers and other stakeholders about the Ticket program?

Answer. We've informed beneficiaries and recipients, employers, service providers and other stakeholders about the Ticket program through:

- The initial Ticket mailings, which we will complete in 2004;
- Media events to kick-off the Ticket program in several States in the first two rounds of Ticket roll-out. I joined former Senator Roth in Wilmington, Delaware to highlight presenting "The First Tickets in the First State" to individuals in Delaware. I also hosted Ticket media events with Senator Ted Kennedy in Boston, MA and Representative J.D. Hayworth in Phoenix, AZ., and with Virginia State officials in Arlington, VA;
- Partnering with the Office of Personnel Management (OPM) to promote the Ticket program throughout the Federal government;
- Partnering with the Department of Labor's Office of Disability Employment Policy to utilize its Employer Assistance Referral Network and create a subunit named Ticket to Hire (TTH), which specializes in matching employers with job-ready candidates from the Ticket program;
- Partnering with private organizations to promote the program to a diverse mix of employer groups;
- Recruitment fairs to educate service providers about the Ticket program and encourage them to become ENs;
- Significant outreach to service providers and others by MAXIMUS, our contracted program manager;
- Our Internet website, which educates and provides resources to Ticket to Work stakeholders;
- National and regional representation, by specialized Ticket to Work staff, at hundreds of conferences and forums that promote the hiring of people with disabilities; and
- SSA's extensive informational materials provided in print and other formats. SSA's Red Book on Work Incentives and a number of other materials are used extensively in the field to inform and train beneficiaries, advocates, service providers and others.

We are working on further enhancements to our outreach and public information efforts. Plans include written and video presentation of Ticket success stories, a new training effort to assist present and potential ENs with information on potential funding sources and analysis of emerging data on the Ticket program to target our informational efforts.

Question. How much funding within the fiscal year 2004 Budget supports training, technical assistance and outreach to these different groups?

Answer. SSA's fiscal year 2004 administrative budget includes \$39 million for BPAO cooperative agreements, P&A grants, and continuation of the Program Manager contract. A large portion of that amount is used to provide training, outreach and public information.

Question. How has SSA provided support to individuals in making well-informed, work-related decisions, as well as in ensuring that their legal rights are protected under new program authorities?

Answer. SSA has a multi-faceted approach to help beneficiaries with disabilities obtain accurate and timely information and support regarding return to work. The approach centers around continued education and training for all direct service employees, the establishment of partnerships with other agencies and organizations, improved workload management and control systems, and the establishment of a corps of full-time Area Work Incentives Coordinators (AWIC). The AWIC will specialize in employment support workloads and services, and serve as the Agency's ombudsman and focal point of contact for advocates.

Two grant programs authorized by the Ticket to Work and Work Incentives Improvement Act of 1999 provide support to individuals regarding their participation in the Ticket program.

BENEFITS, PLANNING, ASSISTANCE AND OUTREACH (BPAO)

SSA awarded 116 cooperative agreements to a variety of community-based organizations for BPAO projects. The goal of the BPAO program is to enable SSA's beneficiaries with disabilities to make well-informed, work-related decisions.

BPAO projects cover every State, Territory, and the District of Columbia. Collectively they employ over 400 Benefits Specialists who explain the complex interrelationship of SSA's benefits, those of other Federal agencies and an individual's local programs. They assess the potential impact of employment on a beneficiary's Federal and State benefits eligibility and overall financial well being. Benefits Specialists then develop a comprehensive framework of possible options and projected results for each as part of the career development process. Benefits assistance in-

volves effective management of benefits as well as problem-solving support as needed. It includes analysis, reassessment, education, advisement and monitoring. Almost 50,000 beneficiaries have received direct services under the program to date.

Outreach activities by the BPAO projects are ongoing efforts to inform beneficiaries, their families, service providers and other stakeholders about the work incentives available. By enhancing awareness and understanding of the supports to be had, the Benefits Specialists alleviate the fear and uncertainty of beneficiaries considering work. The BPAO program has become an important step on the road to economic self-sufficiency for persons with disabilities.

SSA contracted with 3 universities to provide ongoing technical assistance and training to BPAO projects so they may effectively and responsibly serve clientele. Benefits Specialists must pass an intensive 7-day orientation class and successfully complete a field assignment before providing services under the program. In addition, they attend refresher and follow-up courses throughout the award period. This training is necessary to ensure dissemination of accurate and timely information to our beneficiaries. SSA has provided an arena in which persons with disabilities can confidently ask questions of a trained professional who is not a federal employee.

PROTECTION AND ADVOCACY (P&A) GRANTS

The Ticket to Work and Work Incentives Improvement Act of 1999 also granted the Commissioner authority to make payments to P&A systems for the purpose of providing services to beneficiaries with disabilities. Those services include providing information and advice about obtaining vocational rehabilitation and employment services as well as providing advocacy or other services that a beneficiary with a disability may need to secure or regain gainful employment. Under this new program, P&A grantees ensure that beneficiaries' legal rights are protected.

SSA awarded a total of 57 grants to each of the States as well as the District of Columbia, Puerto Rico, the United States Virgin Islands, Guam, American Samoa, the Commonwealth of the Northern Mariana Islands, and one for the Native American community.

In 2002 alone, more than 10,000 beneficiaries with disabilities received P&A services free of charge which ranged from information and referral to legal representation. The P&As gave over two thousand outreach presentations during this period. Through conferences, seminars, publications, websites, and public service announcements on television and radio, the projects made people aware of viable approaches to overcoming employment barriers. Examples of the assistance provided under this program include:

- Fighting discrimination by employers against persons with disabilities;
- Obtaining reasonable accommodations in the workplace;
- Mediating disputes involving job coaches and individual plans for employment;
- Resolving transportation issues related to work;
- Acquiring tuition assistance and accommodations at educational institutions;
- Locating the best Employment Network for a beneficiary's specific circumstances;
- Working to improve Employment Networks' grievance procedures;
- Educating beneficiaries regarding the employment supports and incentives available; and
- Educating the local community regarding the legal rights of individuals with disabilities.

OTHER INITIATIVES

In addition to these programs, SSA plans to create a new position, the Area Work Incentives Coordinator, to provide technical information and assistance to beneficiaries and outside groups and coordinate work incentive-related activities within the field offices of the Area they represent.

At the same time, we plan to provide a customized training curriculum to accommodate training needs specific to each employee's role in administering employment support programs. For example, continuing education on Ticket to Work and related issues of concern to our beneficiaries will allow our public affairs personnel, using their communications skills and community outreach opportunities, to become effective ambassadors for these programs. In addition, our enhanced training will ensure that field and 800-Number personnel will maintain expertise on work incentives and employment support programs to be responsive to inquiries and process actions as appropriate.

SSA is enhancing systems and establishing procedural changes that will assist field personnel in processing actions efficiently and accurately and will provide information to beneficiaries with disabilities who are working or want to work. SSA

is also building these systems to improve workload management control and to provide more management information about beneficiaries with disabilities who are able to return to the workforce. It is important that there be a pool of experts with technical expertise in the complicated issues that can arise with a disability recipient who is pursuing and taking advantage of employment opportunities. But it is equally important that we continue to change the organizational culture to make return-to-work an integral part of the entire Agency's mission.

In addition to providing designated experts, we plan to leverage our resources by heightening the awareness of employment support programs internally and externally and broadening the knowledge of our entire Operations workforce.

Question. How has SSA collaborated with other federal agencies and partners to increase the work opportunities of individuals receiving Social Security and SSI disability payments and what resources are included within the fiscal year 2004 budget request to carry out such activities?

Answer. SSA is collaborating with others in the following research and demonstration projects to increase the work opportunities of individuals receiving Social Security and SSI disability payments. Amounts budgeted for these activities and evaluations in fiscal year 2004 total about \$20 million.

—*Youth Transition Process Demonstration.*—SSA will support State projects to test and deliver needed services to young Social Security and SSI beneficiaries with disabilities to assist them in achieving independence.

—*Disability Research Institute.*—One of the goals of this cooperative agreement with the University of Illinois at Urbana-Champaign is to provide research findings in critical disability policy areas, such as return to work strategies.

—*State Partnership Initiative (SPI).*—States have been testing innovative approaches to coordinating vocational planning and support, employer and employee coaching, financial planning, health and long-term care, and other necessary supports for disability beneficiaries. SSA will be evaluating the effectiveness of these approaches.

—*Disability Program Navigator.*—SSA has partnered with the Department of Labor (DOL) to support Benefit Navigators at DOL One-Stop Career Centers to provide beneficiaries with information on the Ticket to Work program and other SSA work incentives and well as assistance with related programs that may affect their ability to enter and retain employment (Medicare and Medicaid, housing, etc.).

SSA also is collaborating with the U.S. Department of Labor (DOL) to sponsor the Ticket to Hire program. This free nationwide referral service is designed to assist employers in locating and hiring qualified job candidates with disabilities from the Ticket to Work program. Ticket to Hire connects employers to ENs or State VR agencies from SSA's Ticket to Work program with job ready candidates. Ticket to Hire provides the employer with a referral list of ENs in their community. The employer can then contact these organizations to find qualified candidate(s) who are participants in the Ticket to Work program.

Ticket to Hire is a specialized unit of Project EARN (Employer Assistance Referral Network), which is also sponsored by DOL and SSA. If the Ticket to Hire staff is unable to locate organizations with qualified candidates in their database, the vacancy information is shared with EARN. EARN staff then searches a database that includes additional organizations that are employment service providers and may not be participating in the Ticket to Work program.

Question. The fiscal year 2004 budget request proposes obligations of \$2 million for Medicare Savings Program Outreach to continue outreach efforts to all new eligible individuals, as well as to a portion of those previously notified. Specifically, what outreach efforts will be undertaken to newly- and previously-eligible individuals? What portion of those previously eligible will be notified in fiscal year 2004 and subsequent years?

Answer. SSA intends to send Medicare Savings Programs outreach letters annually to all new beneficiaries who meet the statutory income test and are not already receiving help with their share of Medicare expenses. SSA will mail outreach letters to two groups of Medicare beneficiaries who were on the rolls before the previous letter selection:

—Beneficiaries who had too much income for this help before but now meet the statutory income test (e.g., as a couple there was too much income, but the new widow's income now meets the statutory test); and

—One-fifth of people who received outreach letters before who continue to meet the statutory income test and are not already receiving help with their share of Medicare expenses.

SSA will continue to share electronic files of selected potentially eligible beneficiaries of the Medicare Savings Programs with their servicing Medicaid State agencies.

SSA plans to continue the letter and file-sharing activities described above for new and previous eligibles annually. These activities will ensure that every potentially eligible beneficiary receives an outreach reminder letter at least once every five years and States will receive appropriate information each year.

Question. How has the GAO evaluation of outreach efforts guided development of your proposed fiscal year 2004 activities?

Answer. GAO has not yet shared evaluation data or results with SSA. SSA looks forward to receiving the GAO evaluation as a potential source of information that could be used to improve this process.

Question. Earlier this year, the General Accounting Office (GAO) added Social Security's disability programs to its list of High-Risk programs. Your fiscal year 2004 budget request supports making substantial progress towards national implementation of an electronic disability process—AeDib—by the end of fiscal year 2004 as a means to improving the timeliness of and efficiency associated with disability decisions.

How much funding is included in the request to support the AeDib? GAO has stated (GAO-03-225, page 132) that the agency has had "mixed success in past technology investments." How has the agency's previous experience with major technology investments helped guide the design and implementation strategy for this new initiative?

Answer. The Agency will begin national implementation of the Accelerated Electronic Disability System (AeDib) on January 1, 2004. Over an 18-month period the system will be installed in every State Disability Determination Services (DDS) center in the country. We estimate an initial IT investment of about \$150 million during the budget period for AeDib planning, development and implementation. In addition, significant SSA staff effort will be devoted to project as well as related non-IT support costs.

A previous effort to automate the disability process at SSA was called the Reengineered Disability System (RDS). In 1999 Booz Allen Hamilton assessed RDS and made recommendations to the Agency concerning the use of technology to improve future disability processing. AeDib is based on those recommendations.

Many technological lessons were learned from RDS. For example, while RDS was designed to create one processing system for all of the State DDSs, AeDib will not replace the current DDS case processing systems. Instead, each State is upgrading and enhancing its systems in order to accommodate the Electronic Folder.

SSA is building applications that allow the public to file for disability over the Internet. SSA also is creating a fully automated Office of Hearings and Appeals Case Processing and Management System. This system will automate the hearing process from initial receipt through final disposition.

In order to evaluate our progress every step of the way and to continue to meet the goals of the project, each project associated with AeDib has been or will be rolled out in phases. This process allows SSA to gain the experience it needs in order to continue to meet the customer's needs.

To effectively enhance the capabilities of the Electronic Folder and to provide the infrastructure needed for other initiatives, SSA has completed an initial upgrade to its telecommunications infrastructure. SSA also is maximizing the use of Commercial Off-the-Shelf products.

To document and ensure that we target our development work by determining specific areas with the highest paybacks, Booz Allen Hamilton has completed a Cost Benefit Analysis for AeDib.

Question. What actions are planned to ensure that all components, including state disability determination services, have sufficiently trained staff, available technical and program support and adequate resources to implement this initiative and how much is provided within this budget request for these activities?

Answer. AeDib will provide the infrastructure to support paperless and electronic processing of disability claims from initial contact through the hearing decision. To ensure success and ease implementation activities, AeDib has been broken into several interrelated projects.

First, the American public will have the ability to complete disability claims over the Internet. We have already successfully implemented the adult version of the Social Security disability application and medical form. Prior to national implementation, members from the public came to SSA headquarters to test the disability form. Between now and January 2004, we will be adding additional forms to the Internet.

What the Internet provides for the public, the Electronic Disability Collect System (EDCS) provides to field offices. EDCS is used to electronically collect medical infor-

mation previously obtained on paper forms for initial adult and children cases. Regional trainers from across the nation came to SSA headquarters to receive "Train the Trainer" instruction on EDCS. As of February 2003, every field office received EDCS training. Between now and January 2004, additional functionality including hearings and continuing disability reviews will be added to the program.

The next (and most complicated) project is the Electronic Folder. A prototype of the Electronic Folder was completed in October 2002, and pilots are scheduled to run from July 2003 through December 2003. One of the major activities that SSA needed to accomplish to allow the State Disability Determination Services (DDS) to interface with the new Electronic Folder was to provide them with new computer hardware. We accomplished this in September 2002. We provided the hardware training to the DDSs. We are now in the process of upgrading the software. Implementation of the Electronic Folder, combined with EDCS, will significantly change the business process and reduce case processing times.

The last project is to create an automated system known as the Office of Hearings and Appeals Case Processing and Management System (CPMS). Currently OHA has very limited automation. This project will automate the process from initial receipt through the final decision, which will improve case processing and contribute to productivity improvements. We are working closely with our user groups to build a successful CPMS prototype.

Our training strategy also is multifaceted. SSA has conducted AeDib training for regional trainers at SSA headquarters. At SSA headquarters, technical staff has been undergoing extensive training to learn how to use and integrate new technologies.

In order to ensure a successful implementation of the Electronic Folder, SSA will provide onsite technical training and support to the various components. The goal is to ensure that the architecture is operating smoothly and that SSA/DDS staffs supporting the system are provided with expert training. SSA, working with the DDSs, will also provide hands-on business training to all Federal and State components working with the new Electronic Folder.

Our fiscal year 2004 budget includes approximately 300 workyears in order to support these implementation initiatives and meet our goals.

Question. What steps have been taken to secure the privacy of electronic information collected?

Answer. Several steps are being taken to secure the privacy of electronic information for the AeDIB process as well as for other projects SSA is undertaking. Specifically for AeDIB:

- Developers are following the SSA Systems Development Life Cycle, which includes ongoing security review (access controls, separation of duties, integrity, audit trail etc.), on an iterative basis.
- We are currently piloting a secure transport mechanism for disability data.
- A systems manager responsible for the overall project has been named and is drafting a security plan for the project.
- We are in process of awarding a contract for a security risk assessment monitored by the project officer, system manager and security staff.
- We have implemented ongoing monitoring of Electronic Medical Evidence and Security status meetings by Chief Security Officer staff.

Question. What additional steps are being considered to improve the accuracy, timeliness and cost-efficiency of the disability determination process and what is the timeline for their implementation?

Answer. AeDib is one of the key steps SSA is taking to improve the disability process. AeDib rollout will begin in January 2004 and continue for 18 months. While processing time is expected to improve slightly in 2004, this initiative is expected to substantially reduce processing time over the long term.

- AeDib will provide us with tools to move work seamlessly from place to place, increasing access to agency medical and technical expertise, maximizing agency resources, and supporting quality adjudication. The first piece of AeDib is the electronic intake system Electronic Disability Collect System (EDCS) which began in October 2002. By automating data collection, the accuracy of the information will be enhanced and more complete information will be passed to the Disability Determination Services (DDS) and later to the Office of Hearings and Appeals.
- We will be conducting assessments throughout start-up and rollout of the new system and process. Additionally, we will be conducting a post implementation review that will help determine impacts, efficiencies and quality results based on AeDib.
- SSA also is working with the medical community to leverage their electronic processes in coordination with our AeDib medical evidence activities. Our goal

is to increase the electronic exchange of medical evidence to maximize efficiencies in alignment with Health Insurance Portability and Accountability Act (HIPAA) regulations. On May 8, I met with representatives from some of the nation's largest medical professional associations to discuss SSA's medical evidence needs, the process for obtaining evidence, the new HIPAA compliant authorization form, and our vision of a future electronic business process.

SSA has been engaged in a number of efforts to redesign and improve the disability determination process by testing several initiatives over the past several years. Based on our review of their results, we have decided to:

- Encourage early and frequent contacts with claimants during the development process;
- Eliminate the claimant conference at the end of the process; and
- Temporarily extend the “elimination of reconsideration step” feature in the Prototype States that are currently doing this, while SSA develops an alternative approach.

The amount of time the SSA appeals process takes also has been a major concern. SSA has made the following near-term changes to the hearing process, based on analysis of the Hearings Process Improvements (HPI) initiative:

- Include ALJs in early case screening to more quickly identify cases for dismissal and possible on-the-record decisions;
- End the requirement that cases be certified as “ready to hear”, removing a step in the process;
- Allow ALJs to issue fully favorable decisions from the bench immediately after a hearing; and
- Expand the use of technology in the Office of Hearings and Appeals, including video conferencing, speech recognition and digital recording of hearings.

SSA also is assessing its policies and procedures to enable simplification of data collections and case documentation. We have revised and consolidated data collection forms to ensure consistency and accurate data propagation. For example, we are combining 3 forms into a single public-use document as part of the appeals process.

SSA currently reviews at least 50 percent of all title II initial disability allowances made by State agencies on behalf of SSA. The fiscal year 2004 President's budget includes a proposal to apply the same requirement for adult disability allowances in the SSI program. That is, when fully phased in, 50 percent of initial SSI disability allowances would be reviewed, applying consistency across both disability programs.

We expect to make recommendations soon regarding additional steps we can take to improve the disability process.

Question. Commissioner, you have stated that the Hearings Process Improvements (HPI) initiative, which was implemented in 2000, has not worked and that SSA has implemented additional changes to the process, based on your assessment of HPI.

What lessons has SSA learned from the failure of HPI and how were they used to develop and implement the latest changes?

Answer. What we learned during the course of HPI has yielded insights valuable to the further refinement of our hearings processes. We have not yet implemented our contemplated mid-term and long-term process changes. Therefore, these responses chiefly address changes we have made in the short-term.

We learned that the HPI processes included unnecessary case handoffs. In our latest changes, we sought to eliminate these handoffs. For instance, we observed that attorney and paralegal certification of cases as “ready to hear” before sending those cases to Administrative Law Judges (ALJs) for prehearing review was a step of limited value. We have eliminated that step. Though we had initially thought that rotating functional assignments among support staff would improve overall hearing office performance, we discovered that rotation actually undermined the strengths of our staff. Consequently, we discontinued rotations and created a new position, the Case Intake Assistant, with duties that incorporated the previously rotated functions.

HPI taught us the importance of a strong management team in the hearing offices. We are striving to strengthen the management structure in the field. HPI also taught us the importance of prompt implementation of systems support needed to support new initiatives. We are proceeding as expeditiously as possible with the development and implementation of new technology and applications to support the Office of Hearings and Appeals' (OHA) business processes.

Question. Given that implementation of reforms is very costly in terms of additional delay for individuals involved in the process, lost production time, and staff anxiety, what steps were taken to involve all stakeholders in the latest reform and

what resources are included in the fiscal year 2004 request for staff training and support of implementation?

Answer. We haven't undertaken a major reform of the hearing process since HPI. However, we recognize there are significant hearing backlogs and we need to make every effort to move toward reducing those backlogs. For this reason, with the proposed transfer of Medicare hearings to the Department of Health and Human Services in fiscal year 2004, this budget redirects 478 workyears previously used to process Medicare hearings to processing SSA disability hearings and appeals instead. This will enable SSA to process 46,000 more SSA hearings in fiscal year 2004 than in fiscal year 2003 and improve service by reducing the hearings processing time.

We have focused on processing the work with incremental initiatives that could be effectuated in the short term with little delay for individuals involved in the process and minimal, if any, loss of production time. We believe the nature of these changes, our candid discussions with all of the unions representing our employees, and the initiatives' incremental implementation over the past year have helped to minimize any potentially adverse impact on employee morale and productivity. And, despite additional investments in training, savings from initiatives will increase the overall production rate for SSA hearings from fiscal year 2003 to fiscal year 2004.

The budget continues to support base levels of ongoing and new staff training for OHA staff, plus significant training for technological enhancements to the business process in fiscal year 2003 and fiscal year 2004, including training related to implementation of AeDIB. Most of the cost of staff training is the workyear cost, along with related non-payroll expenses for instructors and travel. For fiscal year 2004, we estimate about 250 workyears for OHA training, including about 100 workyears related to AeDIB.

Question. How will the latest reforms improve timeliness, accuracy and efficiency of decision making? What other changes have been implemented to help improve productivity and increase the likelihood of getting the right decision at the earliest possible time?

Answer. We are preparing cases for hearing more quickly and in greater numbers with the aid of contract file assemblers, who furnish clerical support for file preparation. As previously noted, we also have eliminated rotational assignments for case technicians. These actions free case technicians to concentrate their attention on more complex case preparation tasks.

We have asked our most highly trained employees, ALJs, to join other professional hearing office employees in early screening and reviewing cases most likely to warrant on-the-record decisions. ALJ participation in this process facilitates review of a higher percentage of such cases, thus increasing the number of cases that can be decided early, without the necessity of a hearing.

We have implemented a new decision writing program for fully favorable decisions that is easy for ALJs and decision writers to use and fully documents the legal basis for fully favorable decisions. Providing the new program as a tool for their use, we have asked ALJs to use their personal computers to draft any fully favorable decisions they reach as a result of early screening, as well as any decisions that they announce orally at a hearing. This eliminates case handoffs to the decision writers and frees the decision writers to concentrate on more complex cases.

We are providing speech recognition software to ALJs and decision writers to facilitate decision drafting. The introduction of this software will eliminate the need for transcription of dictated decisions by case technicians, shortening case processing time and freeing the case technicians for case preparation duties.

Question. The GAO Report "Social Security Disability: Efforts to Improve Claims Process Have Fallen Short and Further Action is Needed" (GAO-02-826T) found that in fiscal year 2000, about 40 percent of the applicants whose cases were denied at the initial level appealed this decision and about two-thirds of those who appealed were awarded benefits. What resources and activities are supported in the fiscal year 2004 budget request to specifically address this issue and reduce the likelihood that initial decisions are changed upon appeal?

Answer. Our goal is to make the right decision on disability claims as early in the process as possible. We should note, however, that a different decision during the appeals process does not necessarily mean that the initial decision was wrong when it was issued. Unfortunately, currently many months may elapse between the initial determination and the various steps of the appeals process and, during that time, the claimant's medical condition may have worsened. And, we allow a claimant to provide additional information at any time during the process. So a person who may not have met the criteria for disability assistance at the first step may meet those criteria by the time a hearing can be held. This kind of situation shows the importance of reducing the delays and backlogs that currently make the appeals process take so long. (We also are working on finding ways to ensure that complete

information is provided at the initial determination step so that the decision-maker can consider all factors that may affect the decision.) For this reason, I have made eliminating backlogs a primary focus.

As I indicated in my testimony at the March 4, 2003 House appropriations hearing before the Subcommittee, the President's budget request for fiscal year 2004 demonstrates our commitment to continuing efforts to improve service, efficiency and program integrity in the disability program. Issues regarding the appeals process and reducing the likelihood that initial decisions are changed upon appeal are longstanding concerns in the disability program. We expect to make recommendations that address those issues in the coming months, and expect to propose changes that are cost-neutral in terms of the overall impact on SSA's budget.

In order to effectively address the systemic issues in the disability process, we need to get the existing disability workloads under control. Based on the work that has been done on our Service Delivery Assessment, it is clear that eliminating backlogs and processing special workloads are prerequisites for providing good service to the public. Although approximately 40 percent of disability claims are approved within three and a half months of initial application, for applicants who exercise all administrative appeal rights provided under current law and current processes, an average of 1,153 days is required for a final Agency decision. Based on our analysis, almost 50 percent of this time in the process results from the backlog of cases.

We are taking a number of actions in the near term to reduce processing times and increase efficiency. The fiscal year 2004 budget request supports those actions. As indicated above, we are engaged in review of strategies to further improve the disability program and expect to make recommendations soon.

Question. The fiscal year 2004 President's Budget proposes to transfer responsibility for Medicare hearings from SSA to the Department of Health and Human Services (HHS).

What are the actual expenditures and associated workload processed in fiscal years 2000, 2001 and 2002, as well as those estimated in fiscal year 2003?

Answer. The chart below provides actual expenditures and associated workloads for Medicare hearings for fiscal years 2000, 2001 and 2002 as well as those estimated for fiscal year 2003 in the fiscal year 2004 President's budget. The estimates for fiscal year 2003 assume an increase in receipts related to the Medicare, Medicaid and SCHIP Benefits Improvement and Protection Act of 2000 (BIPA) and implementation of a streamlined process for handling Medicare appeals. Neither of these has occurred.

Medicare hearings	Actual fiscal year			Estimate fiscal year 2003
	2000	2001	2002	
Receipts	77,872	77,726	71,576	122,147
Processed	88,084	69,663	77,388	105,000
Pending	35,904	43,517	37,705	54,852
Expenditure (dollars in millions)	\$79	\$74	\$78	\$79

Question. What planning and transition activities are being undertaken with HHS/CMS to ensure that a timely and smooth transition occurs, if legislation is enacted that transfers the Medicare appeals function effective October 1, 2003 as proposed in the President's budget?

Answer. While we have agreed with HHS/Centers for Medicare and Medicaid Services (CMS) in principle to transfer responsibility for the Medicare hearings function effective October 1, 2003, we are still working out the details of the workload transfer. In January 2002, I established an executive level position on my staff to work directly with the CMS Administrator and his staff to provide technical assistance in the design of a hearing process and service delivery plan tailored to the unique needs and opportunities of Medicare appeals. SSA and HHS/CMS have had an ongoing dialogue since that time. These discussions focus on issues such as transfer of cases, sharing of resources (e.g., video conferencing), and systems support. A Memorandum of Agreement that will reflect these decisions is being prepared.

Beginning with fiscal year 2004, consistent with the Administration's plan to transfer the Medicare hearings function to the Department of Health and Human Services, SSA's annual budget request does not include the resources that would be needed to process Medicare hearings. The President's budget now includes the Medicare hearings function and related funding under the Department of Health and Human Services, which is accountable by law for management and administration of the Medicare program.

Question. What amount of budget authority is required in fiscal year 2004 to process fully this workload, if legislation is not enacted consistent with the President's budget?

Answer. Funds to process Medicare hearings are budgeted in HHS/CMS for fiscal year 2004. Consistent with our assumption that HHS/CMS will assume responsibility for the Medicare hearings function beginning October 1, 2003, SSA has not included any resources in its fiscal year 2004 budget request to process this workload.

Question. In January 2001, the General Accounting Office identified strategic human capital management as a governmentwide high-risk area.

What steps are you taking to acquire, develop, and retain an appropriate mix of agency staffing/talent, particularly in light of the Agency's impending retirement wave? What is the agency's plan for creating an organizational culture that promotes high performance and accountability and empowering and including employees in setting and accomplishing programmatic goals? How does the fiscal year 2004 budget support these activities?

Answer. SSA is taking a number of steps to acquire, develop, and retain an appropriate mix of agency staff.

SSA started retirement wave analysis and planning over five years ago. This analysis was the impetus for our Future Workforce Transition Plan (FWTP), which positions us well to transition to the workforce of the future. The FWTP contains milestones regarding recruitment, retention, employee development and a satisfying work environment. It is aligned with our mission, goals and objectives and is integrated in budget, strategic and performance plans. Selected highlights of our activities include:

To acquire staff, SSA:

- Created a national recruitment coordinator position with responsibility for developing and implementing recruitment initiatives SSA-wide;
- Uses recruitment and retention incentives, including above minimum starting salaries, recruitment bonuses, relocation bonuses and retention allowances;
- Uses delegated expedited methods to reduce the time it takes to fill jobs, and continues to work with the Office of Personnel Management to find ways to accelerate the staffing process;
- Is piloting a competency-based hiring process;
- Fills vacancies as early as possible in the fiscal year, subject to budget and hiring authority; and
- Rehires experienced annuitants in times of critical need.

To develop and retain staff, SSA:

- Incorporates organizational values into entry level training and new hire orientation;
- Offers extensive technical and leadership training via Interactive Video and the Intranet. Personal development courses are also available online and can be taken at home.
- Is restructuring curricula around identified competencies to ensure that employees have the knowledge and skills to respond to emerging needs;
- Has a variety of career paths for employee advancement;
- Offers career counseling services;
- Offers national Leadership Development Programs designed to build identified leadership competencies for GS-9 through GS-14 employees, as well as a Senior Executive Service (SES) Career Development Program designed to develop executive leadership in the Agency's succession planning efforts. SSA's organizational components also have a variety of development programs at various grade levels nationwide; and
- Offers SES development opportunities outside of the formal programs.

SSA is creating an organizational culture that promotes high performance and accountability and empowering and including employees in setting and accomplishing programmatic goals. SSA's revised SES performance management system is linked to strategic goals and distinguishes between high and low performance. A revised system for non-bargaining unit GS-15s will be implemented October 1, 2003. An executive level workgroup is currently developing alternative performance systems models for all other employees, taking into account the connection with the awards and promotion systems. Plans for all other employees will take effect with the signing of a new labor contract with AFGE in fiscal year 2004.

Also, SSA sets programmatic goals through our strategic planning process. This process considers our responsibilities to the public we serve and environmental factors such as demographics, health and disability trends, technological advances and workforce trends. Our employees are key to success in accomplishing these programmatic goals. They are actively encouraged to offer suggestions through our

newly automated suggestion program. They are invited to participate on workgroups or provide input as we develop and test new processes.

Additionally, in early fiscal year 2003 I held a series of 11 candid, interactive meetings with all supervisors, managers and executives in the Baltimore/Washington headquarters area, discussing leadership principles, management philosophy and the Agency's four major performance areas. During the summer of fiscal year 2003, I plan to discuss this same set of critical topics with the full management cadre in each of the 10 regional office cities and from field offices in commuting distance of those cities.

The fiscal year 2004 budget supports these activities with a consistent level of baseline funding to accomplish many of the activities cited. Consistent with actual spending in fiscal year 2002, the fiscal year 2004 budget also includes approximately \$4 million in project-specific funding for the following initiatives:

- Interactive Video Teletraining
- Leadership Development Programs: Senior Executive Service, Advanced Leadership Program, Leadership Development Program, and Presidential Management Intern Program;
- Leadership Seminars
- Performance Management Training

SSA's budget also provides funding for participation in LEGIS Fellows Programs, OPM Management Development Programs and Federal Executive Institute programs. Funding to maintain the recruitment marketing program developed in fiscal year 2002 and to advance the competency-based recruitment initiative also is included in the budget.

Question. The Congress appropriated additional funds from fiscal year 1996 through fiscal year 2002 to ensure that the Agency would carry out a 7-year plan to become current in processing CDRs. The fiscal year 2004 request includes dedicated funding of \$1.4 billion, for among other things to process continuing disability reviews.

Is the Agency on schedule to remain current with processing CDRs in fiscal year 2003?

Answer. In fiscal year 2003, SSA is focusing on keeping up with claims workloads so that the number of disability claims pending does not grow. Consequently, we will not be able to process all CDRs necessary to remain current. We began this year under a continuing resolution and operated for four months at last year's level. In addition, we are absorbing an across-the-board rescission of .65 percent and a higher-than-budgeted pay raise. Nevertheless, we will continue to assess our ability to process more CDRs in fiscal year 2003 than reflected in the fiscal year 2004 President's budget, while keeping up with claims receipts, and will increase the number of CDRs processed to the extent that we are able.

Question. What lessons did SSA learn during this 7-year period about efficiently using these funds to stay current with its CDR obligations?

Answer. If SSA is adequately funded for CDRs we can stay current with this workload. However, we also have learned that we need to work closely with the States and balance the resources applied to CDRs with those for processing initial claims. We have been unable to keep up with incoming disability claims receipts since fiscal year 1997. This situation was compounded by a recent surge in initial receipts. As a result, DDSs entered fiscal year 2003 with the highest initial pending level in DDS history. Currently, it is difficult to ensure adequate funding for stewardship activities when they compete for the same discretionary dollars. Specifically, we face two significant competing demands: (1) the need to pay disabled claims as quickly and proficiently as possible; and (2) the need to serve as stewards of the public trust and perform CDRs to protect program integrity in our trust fund and general fund programs.

The discretionary funding cap adjustments for CDRs authorized by Congress for fiscal years 1996 through 2002 were crucial to realizing currency for both the title II and title XVI disability review programs at the close of fiscal year 2002. The discretionary spending cap adjustment for CDRs and other integrity workloads that the President is recommending in the fiscal year 2004 budget would ensure adequate funding for the future to maintain currency with CDRs and process other cost-effective program integrity work thereby, enabling SSA to meet both its stewardship responsibilities and overall service demands.

The Agency would not have achieved currency at the close of fiscal year 2002, nor will it be able to remain current in the future, without the CDR profiling/mailer process. SSA uses highly skilled statistical support from contractors in performing the statistical analyses that determine who can be sent a CDR mailer, what action to take (automated decision logic) when a CDR mailer is returned, and many of the automated functions of both CDR mailer and full medical processing. SSA has a

wealth of data at its disposal resulting from hundreds of thousands of CDR decisions. Over the past several years the contractors' products have enabled SSA to perform mailer, rather than full medical reviews, for several hundred thousand additional CDRs than was possible in the first few years of the 7-year plan.

The CDR mailer process involves little public burden (it is estimated to take approximately 15 minutes to read the instructions and complete the form), and it is also cost-effective. Agency budget documentation indicates that the unit cost of a CDR mailer in fiscal year 2001 was \$27, while the unit cost of a full medical review was \$689. In fiscal year 2001, the CDR mailer accounted for over 50 percent (about 895,000 of 1,731,000) of reviews reported to Congress. In fiscal year 2001 alone, even if the Agency had the workforce capacity, an additional 895,000 full medical reviews would have cost an additional \$592 million when compared to processing the same number of CDR mailer deferral actions. (The Agency did not have the workforce capacity that would have allowed us to accomplish these medical reviews had there been funding available.)

Since its inception, integrity sampling has been a key element in assuring that the process is a legitimate alternative to a full medical review. The CDR mailer process undergoes continuous, rigorous studies and audits, including yearly audits by PricewaterhouseCoopers as agent for SSA's Office of the Inspector General.

Question. What is SSA's plan for remaining current this year and in the future for processing CDRs?

Answer. As previously indicated, in fiscal year 2003 SSA is focusing on keeping up with claims workloads and therefore will not be able to remain current with CDRs this year. SSA plans to include sufficient resources in its budget requests to maintain currency with CDR workloads. In support of that goal, the fiscal year 2004 President's budget includes earmarked funding of \$1.446 billion for SSA program integrity workloads, including CDRs, and a proposal to treat this funding outside the discretionary spending caps.

Question. Please provide the subcommittee with a breakdown of the administrative costs associated with legislative proposals included in the fiscal year 2004 budget. Are these costs fully covered within the fiscal year 2004 budget request for LAE?

Answer. The President's fiscal year 2004 budget for SSA includes eight legislative proposals, only one of which would have significant administrative costs for SSA. That is the proposal for implementation of pre-effectuation reviews (PER) of SSI adult disability allowances, similar to the reviews now in place for Social Security disability program allowances. SSA's fiscal year 2004 LAE request includes \$10 million to implement SSI PER. Generally, SSA's administrative budget requests to Congress are based on current law. We have made an exception to the general practice in this case, due to the likelihood of enactment of SSI PER, based on the progress of this proposal in the 107th Congress and now in the 108th. Implementation of SSI PER will yield substantial program savings.

The other SSA legislative proposals are as follows:

- Improved reporting of pension income from non-covered employment—The Administration is working to determine the best way to obtain noncovered pension information systematically from State and local government employers, for enforcement of the Windfall Elimination Provision (WEP) and Government Pension Offset (GPO) provision of the law. The details of the proposal are still being developed.
- Close the loophole that allows exemption of spouses from the GPO based on one day in covered employment.
- Trust fund compensation for Military Service Wage Credits—This proposal makes the trust funds whole for FICA tax equivalents that remain unpaid by the Department of Defense for 2000 and 2001, including appropriate interest, together with adjustments for prior years. There is no administrative impact.
- SSI Program proposals:
 - Exclude from determination of individual income all interest and dividend income earned on countable liquid resources and revise the infrequent and irregular income exclusion.
 - Remove the restriction on payment of benefits to children who are born or who become blind or disabled after military parents are stationed overseas.
 - Treat all cash military compensation as earned income.
 - Count nonrecurring income only for the month it is received during the transition to retrospective monthly accounting during the first three months of eligibility.

SUBCOMMITTEE RECESS

Senator SPECTER. Thank you all very much. The subcommittee will stand in recess to reconvene at 9:30 a.m., Wednesday, April 9, in room SD-138. At that time we will hear testimony from the Honorable Elaine L. Chao, Secretary, Department of Labor.

[Whereupon, at 11:10 a.m., Tuesday, April 8, the subcommittee was recessed, to reconvene at 9:30 a.m., Wednesday, April 9.]